POLYPHOSPHORIC ACID CATALYZED CONVERSION OF METHOXY-SUBSTITUTED ARYLPROPANOIC AND ARYLBUTANOIC ACIDS TO DERIVATIVES OF METACYCLOPHANEDIONES, 1-INDANONES, AND 1-TETRALONES

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I wish to dedicate this thesis to all members of my wonderful family, my husband Yue Qin, my son Jimmy Qin and my parents. I could not go through all the situations and obtain the degree without their love, understanding, and support.

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LIST OF SYMBOLS AND ABBREVIATIONS

Ar	aryl
AT	acquisition time
bp	boiling point
^{o}C	degree Celsius
calcd	calculated
compd	compound
CT	completed transients
δ	chemical shift in parts per million downfield from tetramethylsilane
d	doublet (spectral)
dd	double doublets
D1	delay 1
DP	direct probe
EI	electron impact
Et	ethyl
eV	electron volt
g	gram
GC	gas chromatography
hd	heavy duty
hr	hour(s)
HRMS	high resolution mass spectrum
Hz	Hertz
J	coupling constant (NMR)

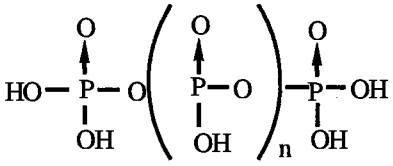
lit	literature
LSIMS	Liquid secondary ion mass spectrometry
m	multiplet (spectral)
Me	methyl
MHz	megahertz
min	minute(s)
mL	milliliter
mm	millimeter (length), millimeter mercury (pressure)
mol	mole(s)
mp	melting point
MS	mass spectrometry
m/z	mass to charge ratio (mass spectrometry)
NMR	nuclear magnetic resonance
obs	observed
OMe	methoxy
pent	pentet
PPA	polyphosphoric acid
ppm	parts per million (NMR)
PW	pulse width
qt	quart
s	singlet
sec	second
SW	spectrum width
t	triplet
t-Bu	*tert*-butyl
TMS	tetramethylsilane
wt	weight

CHAPTER I

INTRODUCTION

Polyphosphoric Acid as Reagent

In recent years, the mixture of polyphosphoric acid (PPA, **1**) has found ever-increasing use in synthetic organic chemistry. First recognized as an exceptional reagent for cyclizations, it has since been used in various acid-catalyzed reactions, including esterification, hydrolysis, condensation, acylation, rearrangement, and others.[1,2]



n=1,2,3,4,...or higher values

PPA, **1**

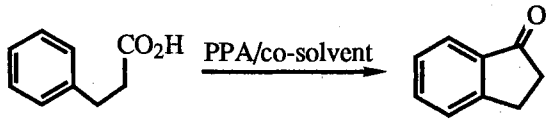
The effectiveness of PPA as a reagent in organic chemistry probably is the result of several different properties of the mixture. It is a liquid and serves as a good solvent medium for many types of organic compounds. PPA contains both acidic and anhydride groups; water produced during the course of a reaction is rapidly removed by reaction with anhydride linkages, generating new acidic sites. Since water is a stronger base than many of the organic compounds involved in the reactions, its removal is very important in preserving the effective acidity of the reaction mixture.[1]

The reactions which have been carried out in PPA are of the types that can be accomplished with other acid catalysts or dehydrating agents. In many cases, the use of PPA offers advantages in yield, ease of manipulation, or less side reactions. PPA offers advantages over strongly acidic reagents such as aluminum chloride or concentrated sulfuric acid; as a result, molecules containing functional groups, such as ester groups, which are sensitive to the more vigorous reagents may be dealt with satisfactorily in PPA. Because PPA is not an oxidizing agent and has little or no tendency to enter into substitution on aromatic nuclei, it gives a further advantage over concentrated sulfuric acid.[1] Rearrangement of carbon skeleton is less likely to be encountered in reactions carried out in PPA than those in sulfuric acid, aluminum chloride, and other more acidic reagents.[1] As compared to hydrogen fluoride, particularly for cyclizing aryl-substituted carboxylic acids, it has the advantage that its handling requires no unusual precaution, so that simple apparatus can be used.[3] In some synthetic processes, the use of PPA permits combining two or more steps, so that the isolation of an intermediate is avoided. As an important example, many cyclic ketones can be made directly from aryl-substituted carboxylic acids or their esters as an alternative to preparation of acid chlorides and a separate ring closure with aluminum chloride.[1]

Experimental difficulties sometimes arise in the isolation of a product prepared in PPA as a result of hydrolyzing the excess reagent and diluting it with water to the point where the solubility of the product is slight. If the product is a base, it will be necessary to neutralize the diluted phosphoric acid before isolation. Since the reaction usually is carried out in amounts of PPA sufficient to serve as the solvent as well as the reagent, the quantity of aqueous solution may become inconveniently large. The use of co-solvents with PPA has been found to be advantageous, either when the solubility of organic substrates in PPA is not high or when the proportion of PPA to substrates is reduced. Co-solvents are typically divided into two types; those which are miscible with PPA and often water

miscible on work-up such as sulfolane,[4] acetic acid,[5-8] ethanol/acetone,[9] and acetone/water;[10] and those which are immiscible with PPA and form a biphasic system such as xylene, toluene,[11,12] benzene,[13] cyclohexane,[13] hexane,[14] dimethoxyethane,[15] chlorobenzene,[16,17] and *o*-dichlorobenzene.[18] Guy and Guette[12] investigated the cyclo-condensation of 3-benzenepropanoic acid (**2**) to 1-indanone (**3**) in PPA in the presence of various co-solvents (Scheme 1-1). They learned that in the preparation of 1-indanone (**3**) by using 10x by weight excess of PPA at 70 °C for 1.3 hour, a 94% yield (based on GC) of **3** was obtained. However, when xylene was used as co-solvent (in equal quantity to PPA) at 100 °C for three hours, the amount of PPA could be cut down to 4x by weight and a 93% yield of **3** was obtained. Work-up was also found to be easier with less PPA for hydrolysis and disposal.

Scheme 1-1



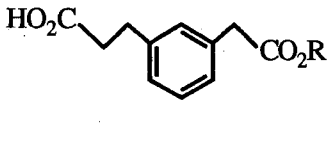
2 **3**

Since polyphosphoric acid is a complex mixture, it is not used to study the mechanisms of the reactions of organic compounds as has been done with sulfuric acid.[19] Because of its high viscosity, it is a poor medium for crystallization and it is not surprising that reaction intermediates have not been reported. At present the mechanism by which it operates on organic compounds is uncertain. The most obvious is that it functions as a protonic acid, as a Lewis acid, and as a phosphorylating agent.[1]

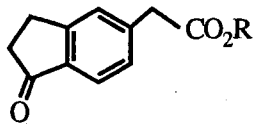
Many 1-indanones have been made in high yields from the corresponding 3–arylpropanoic acids or their esters by warming with PPA. Some examples of 1-indanones include: 4,5-dimethoxy, 99%;[20] 5,6-dimethoxy, 90%;[20,21] 2-benzene, 60%;[22] 3-benzene,

77%;[23] 6-methoxy-3-methyl, 22%, 21% from ester;[24] 6-methoxy-3,3-dimethyl, 33%, 31% from ester;[24] 6-methoxy, 43%, 18% from ester;[24] 5-methoxy-3-benzene, 66%;[25] 3-(4-methoxybenzene), 20%;[25] 3,3-dimethyl, 78%, 97% from ester;[24] 5,6-dimethoxy-2-benzene, 30%;[22] 5-methoxy-2-benzene, 40%;[22] 6-methoxy-2-benzene, 20%;[26] 3-ethyl, 91%;[25] 4-methyl, 71%;[27] and 5,6,7-trimethoxy, 91%.[20] Other early examples of the PPA-catalyzed cyclizations to substituted 1-indanones have been described.[28-43] These examples include several methoxy-substituted 1-indanones which could be obtained either only in low yields or not at all by other reagents. Self-condensation of the products under the influence of the PPA usually can be minimized by employing mild reaction conditions.[19,44-47]

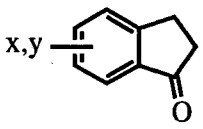
More recent examples include the following: the preparation of anti-inflammatory benzeneacetic acid containing 1-indanone ring by PPA treatment of the di-acid or ester **4** at 100 °C to give 5-substituted-1-indanone **5**[48] and the cyclization in PPA of several methyl and methoxy-substituted arylpropanoic acids to the corresponding 1-indanones (**6**) in 40-70% yields.[49]



4, R=H, Et



5, R=H, Et

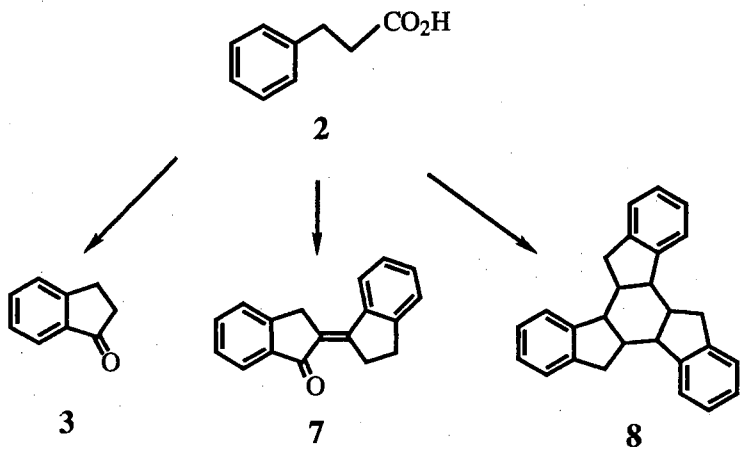


6, x,y=Me's or OMe

The effect of temperature and the amount of PPA on the cyclization of 3-benzenepropanoic acid (**2**) to 1-indanone (**3**) has been studied.[50] Condensation products (**7**, **8**) were observed at high temperatures.

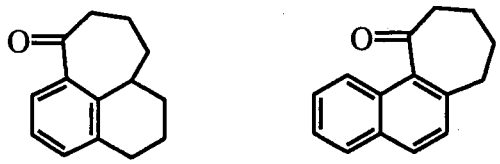
The cyclization of 4-arylbutanoic acids in PPA readily gives 1-tetralones and early examples are discussed and tabulated in the review of Popp and McEwen.[51] Further references are covered in other reviews.[52-54] Only a few examples of 1-tetralones will be

given here to indicate the general scope and yields obtained: 7-methoxy, 85%;[55] 5,7-dimethyl, 98%;[56,57] 4,5,8-trimethoxy, 66%;[58] 5-methoxy-7-methyl, 64%;[59] 6,7-dimethoxy-3-methyl, 87%;[60] 5,7,8-trimethoxy-2-methyl, 95%;[61] and 4,7-dimethyl, 91%,[62] 88%.[57]



2 **3** **7** **8**

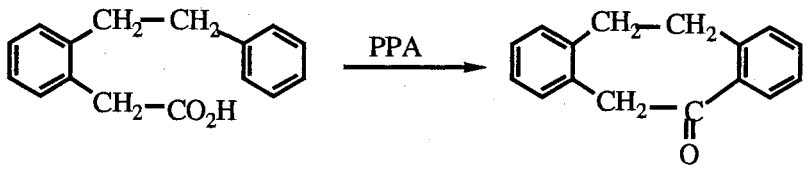
PPA can also be used to make seven-membered rings. 7-Keto-1,2,3,7,8,9,10, 10a-octahydrocyclohepta-[de]-naphthalene (**9**) has been made in 95% yield[63] from 4-(1,2,3,4-tetrahydronaphthalene)butanoic acid, and the 1,2-naphthosuberone (**10**) in 80-95% yield[64] from the corresponding acid.



9 **10**

The following appears to be the only example of PPA cyclization producing an eight-membered ring ketone **12** in good yield (Scheme 1-2). It employs a much larger ratio of PPA to acid (50:1) than is needed with the small ring compounds[65] to minimize the formation of polymers.

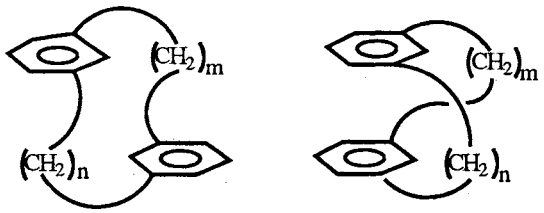
Scheme 1-2



11 **12**

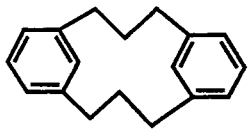
Syntheses and Properties of Metacyclophanes

Considerable interest has existed in synthesizing and studying the properties of a class of compounds known as cyclophanes.[66-68] Of particular interest has been [m.n]-metacyclophanes because, in general, two different conformations, *syn* and *anti*, can exist (Fig. 1-1).[69] And for [3.3]metacyclophane (**13**), *syn-anti* and torsional motions in the connecting chains are expected to have energy barriers which could be studied by dynamic NMR spectroscopy.[69]



Anti *Syn*

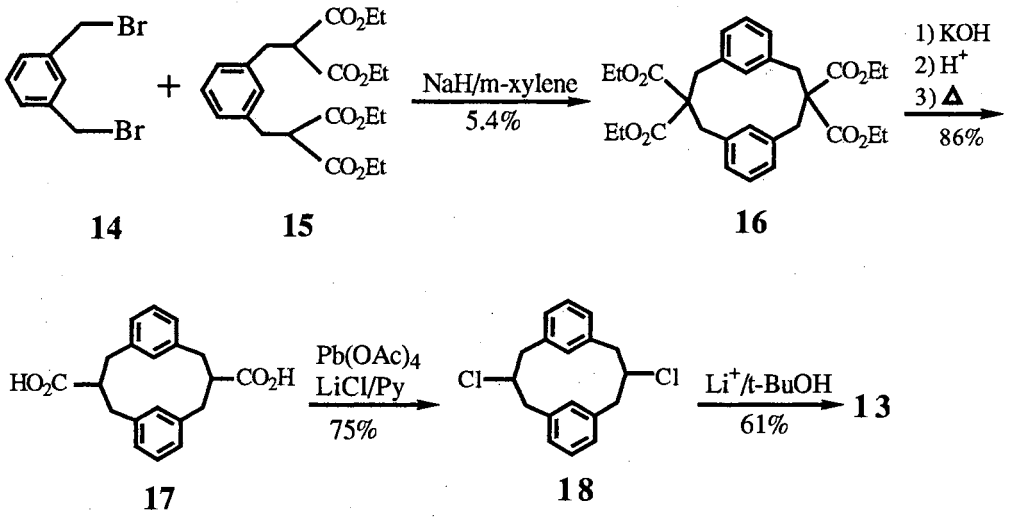
Figure 1-1. *Syn* and *anti* conformations of metacyclophanes



13

The first synthesis of the parent structure (**13**) employed the alkylation of malonic esters (Scheme 1-3). The dibromo compound (**14**) and the dimalonate (**15**) were used. Under the usual conditions, boiling xylene and excess NaH, the [3.3]metacyclophane tetraester (**16**) was isolated in only 5.4% yield.[70]

Scheme 1-3

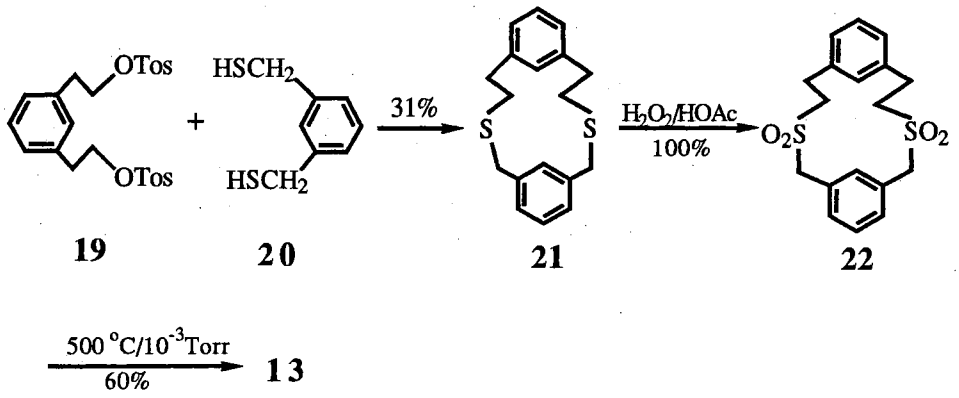


The introduction of methods for preparing dithiacyclophanes[71-83] and converting them *via* sulfur extrusion to cyclophanes[72,74,77,78-81,83] led to a new and general approach for preparing a variety of cyclophanes. In Scheme 1-4, [3.3]metacyclophane (**13**) was made in a good yield by the bisthioether route which involves the synthesis of the [4.4]dithiametacyclophane (**21**) and the corresponding bissulfone (**22**) followed by a thermal extrusion of sulfur dioxide in a double ring contraction.[84,85]

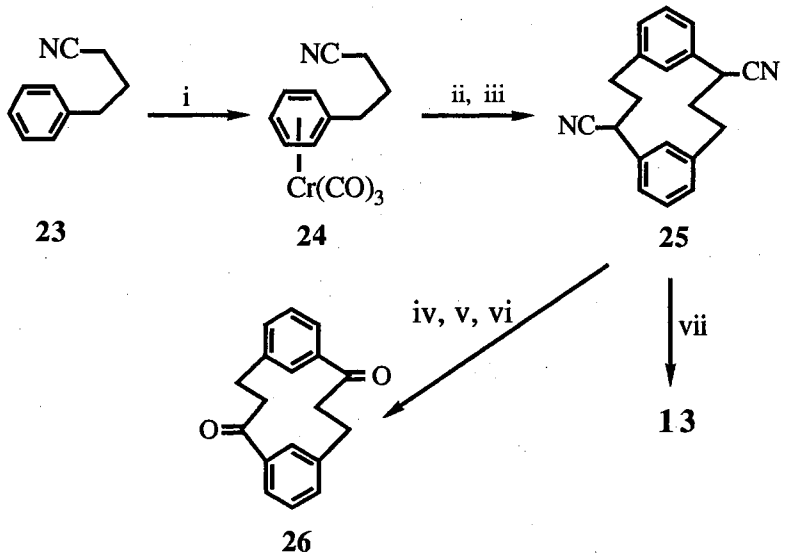
The coordination of 3-benzenepropionitrile with chromium hexacarbonyl followed by treatment of the resulting arene-chromium complex with lithium diisopropylamide and then iodine produced 1,10-dicyano[3.3]-metacyclophane (**25**) in 84% yield.[69] The process involves intermolecular nucleophilic addition to the coordinated arene, followed by cyclization of the dimer; iodine completes the addition/oxidation procedure for nucleophilic

aromatic substitution of hydrogen. Reductive cleavage of the cyano groups produces the parent hydrocarbon **13** as shown in Scheme 1-5.[69]

Scheme 1-4



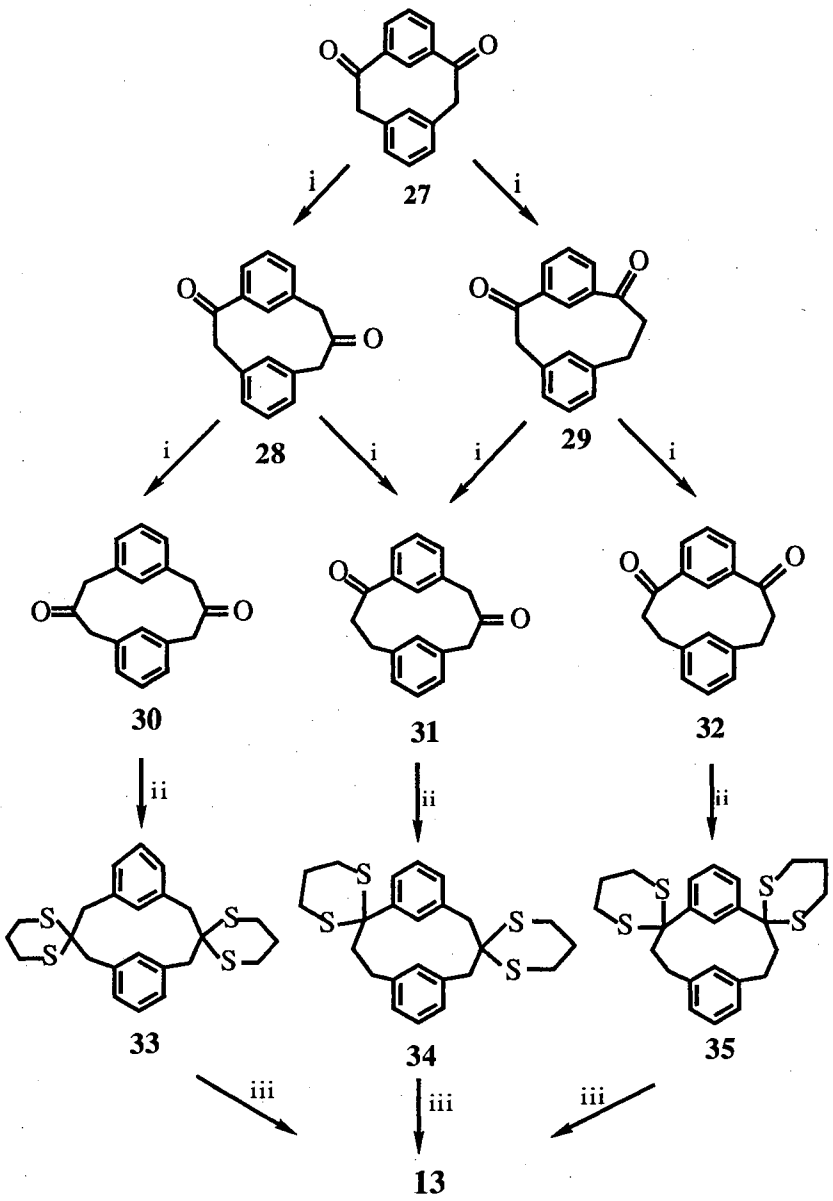
Scheme 1-5



i. $Cr(CO)_6$, ii. $LiN(i\text{-}Pr)_2$, iii. I_2, iv. $LiN(i\text{-}Pr)_2$,
v. O_2, vi. Na_2SO_3, vii. Na/NH_3.

An effective route (Scheme 1-6) to [3.3]metacyclophane (**13**) relies on double ring expansion by diazomethane to the readily available [2.2]metacyclophane-1,10-dione (**27**) and led to **13** in about 18% overall yield.[86]

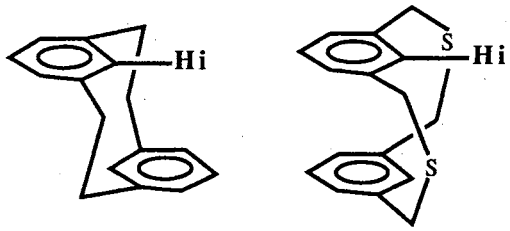
Scheme 1-6



i. CH_2N_2, ii. propane-1,3-dithiol, iii. Raney nickel.

The ring expansion process also made available the three isomeric dioxo[3.3]metacyclophanes (**30**, **31** and **32**) as a mixture from which pure isomers could be obtained by careful separation.[86]

In parent [2.2]metacyclophane (**36**), the *anti* geometry is observed exclusively. The upfield shift of the aromatic proton **Hi** in **36a** (δ 4.17) is a useful probe for the assignment of the *anti* geometry since **Hi** is constrained directly over the pi-electron cloud of aromatic ring.[69,87] *Syn* geometry as typified by 2,11-dithia[3.3]metacyclophane (**36b**) has **Hi** positioned downfield, in the usual range for arene hydrogens (e.g., δ 6.82 for **36b**).[69,88] The NMR chemical shift criterion is useful for assigning geometries to other [m.n]metacyclophanes, but ambiguities often arise when substituents other than H are present.[89,90]



36a **36b**

The *anti* arrangement for [m.n]metacyclophanes was generally thought to be the thermodynamically more stable conformation, partly because few *syn*-[m.n]metacyclophanes were reported in the early development of the area. Now numerous examples of *syn*- and *anti*-[m.n]metacyclophanes are known.[90] The preference for *syn* or *anti* geometry, although not completely understood, is strongly dependent on both the lengths of the connecting chains and on the substitution pattern of cyclophanes.[89,90]

Much interest has arisen in understanding the dynamic process of [m.n]metacyclophanes as observed by variable-temperature NMR spectroscopy.[90] Dynamic behavior has been interpreted in terms of *anti-anti, syn-syn*, or *syn-anti* interconversions as

shown in abbreviated form in Fig. 1-2.[90-106] There are conformational changes involving substituents and/or the alkyl bridging chains in [m.n]metacyclophanes, dithia[m.n]metacyclophanes, and dithia[m.n]metapyridinophanes.[88,90,107-112] An *anti*, longitudinal conformational isomerism has also been reported.[110]

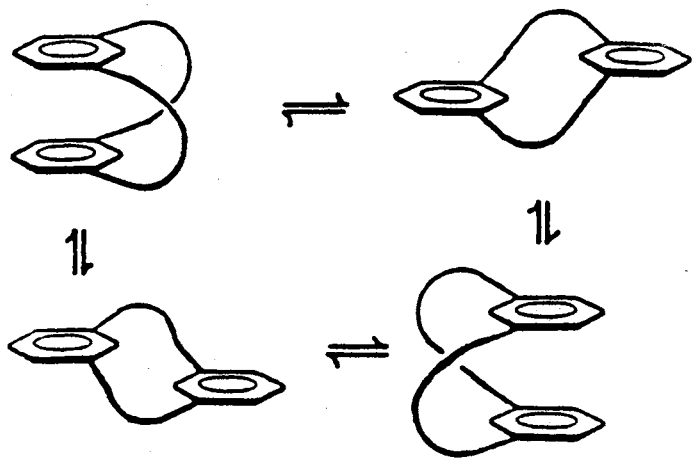


Figure 1-2. Conformational isomerism *via syn-anti* interconversion.

An x-ray crystal structure determination of the parent [3.3]metacyclophane has been reported.[69] The results show that the solid-state structure is roughly in the chair-chair conformation (Fig. 1-3), but there are some significant distortions from this idealized conformational description. The first distortion is that the rings are not parallel but are tilted at an angle of 24° to each other. The sense of the tilt brings atoms C9 and C18 closer to each other so that the mean distance from the best plane of the other ring is 2.9 Å and atoms C6 and C15 further away from each other (4.0 Å). If this were the only distortion, the hydrogen atoms on C9 and C18 would be approximately 2.4 Å apart. There is a second distortion, a twist of the aromatic rings by roughly 15° about an axis through the center of each ring. The effect of this twist is to move the hydrogens on C9 and C18 apart (2.7 Å). This twist also gives a chirality to the entire molecule, and since the space group

is chiral, all molecules in the crystal have the same sense of chirality. It is not clear whether this solid-state resolution occurs in microcrystalline domains or throughout the entire crystal. In general, bond distances and angles agree with accepted values. The mean carbon-carbon interatomic distance in the aromatic rings is 1.389 Å. The mean sp^2-sp^3 carbon-carbon distance is 1.519 Å, and the mean sp^3-sp^3 distance is 1.538 Å. The methylene groups attached to the aromatic rings are not in the plane of the ring but 0.15 Å out of the ring plane. All of the C-CH_2-C angles are significantly greater than 109°. The mean angle is 114.9°.

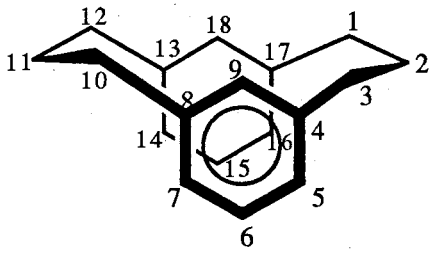


Figure 1-3. Chair conformation of [3.3]metacyclophane bridges.

^{17}O NMR of 1-Indanones

The use of ^{17}O NMR spectroscopy as a probe for a variety of structural questions is growing rapidly.[113,114] Despite poor receptivity, the ^{17}O nucleus has proved to be a convenient nucleus for study by NMR techniques due to the availability of water and dioxygen enriched in ^{17}O and the relatively small magnitude of ^{17}O quadrupole moment. The large chemical shift range for this nucleus makes it particularly attractive for examining the influences of subtle changes in molecular structure. The numerous recent publications in the field of oxyanion chemistry demonstrate the usefulness of ^{17}O as an analytical tool, and for metal carbonyls, ^{17}O NMR sometimes appears to be superior to ^{13}C NMR.[113] From previous remarks concerning chemical shifts and the relaxation of ^{17}O, it is clear that

^{17}O NMR will be a powerful tool in studies concerned with π-bond order, hydrogen bonding, labeling experiments, and the dynamic NMR of small molecules. Quite often oxygen atoms are located at the reactive sites of a molecule. Oxygen NMR is thus a convenient tool either for following the course of a reaction or for relating reactivity with spectroscopic properties.[113]

Recent studies have shown that quantitative relationships can be developed between downfield shifts of ^{17}O NMR data and torsion angles for aromatic nitro compounds,[115] acetophenones,[116] aromatic carboxylic acids and derivatives,[117] and aryl ketones.[118] Large downfield shifts for ^{17}O NMR data of carbonyl groups on introduction of alkyl groups promixate to the carbonyl function in a variety of systems have also been reported.[116-120] Correlations between ^{17}O NMR data and in-plane bond angle distortions for hindered 3-substituted phthalic anhydrides[119] and multisubstituted phthalimides[120] have been found. There are reports which have suggested that local van der Waals interactions are responsible for deshielding shifts for several nuclei in sterically hindered systems,[121,122] and that ^{17}O chemical shifts for certain rigid, planar amides, anhydrides, and quinones may be correlated with their repulsive van der Waals energies.[123]

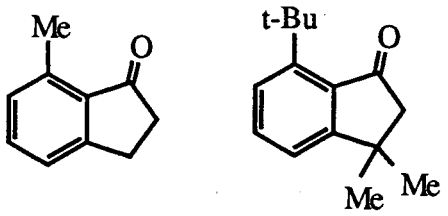
More recently, ^{17}O NMR data for alkyl-substituted 1-indanones were reported.[124] Large changes in chemical shift are observed for indanones depending upon the size and location of the substituent. An excellent additivity of substituent effects for ^{17}O chemical shifts of the substituted compounds was found. Furthermore, the largest downfield chemical shifts (21-36 ppm) arose from introduction of a substituent proximate to the carbonyl group (7-position) which were correlated with repulsive van der Waals energies. In multisubstituted indanones substituent effects are also additive, and the downfield shifts caused by alkyl groups proximate to the carbonyl are large enough to be used to distinguish between positional isomers. For example, the observed ^{17}O value for 4,5,7-

trimethyl-1-indanone is 512.6 ppm (calculated 513.4) whereas the calculated value for the alternative 4,6,7-isomer is 518.5 ppm.

Molecular mechanics calculations were carried out on 1-indanone (**3**), 7-methyl-1-indanone (**37**), and 7-*tert*-butyl-3,3-dimethyl-1-indanone (**38**). The carbonyl group and the aromatic ring were found to be coplanar for **3** and **37**; however, a small torsion angle rotation (7°) was predicted for **38**.[124] These calculations clearly indicate that torsion angle change is not a major contributor to the large downfield shifts observed for the hindered indanones. As was observed in other systems,[123] the C-C=O bond angle, estimated by the MM2 method, for the hindered compounds are flared away from the substituent within the plane of aromatic ring in the more hindered system; for example, compare 127° for 1-indanone (**3**), 128° for 7-methyl-1-indanone (**37**), and 130° for 7-*tert*-butyl-3,3-dimethyl-1-indanone (**38**). These results suggest that van der Waals interactions should play an important role in determining the chemical shifts for the hindered indanones.[124]

Figure 1-4 shows a plot of the data obtained from both the methyl- and *tert*-butyl-1-indanone pairs added to data for other carbonyl systems that were reported earlier.[124] This plot demonstrates that a reasonable relationship exists between repulsive van der Waals energies and ^{17}O chemical shifts and expands upon the wide variety of the structural types for which this relationship holds. These results also provide support for the conclusion that repulsive van der Waals interactions are important in determining downfield NMR chemical shifts of many nuclei in hindered systems.[121,122]

It has been clearly demonstrated that downfield chemical shift changes in the ^{17}O NMR data for hindered carbonyl systems can result from two distinctly different phenomena: torsion angle rotation and, when such rotation is not possible, from repulsive van der Waals interaction.[124] Methoxy substituted 1-indanones are rigid and nearly planar systems, which can be used to study the significance of repulsive van der Waals interactions on ^{17}O chemical shifts.



37 38

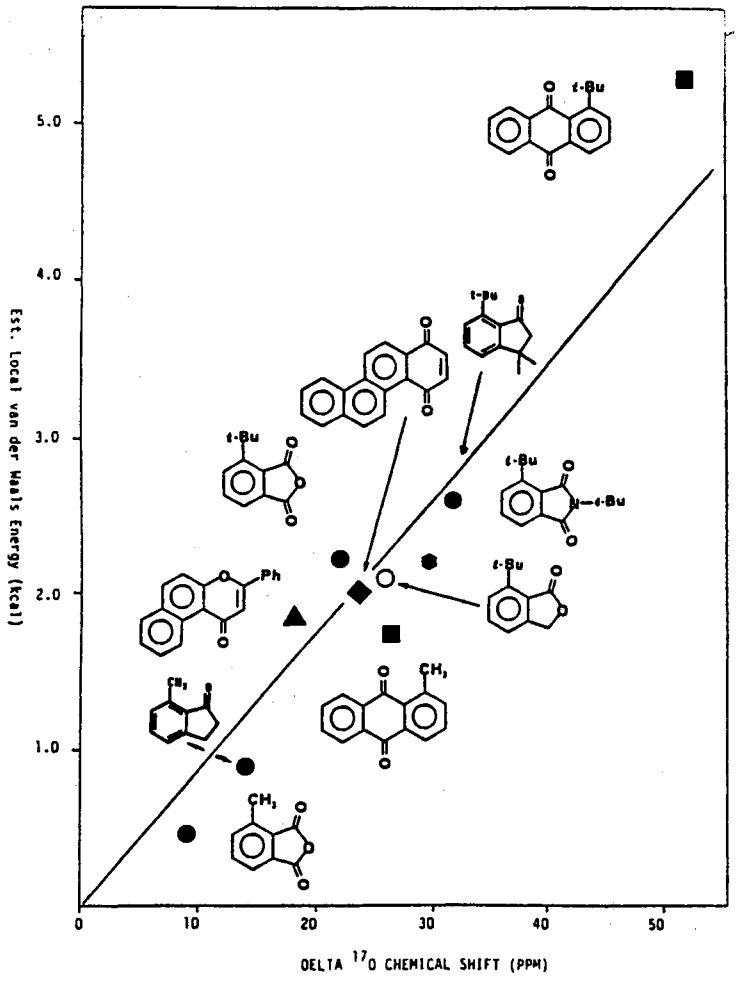


Figure 1-4. Relationship between estimated repulsive van der Waals interactions and ^{17}O chemical shift difference values.[124]

CHAPTER II

HISTORICAL BACKGROUND AND IDENTIFICATION OF NEW COMPOUNDS

Polyphosphoric acid (PPA) is currently the most widely used reagent for acid-catalyzed cyclization of 3-arylpropanoic acids to the corresponding 1-indanones.[1,2] This reaction has been successfully applied to prepare a broad series of alkyl-substituted 1-indanones.[124] Recently, a broad selection of 1-indanones with mixed substitution of alkyl and methoxy group was needed for an ^{17}O NMR study and PPA[20] was successfully used to cyclize 15 substituted 3-arylpropanoic acids to the corresponding 1-indanones. But attempts to cyclize 3-(2-methoxybenzene)propanoic acid (**39a**) and 3-(2,4-dimethoxy-benzene)propanoic acid (**39b**), with this reagent, gave only a 2.0% yield of the expected 4-methoxy-1-indanone (**41a**) and none of 4,6-dimethoxy-1-indanone (**41b**). Instead, colorless products with high melting points, insoluble in ether but sparingly soluble in dichloromethane, were isolated in about 95% (weight) crude yields. This unusual behavior initially prompted attempts to obtain even low yields of **41a** and **41b** but also to identify the unknown materials and learn about their formation.

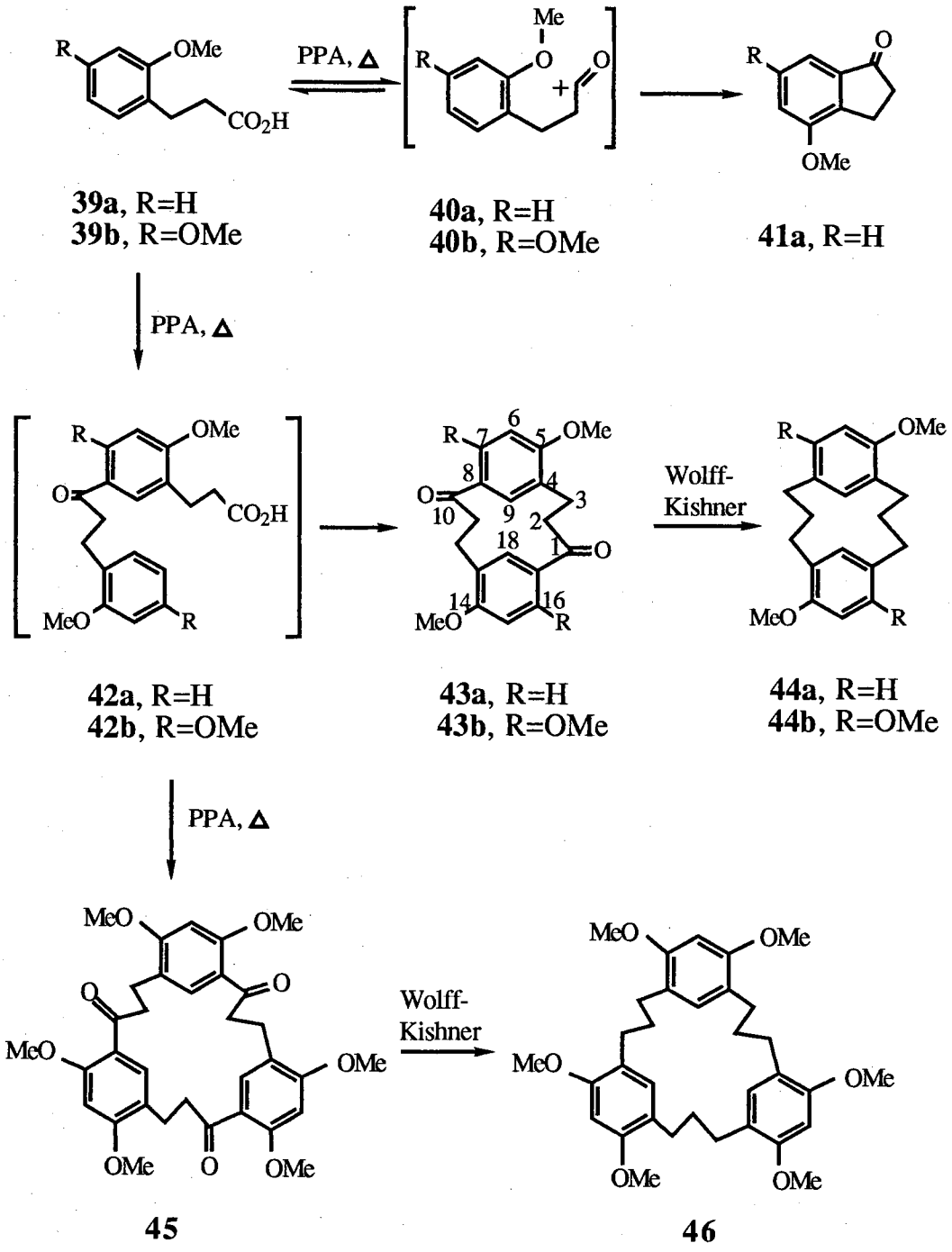
A literature search of the cyclization of the three isomeric, monomethoxy, 3-benzenepropanoic acids showed considerable variation in response to treatment with PPA. While 3-(3-methoxybenzene)propanoic acid was readily cyclized to a mixture of 5- and 7-methoxy-1-indanone in 85% yield,[34] 3-(2-methoxybenzene)propanoic acid (**39a**) and 3-(4-methoxybenzene)propanoic acid (**39c**) showed a drastically different behavior. The former failed to give 4-methoxy-1-indanone (**41a**)[125] and the latter gave low yields

(4.5%,[126] 11%[127] and 43%[2]) of 6-methoxy-1-indanone (**41c**). In comparison, cyclization in HF in a sealed container gave a 36% yield of **41c**.[128] To account for the failure to form **41a** from **39a** in PPA, it has been suggested[125] that the acylium ion, **40a** in Scheme 2-1, interacts with the *ortho* methoxy group rendering the aromatic ring more electropositive and thus resistant to cyclization. But no mention of unusual products such as shown in Scheme 2-1 has been reported for **39a** and **39b**. A subsequent literature search showed that 5-(2-methoxybenzene)pentanoic acid has been converted in 30% yield to the homologous 7,18-dimethoxy[5.5]metacyclophane-1,12-dione in PPA.[129]

The above information prompted a high-dilution run (500 g PPA, 2.0 g **39a** in a Waring Blendor[130]) in an attempt to prepare some 4-methoxy-1-indanone (**41a**). The latter, identical with **41a** prepared by independent synthesis,[131,132] was isolated in 2.0% yield by steam distillation. The remaining material (95% weight) was an ether-insoluble, white solid with high melting point. Similar dilution studies failed to give 4,6-dimethoxy-1-indanone (**41b**) from **39b**. Addition of chlorobenzene as a solvent/diluent did not improve the yield of **41a** significantly and did not increase the formation of **41b**.

Sublimation (235 °C/0.1mm and 280 °C/0.1mm) of the ether-insoluble products from **39a** and **39b** gave 46% and 49% yields, respectively, of 5,14-dimethoxy[3.3]-metacyclophane-1,10-dione (**43a**, EIMS 324, mp 234-235 °C) and 5,7,14,16-tetra-methoxy[3.3]metacyclophane-1,10-dione (**43b**, EIMS 384, mp 279-280 °C). The ^{1}H NMR spectra showed the expected ratios of ArH:CH_2:OCH_3 as 3:4:3 for 5,14-dimethoxy-[3.3]metacyclophane-1,10-dione (**43a**, Fig. 2-1) and 1:2:3 for 5,7,14,16-tetramethoxy-[.3.3]metacyclophane-1,10-dione (**43b**, Fig. 2-3). The ^{13}C NMR spectra showed single carbonyl signals for both compounds and one methoxy signal (55.60 ppm) for **43a** (Fig. 2-2) but two methoxy signals (55.46 and 55.79 ppm) for **43b** (Fig. 2-4). These data suggested both products were highly symmetrical ketones and led to the conclusion that the two diones **43a** and **43b** had formed.

Scheme 2-1


R
OMe
CO2H
PPA, Δ
Me
O
+
39a, R=H
39b, R=OMe
40a, R=H
40b, R=OMe
41a, R=H
PPA, Δ
MeO
42a, R=H
42b, R=OMe
43a, R=H
43b, R=OMe
Wolff-
Kishner
44a, R=H
44b, R=OMe
PPA, Δ
45
46

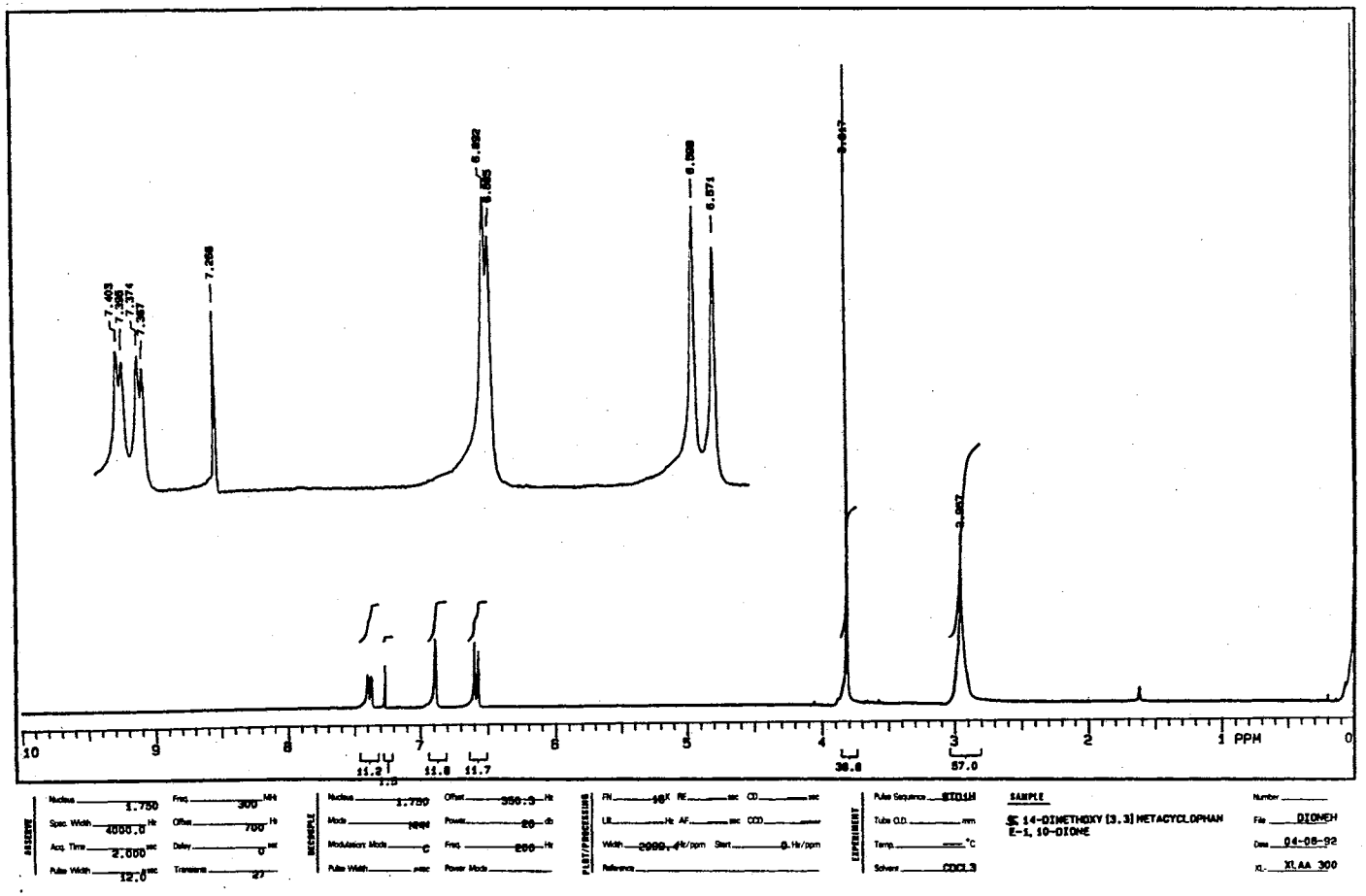


Figure 2-1. ^{1}H NMR spectrum of 5,14-dimethoxy[3.3]metacyclophane-1,10-dione (**43a**).

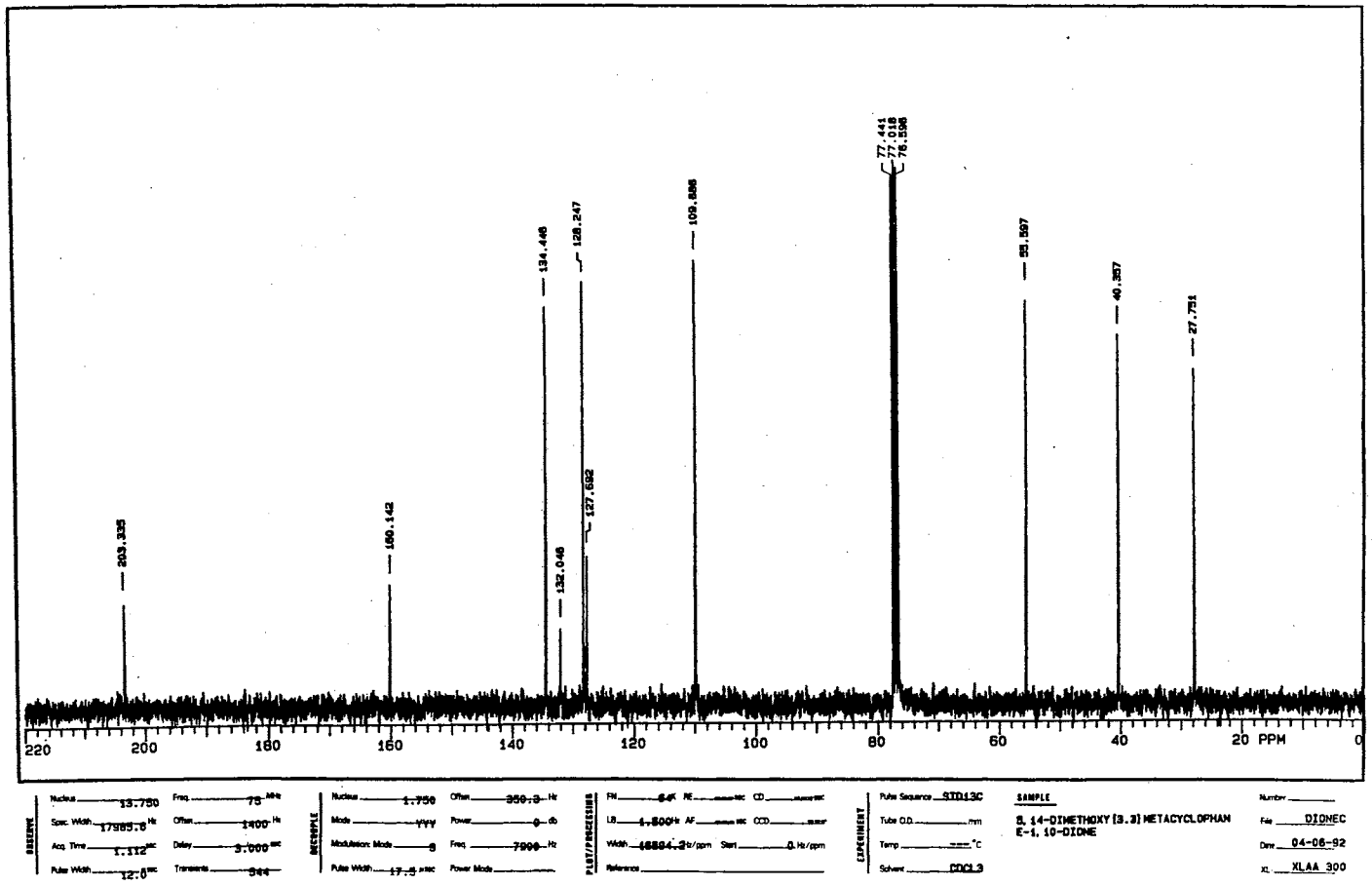


Figure 2-2. ^{13}C NMR spectrum of 5,14-dimethoxy[3.3]metacyclophane-1,10-dione (**43a**).

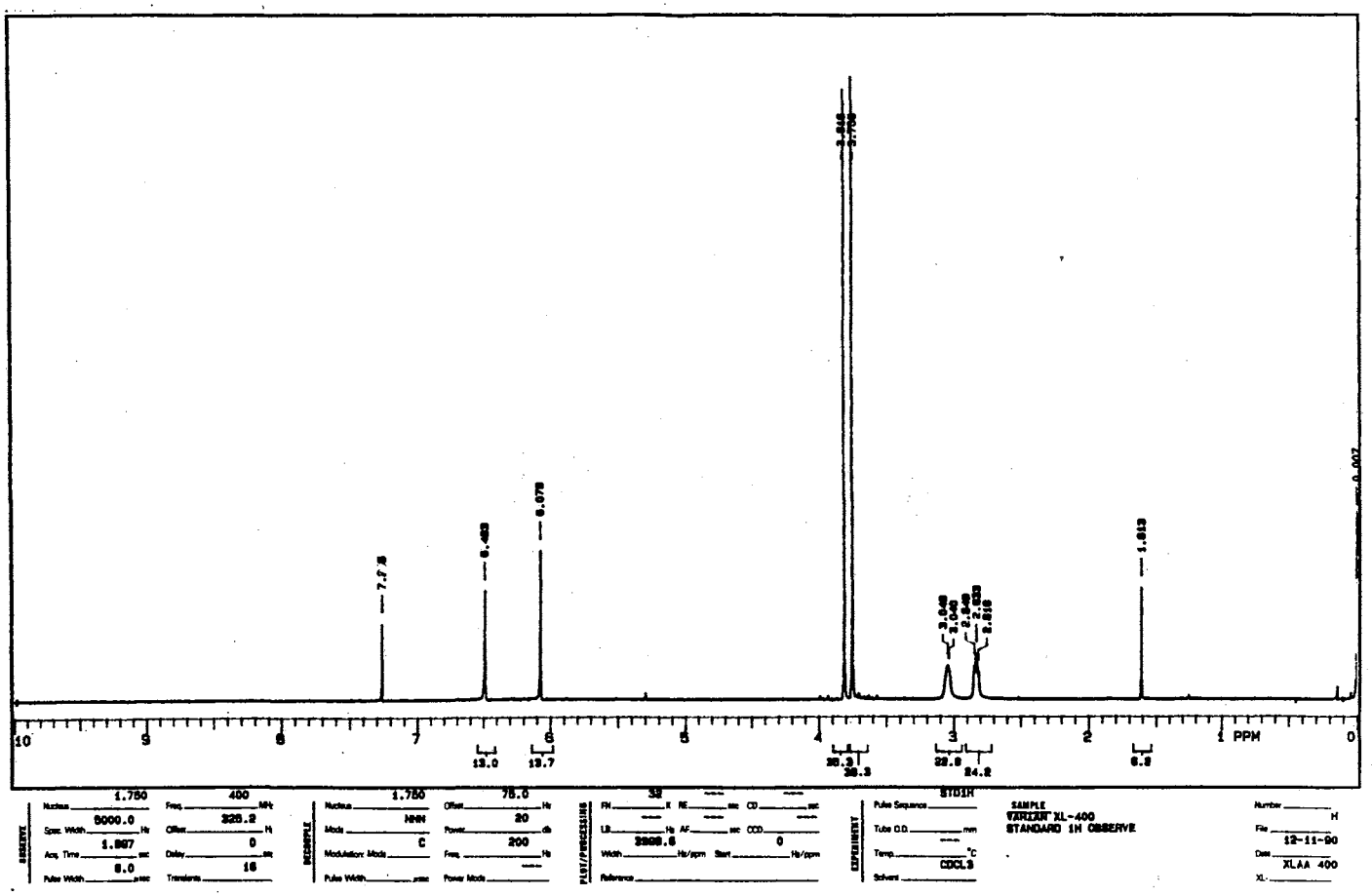


Figure 2-3. ^{1}H NMR spectrum of 5,7,14,16-tetramethoxy[3.3]metacyclophane-1,10-dione (**43b**).

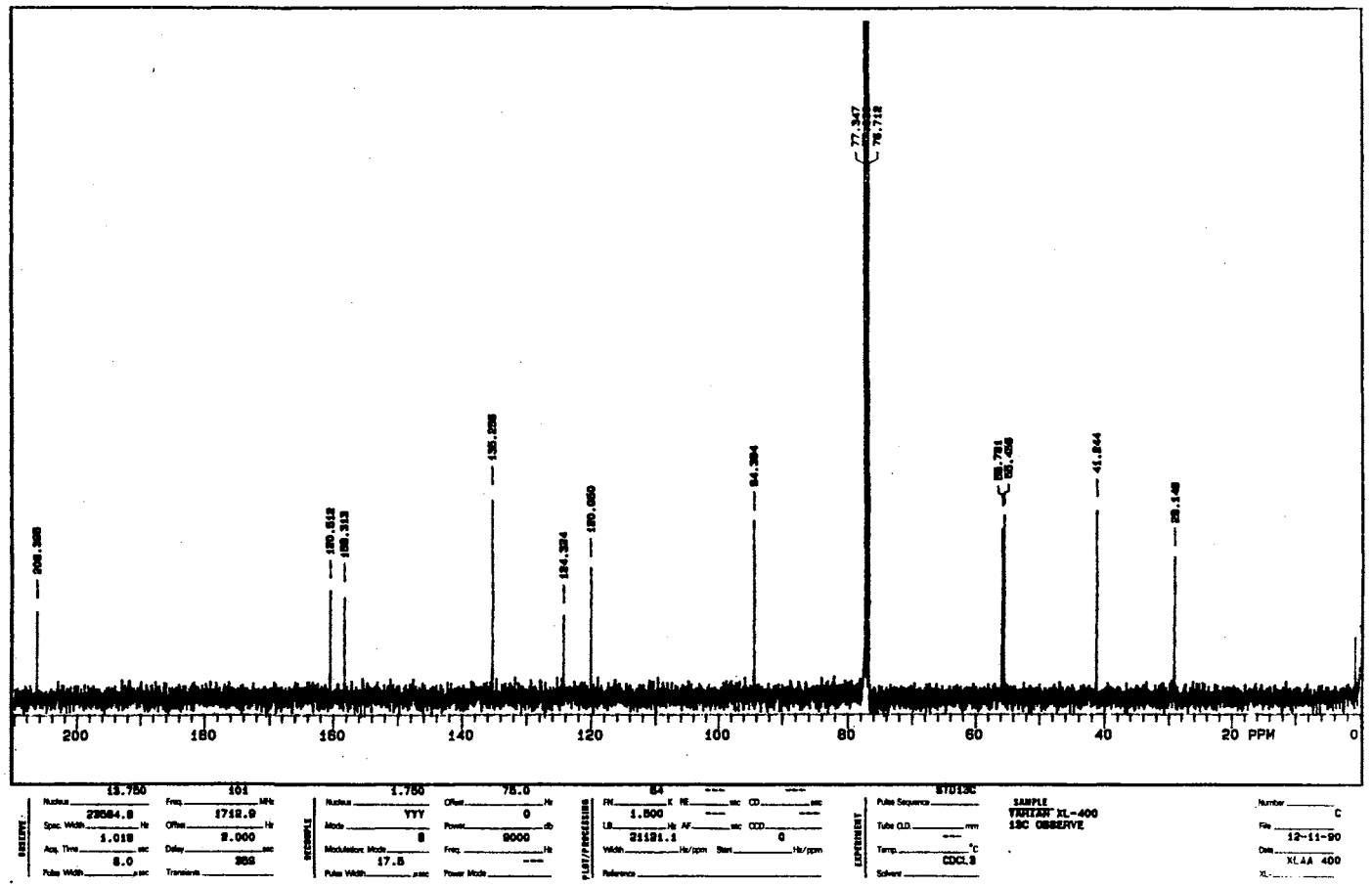


Figure 2-4. ^{13}C NMR spectrum of 5,7,14,16-tetramethoxy[3.3]metacyclophane-1,10-dione (**43b**).

Wolff-Kishner reduction[133] of diones **43a** and **43b**, including remethylation[134] to compensate for methoxy-group cleavage, gave 5,14-dimethoxy[3.3]metacyclophane (**44a**) and 5,7,14,16-tetramethoxy[3.3]metacyclophane (**44b**) in 70% and 80% yields, respectively. The combined data, including EIMS, ^{1}H NMR and ^{13}C NMR, and CH analyses, obtained from **44a** and **44b** are consistent with the proposed structures and the symmetry suggested by NMR spectral data. Considering **44b** as an example, the ^{1}H NMR spectrum shows the ratio of ArH:CH_2:OCH_3 as 1:3:3 and the ^{13}C NMR spectrum gives two signals for the methylene carbons, one signal for methoxy carbon and four signals for aromatic carbons.

Rigorous proof for the correctness of structures **43a**, **43b**, **44a**, and **44b** came from single crystal x-ray crystallographic studies of **43a** (Fig. 2-5) and **44b** (Fig. 2-6). In the solid state, **43a** exists with a crystallographic center of symmetry within the molecule. The aromatic rings are in *anti* conformation and on parallel planes. The methoxy group is nearly coplanar with the aromatic ring (O2 0.034 Å; C21 0.029 Å from the plane). Unfortunately the x-ray structure of 5,7,14,16-tetramethoxy[3.3]metacyclo-phane-1,10-dione (**43b**) could not be solved, so the carbonyl oxygens of **43b** were removed and the x-ray structure of resulting product, 5,7,14,16-tetramethoxy[3.3]metacyclophane (**44b**), was obtained. Metacyclophane **44b** crystallizes with two molecules (a and b) per asymmetric unit which show comparable bond angles and distances. Both show *syn* conformation of aromatic rings, the planes of which subtend angles of 23.79 and 23.95° for molecules a and b respectively. Both show three carbon bridging chains in 'chair' conformation. Each molecule shows the methoxy carbon atoms of one ring to be significantly distorted from the plane of the aromatic ring and oxygen atoms [Molecule a: C13a-C18a (C21a, C22a; 0.339, 0.481 Å from plane, whereas C4a-C9a (C19a, C20a; 0.117, 0.054 Å from the plane); Molecule b: C13b-C18b (C21b, C22b; 0.513, 0.657 Å from the plane, whereas C4b-C9b (C19b, C20b; 0.037, 0.013 Å from the plane].

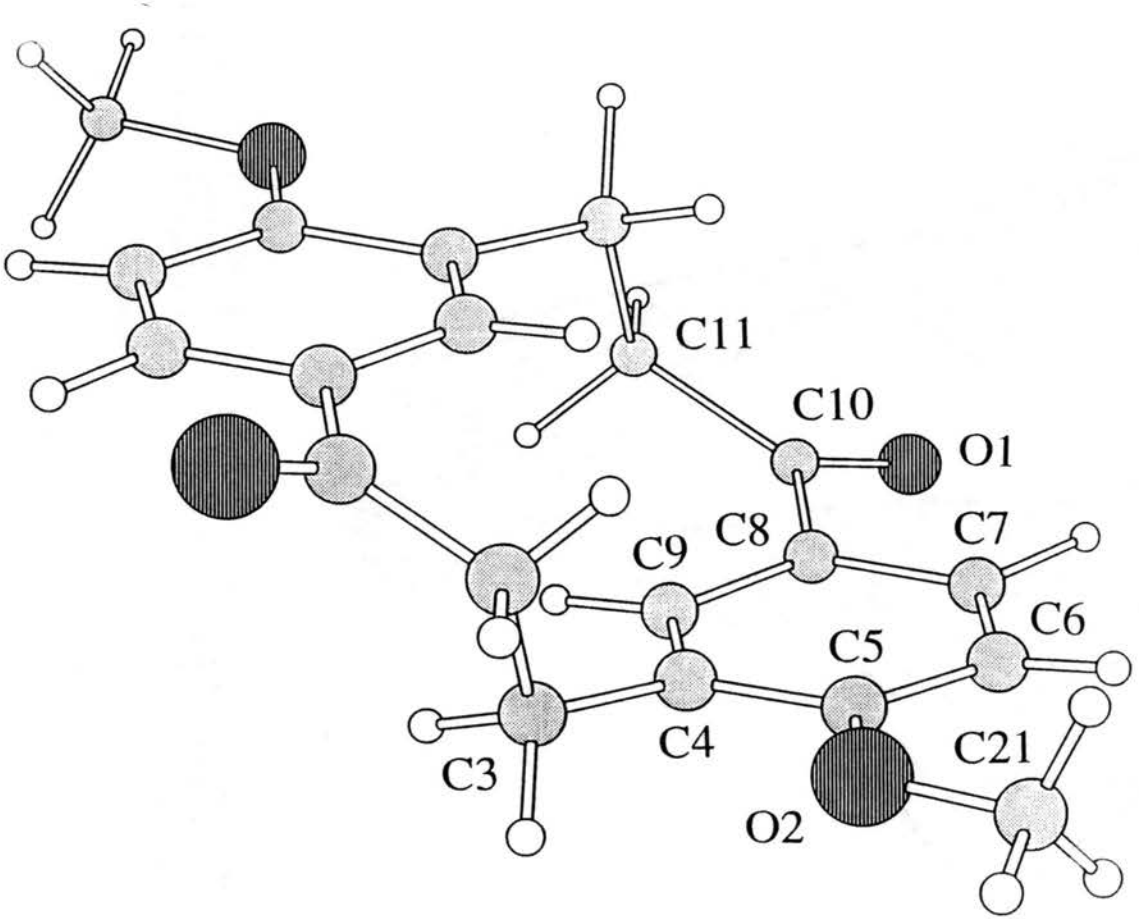


Figure 2-5. Projection view of 5,14-dimethoxy[3.3]metacyclophane-1,10-dione (**43a**).

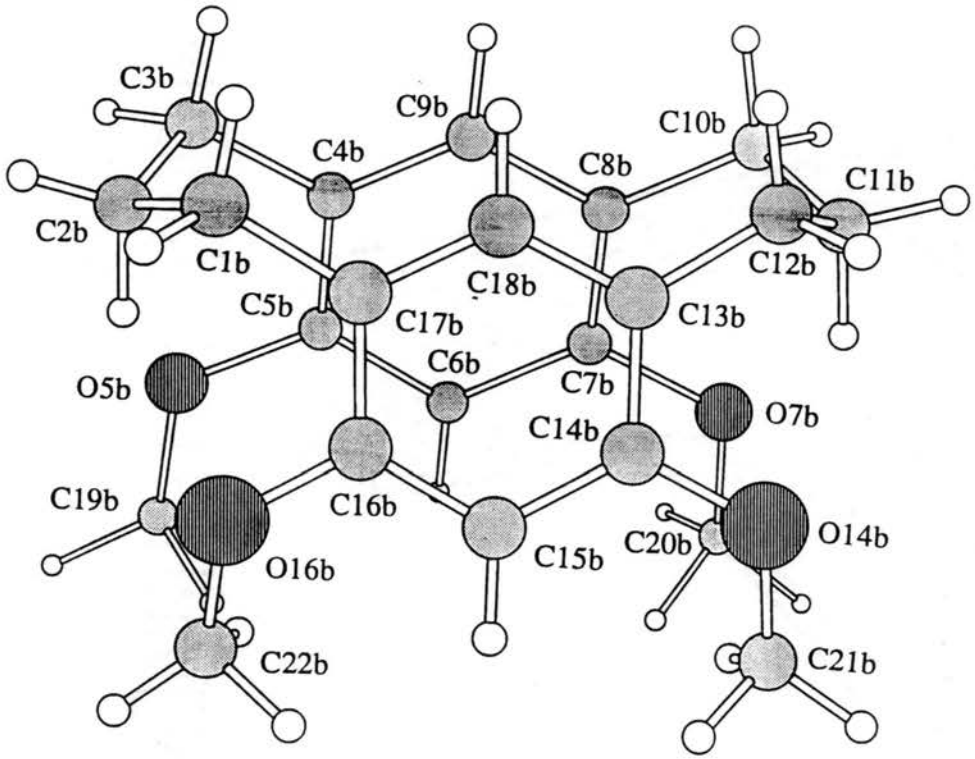
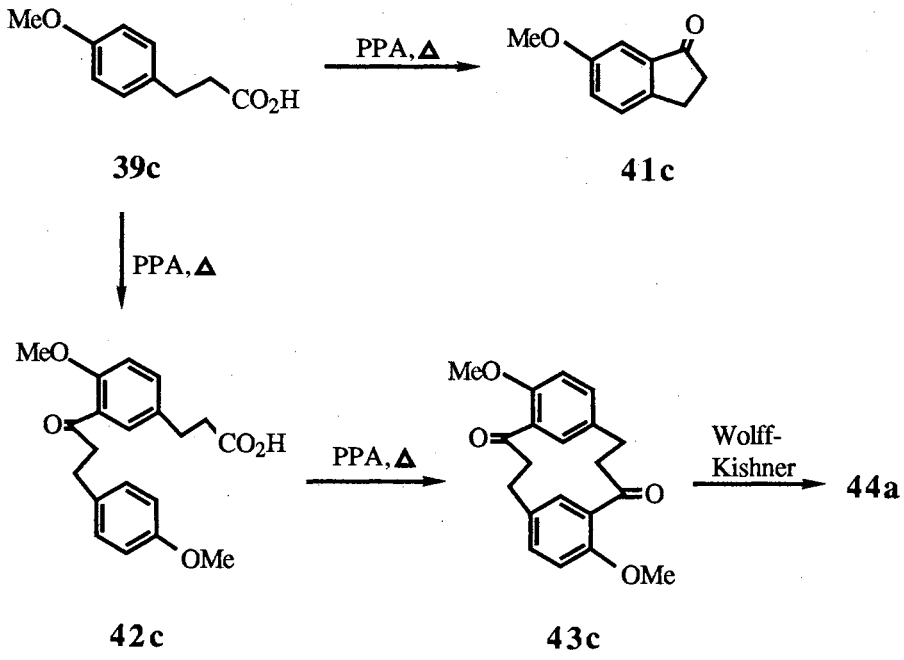


Figure 2-6. Projection view of 5,7,14,16-tetramethoxy-[3.3]metacyclophane (**44b**), molecule b.

When it became evident that methoxy-substituted [3.3]metacyclophane-1,10-diones (**43a** and **43b**) were being formed, the *para* isomer, 3-(4-methoxybenzene)propanoic (**39c**), was included in the study as shown in Scheme 2-2 to compare the influence of the position of the methoxy group on the formation of the metacyclophanedione and to explore the utility of this one-step procedure for the synthesis of substituted [3.3]metacyclophanes.

Scheme 2-2



The treatment of 3-(4-methoxybenzene)propanoic acid (**39c**) with PPA gave a mixture of 6-methoxy-1-indanone (**41c**), *p*-methoxy-3-(*p*-methoxyhydrocinnamoyl)hydrocinnamic acid (**42c**), and 7,16-dimethoxy[3.3]metacyclophane-1,10-dione (**43c**). The yields (17, 26, 40, and 65%) of steam-distilled **41c** increased when the ratio of PPA (500 g) to **39c** (17, 36, 81, and 278 g) was increased. The yields of the other reaction products (**42c** and **43c**), which were extracted into dichloromethane and then purified by sublimation, were unchanged. The reaction mixture is heterogeneous, at least during the

mixing stage, so that there is little control over concentration. However, the yield from this series of reactions demonstrates that some control exists over intra- and intermolecular reaction. The reactivity of the aromatic ring, as influenced by the position and number of methoxy groups, is probably more important in determining the ratio of 1-indanone to metacyclophanedione since the yields of 1-indanones from 3-(2-methoxybenzene)-propanoic acid (**39a**) and 3-(2,4-dimethoxybenzene)propanoic acid (**39b**) were not significantly influenced by changing the concentration of starting material in PPA. The structures of *p*-methoxy-3-(*p*-methoxyhydrocinnamoyl)hydrocinnamic acid (**42c**) and 7,16-dimethoxy[3.3]metacyclo-phane-1,10-dione (**43c**) are consistent with spectral data (MS, ^{1}H NMR, ^{13}C NMR) and CH analysis. The ^{1}H NMR and ^{13}C NMR spectra of **43c** are shown in Figures 2-7 and 2-8.

The intermediate keto acids **42a**, **42b**, and **42c** are direct precursors of cyclic diones **43a**, **43b**, and **43c**. Keto acids **42a** and **42b** appear to be too reactive to survive since they were not found. However, *p*-methoxy-3-(*p*-methoxyhydrocinnamoyl)hydro-cinnamic acid (**42c**), shown in Scheme 2-2, was isolated in 14% yield, purified by sublimation and recrystallization, and characterized. The cyclization of keto acid **42c** at 80 ^{o}C for 30 min in PPA gave a mixture of 7,16-dimethoxy[3.3]metacyclophane-1,10-dione (**43c**, 30%) and recovered starting keto acid **42c** (35%). A second cyclization of keto acid **42c** for 1 hr at 80 ^{o}C gave 28% recovery of **42c** and 44% yield of dione **43c**. The neutral residue, after removal of dione (**43c**) by sublimation, was shown to contain a cyclic tetraone $C_{44}H_{48}O_{12}$ (EIMS 648; +LSIMS 649). Wolff-Kishner reduction[133] of 7,16-dimethoxy-[3.3]metacyclophane-1,10-dione (**43c**), including remethylation,[134] gave 5,14-dime-thoxy[3.3]metacyclophane (**44a**) in 67% yield.

Evidence for higher cyclic polyones was found. A mass spectrum (mol wt 810, m/z 811 using +LSIMS) of the sublimation residue from 5,14-dimethoxy[3.3]meta-cyclophane-1,10-dione (**43a**) showed the presence of a cyclic pentamer. This cyclic

pentamer also has a highly symmetrical structure showing single peaks in the methoxy and carbonyl regions of the ^{13}C NMR spectrum. In a like manner, 5,7,14,16,23,25-hexamethoxy[3.3.3]metacyclophane-1,10,18-trione (**45**) was isolated in about 10% yield as a residue from the sublimation of **43b** and it was identified through its MS spectrum (mol wt 576, m/z 577 using +LSIMS) and a ^{13}C NMR spectrum which showed a single carbonyl and two methoxy groups. The trione **45** was reduced by Wolff-Kishner reduction,[133] including remethylation[134] to 5,7,14,16,23,25-hexamethoxy[3.3.3]metacyclophane (**46**) as shown in Scheme 2-1. The ^{13}C NMR spectrum of **46** showed a single methoxy signal and the mass spectrum showed the expected mol wt (534 EIMS).

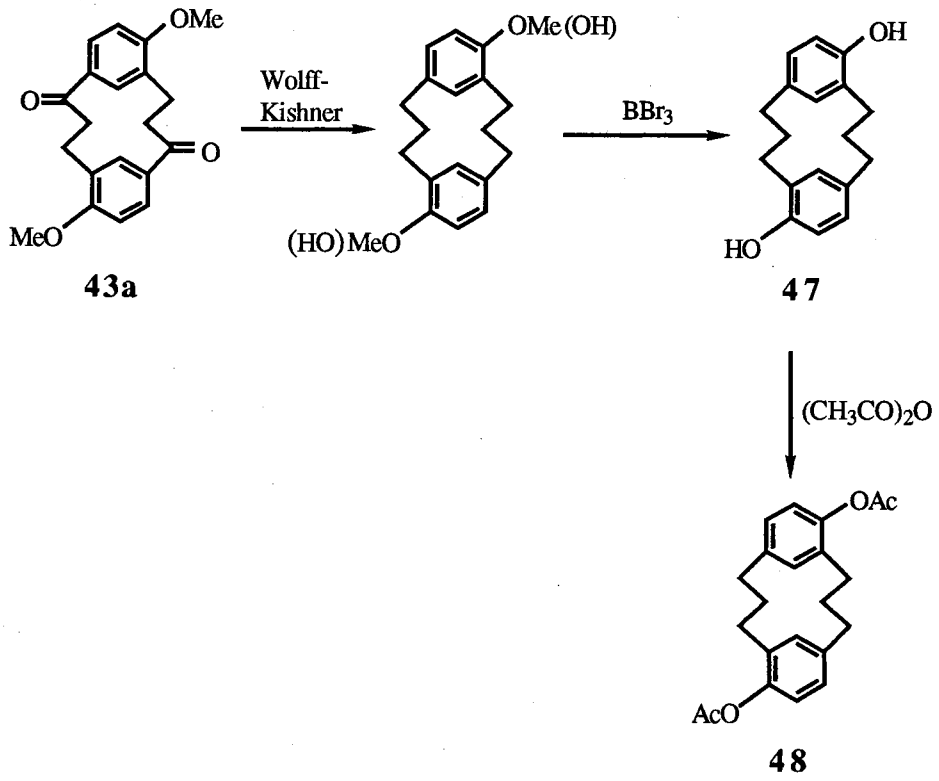
The stability of 5,14-dimethoxy[3.3]metacyclophane-1,10-dione (**43a**) was tested by heating a pure sample (0.93 g) in PPA (500 g) at near 80 ^{o}C for 30 min. A pink tint developed during the reaction. There was no significant change at this stage since recovered dione **43a** was not altered as shown by comparison of mp and the mp of an admixture as well as ^{1}H NMR and ^{13}C NMR spectra. The sample of recovered dione **43a** sublimed readily and gave only 30 mg of residue. No bicarbonate soluble products were found.

Derivatives of [3.3]metacyclophane have been prepared as shown in Scheme 2-3. 5,14-dimethoxy[3.3]metacyclophane-1,10-dione (**43a**, 5.0 g) was reduced by Wolff-Kishner reduction[133] and the mixture of 5,14-dimethoxy[3.3]metacyclophane (**44a**) and 5,14-dihydroxy[3.3]metacyclophane (**47**) was demethylated with boron-tribromide. The demethylated product was extracted with dichloromethane and purified by sublimation at 150 ^{o}C/0.1mm. A white crystalline product was obtained in 82% overall yield (EIMS 268, mp 183-185 ^{o}C). All the data obtained, including EIMS and ^{1}H NMR and ^{13}C NMR data are consistent with the structure of 5,14-dihydroxy[3.3]metacyclophane (**47**).

5,14-Diacetoxy[3.3]metacyclophane (**48**) also was prepared in 96% yield by heating 5,14-dihydroxy[3.3]metacyclophane (**47**) in acetic anhydride for three hours. The

diester **48** was extracted with ether and the excess acetic anhydride was washed away with saturated sodium bicarbonate solution and water. All the data obtained from **48**, including EIMS, ^{1}H and ^{13}C NMR, also are consistent with the proposed structure.

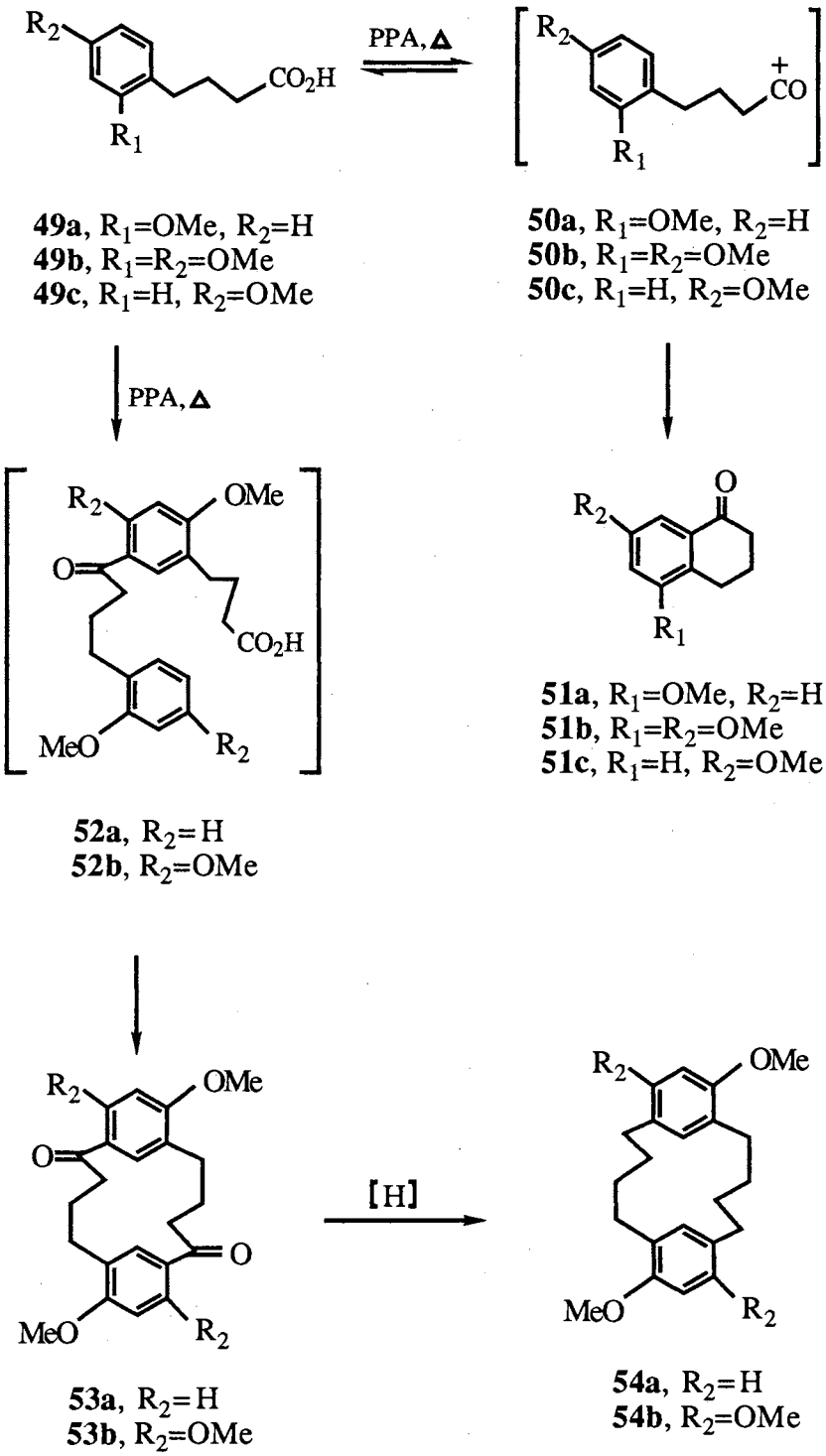
Scheme 2-3



43a **47** **48**

Similar reactions were carried out as shown in Scheme 2-4 on 4-(2-methoxybenzene)butanoic acid (**49a**), 4-(2,4-dimethoxybenzene)butanoic acid (**49b**), and 4-(4-methoxybenzene)butanoic acid (**49c**) in order to explore the influence of methoxy group and carbon number of side chain on the formation of metacyclophanediones and the possibility of preparing methoxy-substituted [4.4]metacyclophanediones by this one-step method.

Scheme 2-4



49a, R_1=OMe, R_2=H
49b, R_1=R_2=OMe
49c, R_1=H, R_2=OMe

50a, R_1=OMe, R_2=H
50b, R_1=R_2=OMe
50c, R_1=H, R_2=OMe

51a, R_1=OMe, R_2=H
51b, R_1=R_2=OMe
51c, R_1=H, R_2=OMe

52a, R_2=H
52b, R_2=OMe

53a, R_2=H
53b, R_2=OMe

54a, R_2=H
54b, R_2=OMe

4-(2-Methoxybenzene)butanoic acid (**49a**) and 4-(2,4-dimethoxybenzene)butanoic acid (**49b**), needed for Scheme 2-4, were prepared as the follows: 4-(2-hydroxybenzene)butanoic acid was prepared in 84% yield by the oxidation of 1-tetralone with Oxone in 50% acetic acid at room temperature for 18 hours. After methylation[134] with dimethylsulfate and hydrolysis (NaOH/95%EtOH/H_2O), 4-(2-methoxybenzene)butanoic acid (**49a**)[135] was obtained as a brown crystalline product which was purified by sublimation at 74 °C/0.1mm to a colorless product. 3-(2,4-Dimethoxybenzoyl)propanoic acid was prepared in 50% yield from 1,3-dimethoxybenzene and succinic anhydride by Friedel-Crafts reaction and then purified by recrystalization from water.[135] Reduction of this keto acid by hydrogenation (HOAc, 10% Pd/C, 55psi, 55 °C) gave 4-(2,4-dimethoxybenzene)butanoic acid (**49b**)[136] in 99% yield. 4-(4-Methoxybenzene)butanoic acid (**49c**) was purchased.

The products and yields from the cyclization of three 4-arylbutanoic acids **49a**, **49b**, and **49c** in PPA (Scheme 2-4) differ as shown in Table 2-1. 4-(4-Methoxybenzene)butanoic acid (**49c**) cyclizes to 7-methoxy-1-tetralone (**51c**) in 99% yield (**49c**:PPA = 2.0:500) and 78% yield (**49c**:PPA = 7.5:500). No dione was observed in these cyclization reactions. The cyclization of 4-(2-methoxybenzene)butanoic acid (**49a**) and 4-(2,4-dimethoxybenzene)butanoic acid (**49b**) in PPA, however, gave both 1-tetralones [5-methoxy-1-tetralone (**51a**) and 5,7-dimethoxy-1-tetralone (**51b**)] and [4.4]metacyclophanediones [6,16-dimethoxy[4.4]metacyclophane-1,11-dione (**53a**) and 6,8,16,18-tetramethoxy[4.4]metacyclophane-1,11-dione (**53b**)]. The yields of 1-tetralones (**51a, 51b**) and [4.4]metacyclophane-1,11-diones (**53a, 53b**) depend on the ratio of arylbutanoic acids (**49a, 49b**) to PPA (Table 2-1). When the ratio of 4-arylbutanoic acids **49a, 49b** to PPA increases, the yields of methoxy-substituted 1-tetralones (**51a** and **51b**) decrease and as expected, the possibility for intramolecular cyclization increases when the reaction system is diluted. The yields of **53b** decrease because of the formation of polymers.

Table 2-1. Yields of 1-Tetralones (51a, 51b, and 51c) and Diones (53a, 53b) from Varying Amounts of Arylbutanoic Acids (49a, 49b, and 49c) in 500 g PPA

Arylbutanoic acids (g)	1-Tetralones (%)	Diones (%)
49a	**51a**	**53a**
2.0	28	30
5.0	9	30
7.5	4	30
49b	**51b**	**53b**
2.0	14	54
5.0	9	42
7.5	5	11
49c	**51c**	
2.0	99	
7.5	78	

5-Methoxy-1-tetralone (**51a**) was isolated and purified by sublimation (84 ^{o}C/0.1mm) and 5,7-dimethoxy-1-tetralone (**51b**) was isolated by ether extraction and then purified by extraction through neutral alumina with light petroleum ether. Their structures were determined by EIMS, ^{1}H NMR, and ^{13}C NMR. The ether-insoluble products from 4-(2-methoxybenzene)butanoic acid (**49a**) and 4-(2,4-dimethoxybenzene)butanoic acid (**49b**) were sublimed at 220 ^{o}C/0.1mm, and 255 ^{o}C/0.1mm to give 6,16-dimethoxy[4.4]-

metacyclophane-1,11-dione (**53a**, EIMS 352, mp 255-256 °C) and 6,8,16,18-tetramethoxy[4.4]metacyclophane-1,11-dione (**53b**, EIMS 412, mp 306-308 °C), respectively. The ^{1}H NMR spectra show the ratios of ArH:CH_2:OCH_3 as 1:2:1 for **53a** (Fig.2-9) and 1:3:3 for **53b** (Fig. 2-11) as expected. The ^{13}C NMR spectra showed one carbonyl signal and one methoxy signal for **53a** (Fig. 2-10). All these data are consistent with the proposed structure and the symmetry suggested by NMR spectra.

The reduction of 6,16-dimethoxy[4.4]metacyclophane-1,11-dione (**53a**) and 6,8,16,18-tetramethoxy[4.4]metacyclophane-1,11-dione (**53b**) was carried out smoothly by catalytic hydrogenation (AcOH, 10% Pd/C, 55 psi, 55 °C) to give 6,16-dimethoxy[4.4]metacyclophanes (**54a**) and 6,8,16,18-tetramethoxy[4.4]metacyclophane (**54b**) in 88% and 90% yields, respectively. The combined data obtained from **54a** and **54b**, including EIMS, ^{1}H NMR and ^{13}C NMR also are consistent with the proposed structures and the symmetry suggested by NMR spectra.

Evidence for the formation of other higher cyclic polyones was found. A mass spectrum (mol wt 618, m/z 619 using +LSIMS) of the sublimation residue from 6,8,16,18-tetramethoxy[4.4]metacyclophane-1,11-dione (**53b**) showed the presence of a cyclic trione. This cyclic trione also has a highly symmetrical structure showing two peaks in methoxy region and single peak in carbonyl region of the ^{13}C NMR spectrum. Two cyclic polyones were observed from the mass spectrum of sublimation residue of 6,16-dimethoxy[4.4]metacyclophane-1,11-dione (**53a**), a cyclic trione (mol wt 528, m/z 529 using +LSIMS) and a cyclic tetraone (mol wt 704, m/z 705 using +LSIMS) The seperation, purification, and identification of these cyclic polyones remain.

It has been found that 2-methoxy-5-(*o*-methoxybenzeneacetyl)benzeneacetic acid (**57**) is the major product when 2-methoxybenzeneacetic acid (**55**) was treated with PPA (Scheme 2-5). The yield of keto acid **57** depends on the reaction temperature and the ratio of **55** to PPA as shown in Table 2-2. A low ratio of 2-methoxybenzeneacetic acid to PPA

(2.0/500) and the low temperature (60 °C) favors the formation of keto acid **57**. Keto acid **57** which was isolated by sodium bicarbonate wash and purified by the sublimation at 160 °C/0.1mm is a colorless crystalline compound (EIMS 314, mp 165-166 °C). The ^{1}H NMR spectrum (Fig. 2-13) shows two signals for the methylene protons (δ 3.69 and 4.22) which are strongly deshielded by both aromatic ring and the carbonyl or carboxy group. The ^{13}C NMR spectrum (Fig. 2-14) shows two carbonyl groups, twelve aromatic carbons, two methoxy groups, and two methylene carbons. All these data are consistent with the proposed structure.

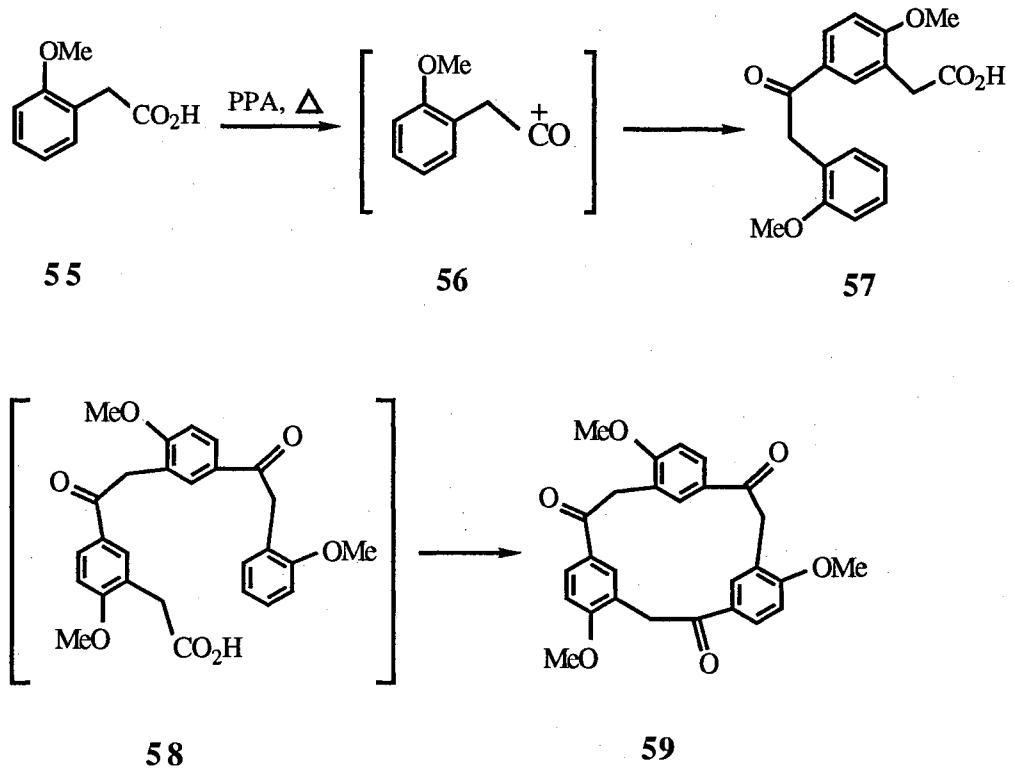
Table 2-2. Yields of Keto Acid 57 and Trione 59 under Different Reaction Conditions

55 :PPA	Temperature (°C)	Yields of **57** (%)	Yields of **59** (%)
2.0 : 500	82	29	11
2.0 : 500	74	53	10
2.0 : 500	60	58	10
2.0 : 500	50	mainly **55**	
10.0 : 500	80	0	

The sodium bicarbonate insoluble material was extracted with methylene chloride and then sublimed at 220 °C/0.1mm. The sublimed material was washed thoroughly with ether to remove a pale yellow color. A white powder was obtained in 10% yield and identified as 4,12,20-trimethoxy[2.2.2]metacyclophane-1,9,17-trione (**59**) through its MS spectrum (mol wt 444, m/z 445 using +LSIMS), ^{1}H NMR spectrum (Fig. 2-15) which showed the ratio of ArH:CH_2:OCH_3 as 3:2:3, and ^{13}C NMR spectrum (Fig. 2-16) which showed a single carbonyl and single methoxy group. The yield of 4,12,20-

trimethoxy[2.2.2]metacyclophane-1,9,17-trione (**59**) appears to be independent of the reaction temperature but is influenced by the concentration of 2-methoxybenzeneacetic acid (**55**) in PPA (Table 2-2). When the amount of PPA is increased, the yield of trione **59** is increased. No dione was found in these cyclization reactions.

Scheme 2-5



Attempts to cyclize 2-methoxy-5-(*o*-methoxybenzeneacetyl)benzeneacetic acid (**57,** 1.5 g) in PPA (390 g) for 30 min at 66 °C resulted in recovery of 1.2 g (80%) starting keto acid **57**. Mass spectra showed the formation of higher polyones (mol wt 444, m/z 445 using +LSIMS for the trione **59** and mol wt 592, m/z 593 using +LSIMS for the tetraone) and higher keto acids (mol wt 462, m/z 463 using +LSIMS for the triketoacid and mol wt 610, m/z 611 using +LSIMS for the tetraketoacid). No dione was observed in this

reaction. A second run of **57** (1.1 g) in PPA (500 g) for 30 min at 84 °C gave 0.4 g (43%) recovery of **57**. No dione, no higher keto acids, and no higher polyones were observed in this higher temperature run. The formation of 4,12,20-trimethoxy[2.2.2]-metacyclophane-1,9,17-trione (**59**) during the above reactions indicates that the acylation reaction of 2-methoxybenzeneacetic acid (**55**) in PPA could be reversible.

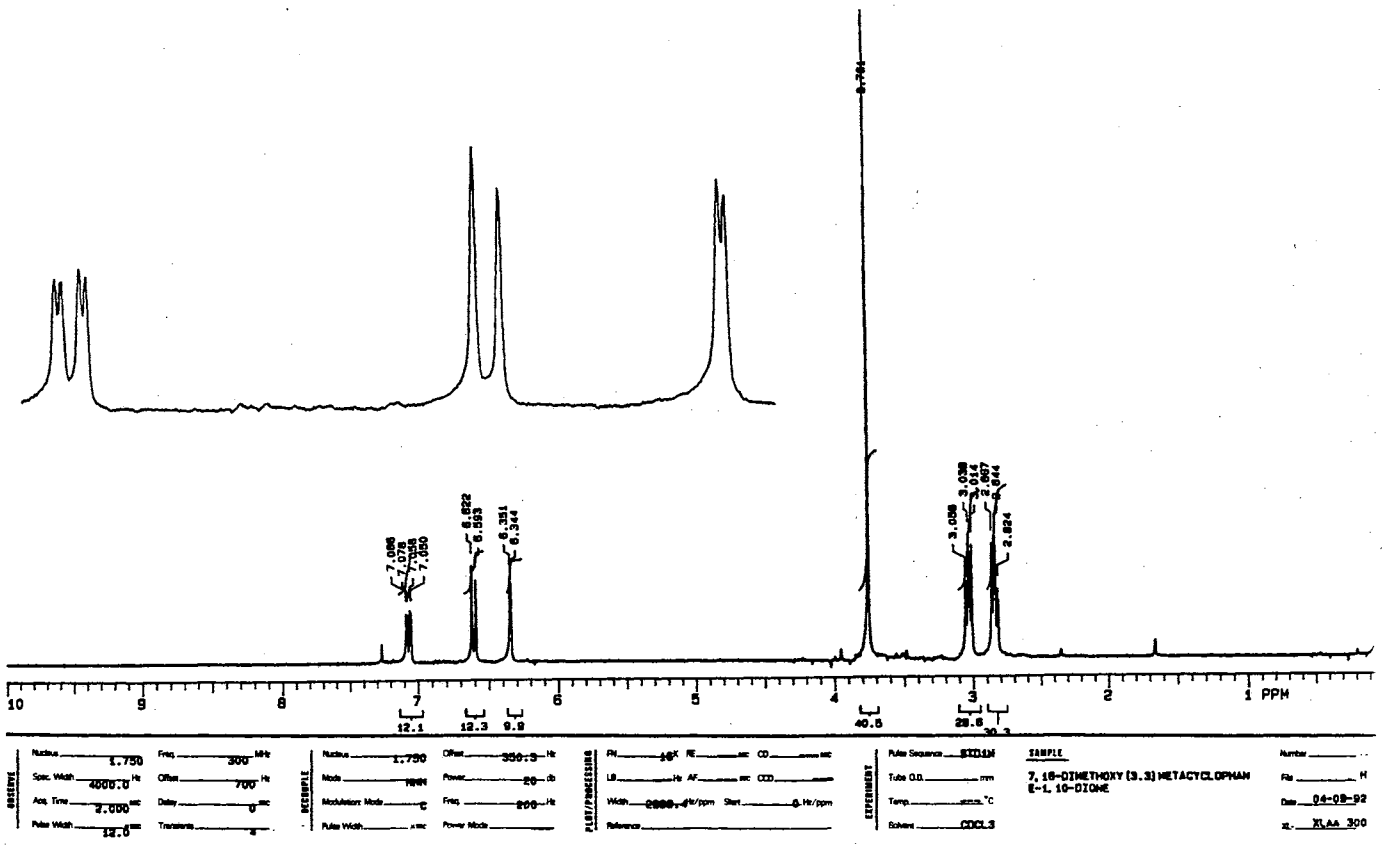


Figure 2-7. ^{1}H NMR spectrum of 7,16-dimethoxy[3.3]metacyclophane-1,10-dione (**43c**).

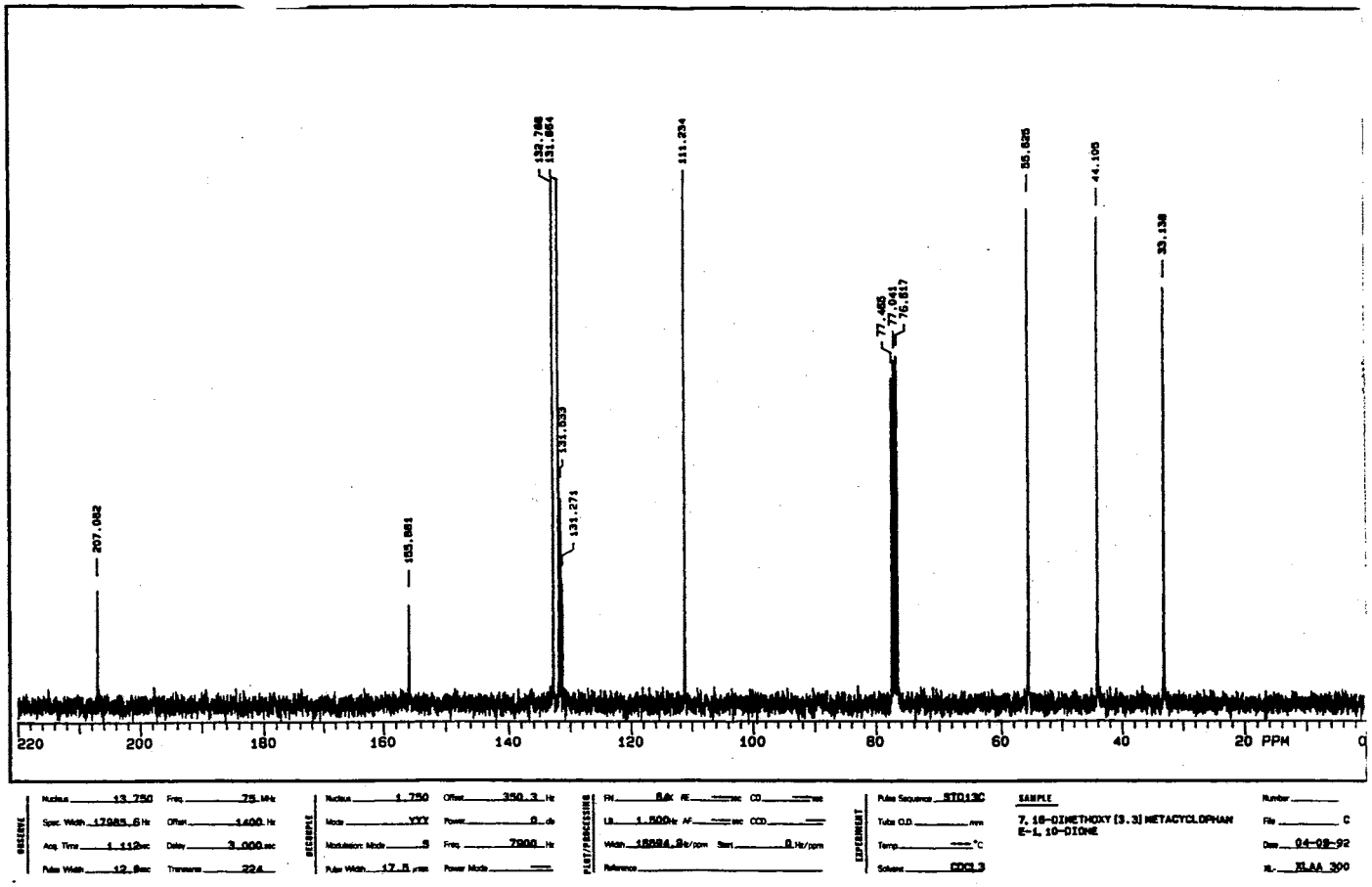


Figure 2-8. ^{13}C NMR spectrum of 7,16-dimethoxy[3.3]metacyclophane-1,10-dione (**43c**).

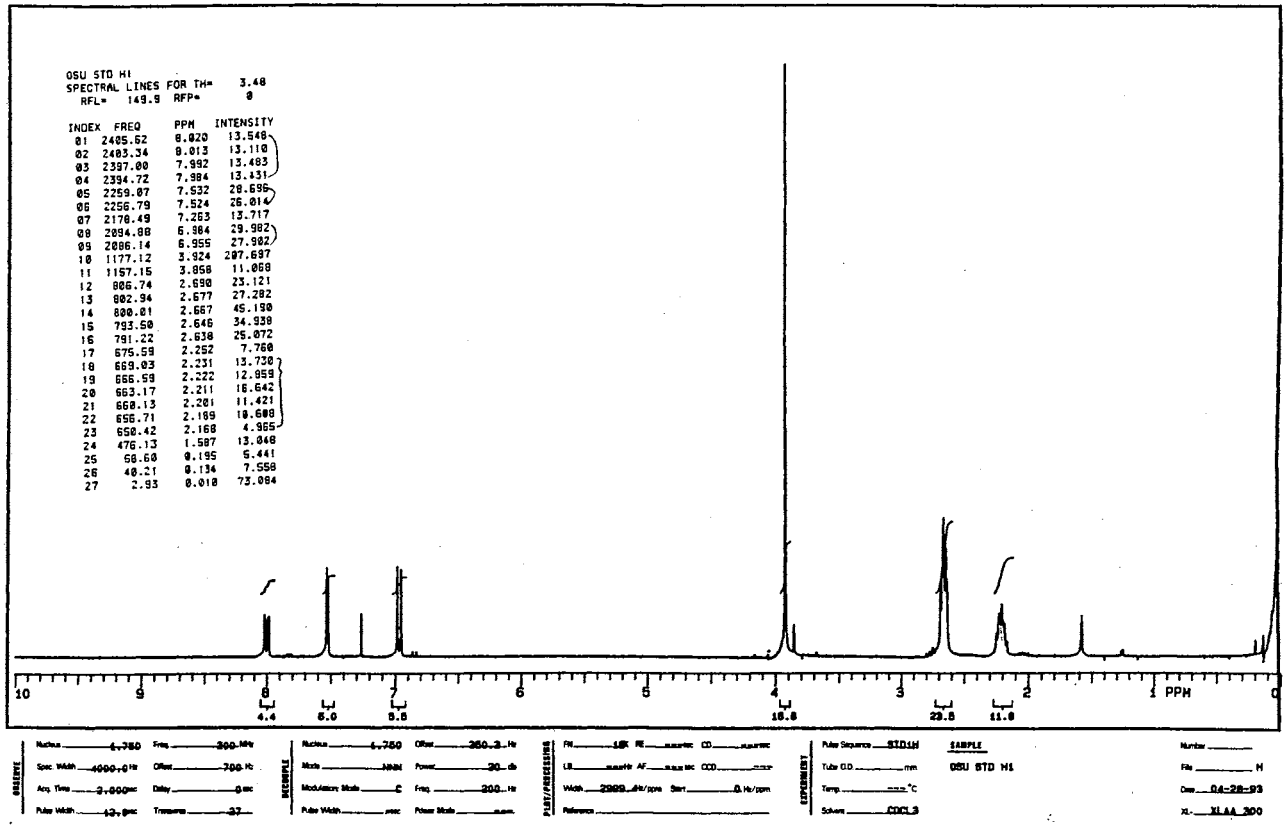


Figure 2-9. ^{1}H NMR spectrum of 6,16-dimethoxy[4.4]metacyclophane-1,11-dione (**53a**).

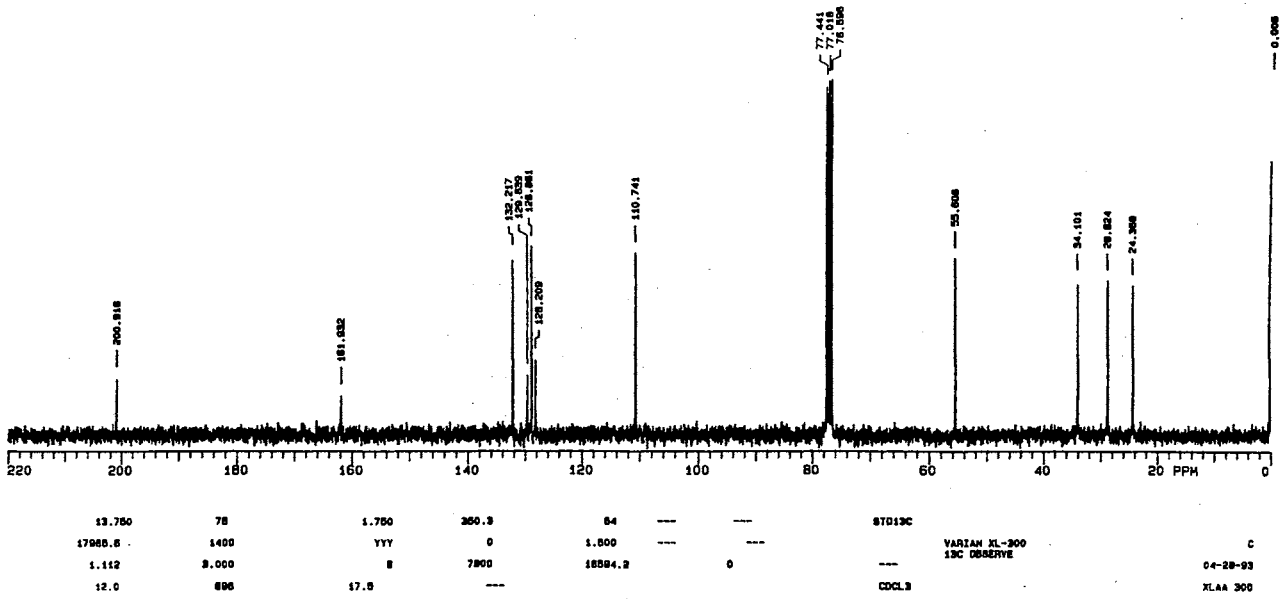


Figure 2-10. ^{13}C NMR spectrum of 6,16-dimethoxy[4.4]metacyclophane-1,11-dione (**53a**).

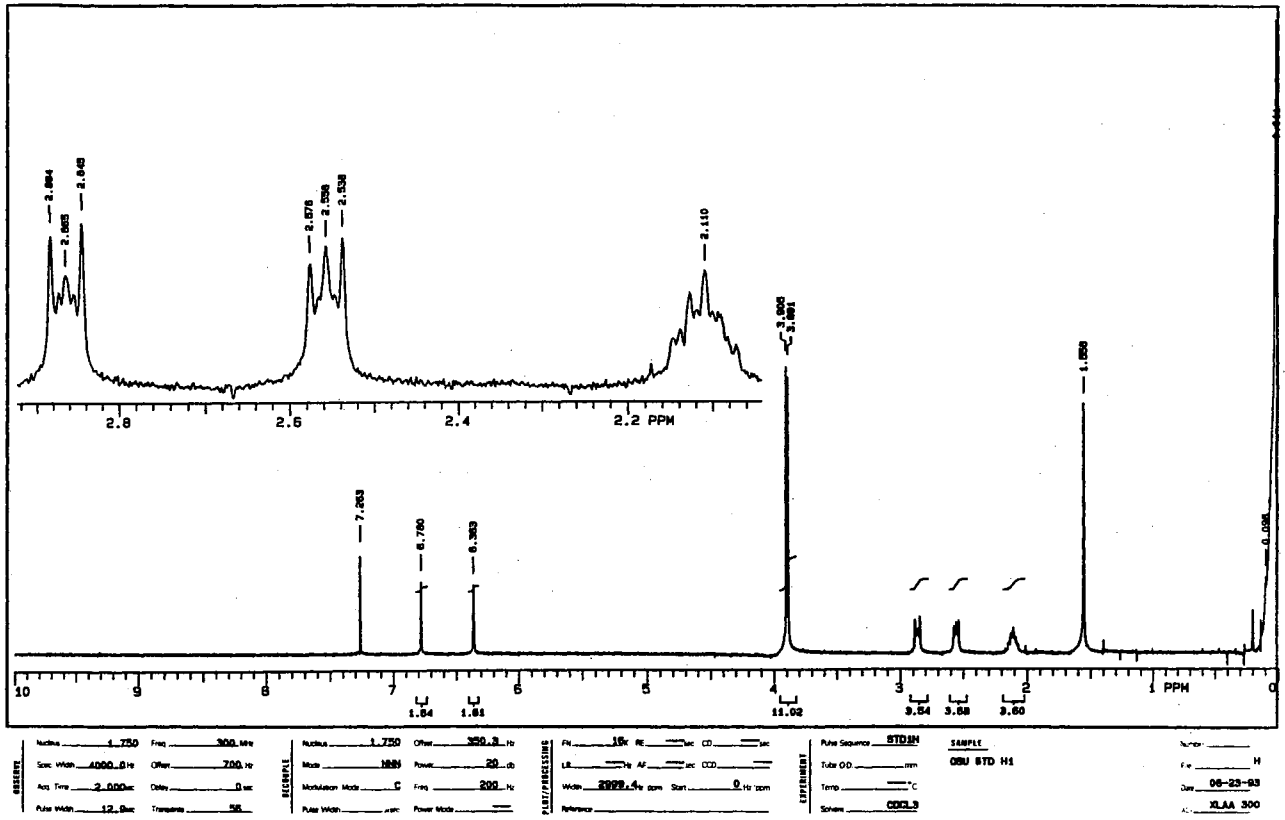


Figure 2-11. ^{1}H NMR spectrum of 6,8,16,18-tetramethoxy-[4.4]metacyclophane-1,11-dione (**53b**).

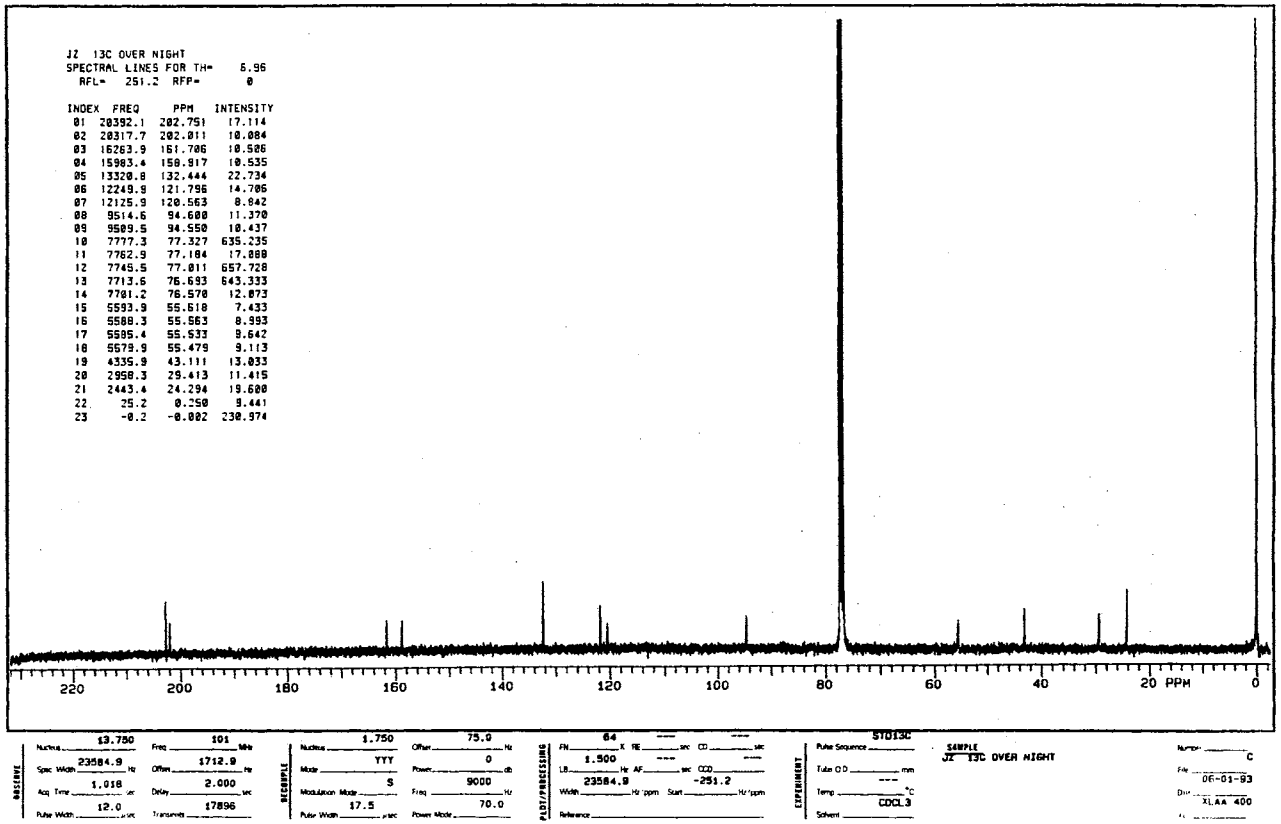


Figure 2-12. ^{13}C NMR spectrum of 6,8,16,18-tetramethoxy-[4.4]metacyclophane-1,11-dione (**53b**).

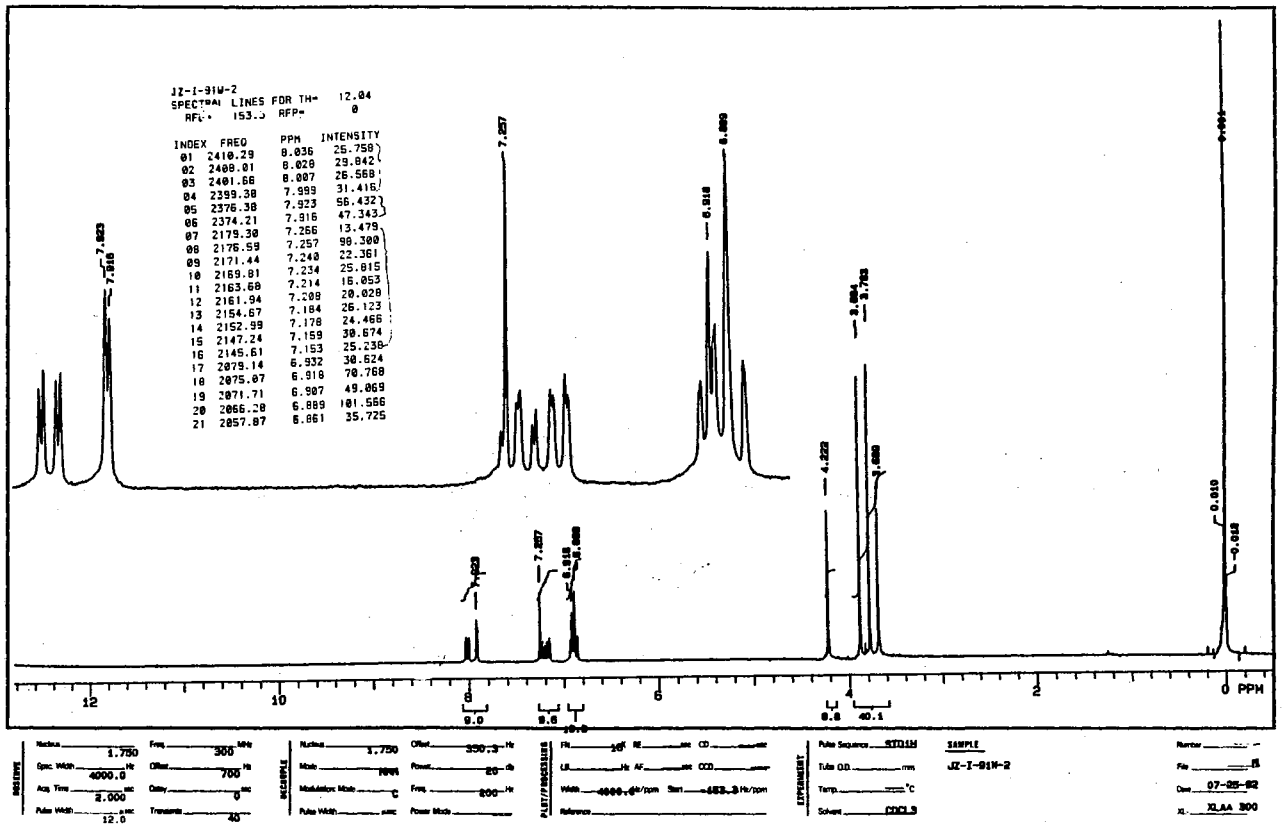


Figure 2-13. ^{1}H NMR spectrum of 2-methoxy-5-(*o*-methoxybenzeneacetyl)-benzeneacetic acid (**57**).

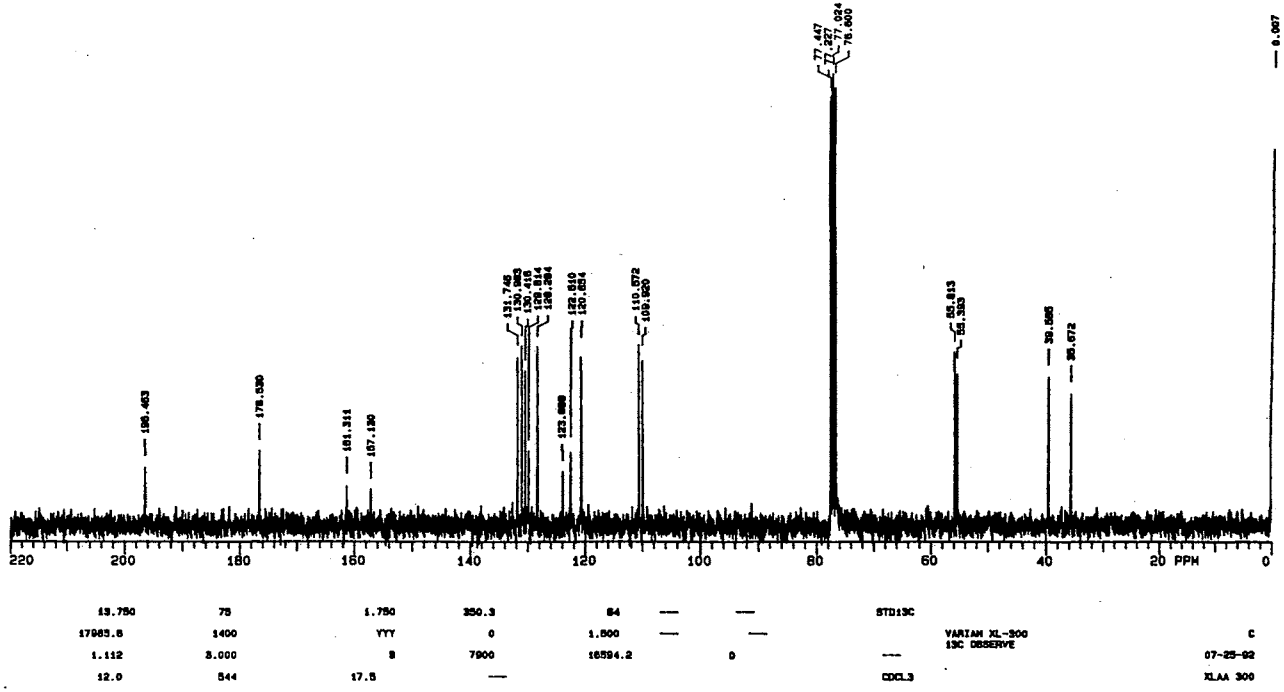


Figure 2-14. ^{13}C NMR spectrum of 2-methoxy-5-(*o*-methoxybenzeneacetyl)-benzeneacetic acid (**57**).

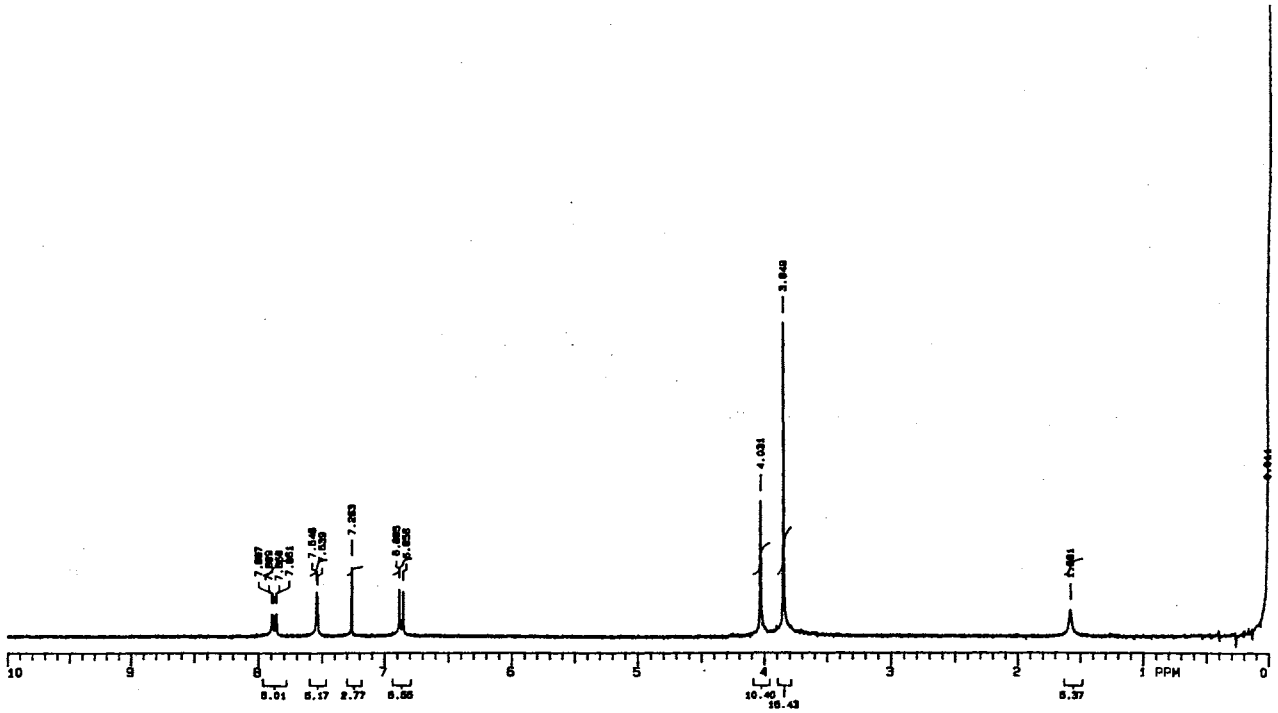


Figure 2-15. ^{1}H NMR spectrum of 4,12,20-trimethoxy[2.2.2]metacyclophane-1,9,17-trione (**59**).

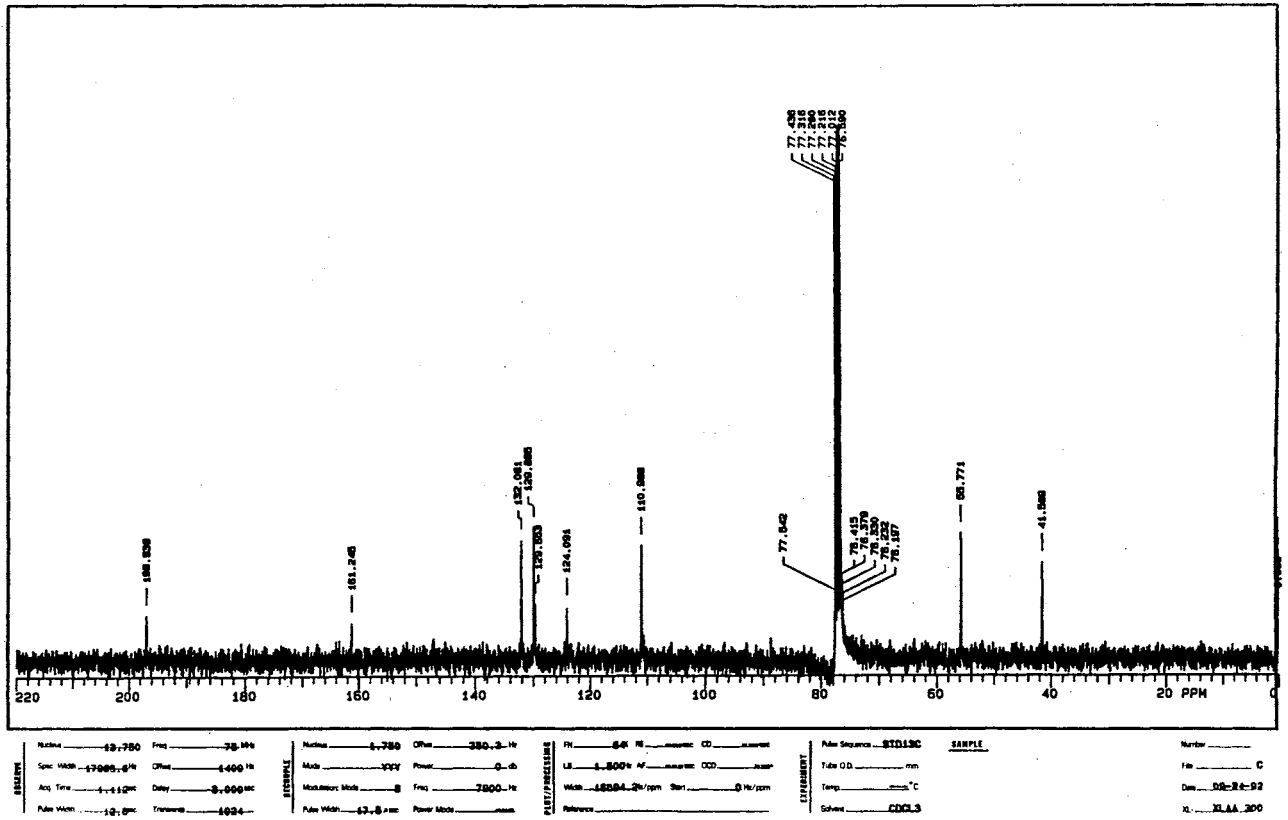


Figure 2-16. ^{13}C NMR spectrum of 4,12,20-trimethoxy[2.2.2]metacyclophane-1,9,17-trione (**59**).

CHAPTER III

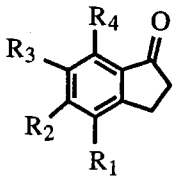
THE ROLE OF METHOXY GROUPS IN PPA-CATALYZED CYCLIZATION

In the PPA-catalyzed reactions of 3-(2-methoxybenzene)propanoic acid (**39a**) and 3-(2,4-dimethoxybenzene)propanoic acid (**39b**), intermolecular cyclization takes place instead of the expected intramolecular cyclization to 1-indanones. Here two questions need answering. First, why do some methoxy-substituted 3-arylpropanoic acids readily cyclize to 1-indanones as shown in Table 3-1 and others form methoxy-substituted [3.3]meta-cyclophane-1,10-diones (**43a** and **43b**). Also, why do 3-(4-methoxybenzene)propanoic acid (**43c**), 4-(2-methoxybenzene)butanoic acid (**49a**), and 4-(2,4-dimethoxybenzene)-butanoic acid (**49b**) cyclize to monomeric products such as 6-methoxy-1-indanone (**41c**), 5-methoxy-1-tetralone (**51a**), and 5,7-dimethoxy-1-tetralone (**51b**), as well as dimeric products such as 7,16-dimethoxy[3.3]metacyclophane-1,10-dione (**43c**), 6,16-dimethoxy[4.4]metacyclo-phane-1,11-dione (**53a**), and 6,8,16,18-tetramethoxy[4.4]meta-cyclo-phane-1,11-dione (**53b**). Second, why *p*-methoxy-3-(*p*-methoxyhydrocinnamoyl)-hydrocinnamic acid (**42c**) is isolated but keto acids **42a** and **42b** are not found.

The first thing which was considered is the effect of the methoxy group because all the 3-arylpropanoic acids (**39a**, **39b** and **39c**) as well as related 4-arylbutanoic acids (**49a**, **49b**, **49c**) and arylacetic acid (**55**) which could form metacyclophanediones have methoxy groups located in a *meta* relationship to the positions that intramolecular cyclization occurs and *para* or *ortho* relationship to the position that intermolecular

cyclization would take place (Fig.3-1). This suggests the position that intermolecular cyclization would take place could be highly activated by either one methoxy group (*para* for **39a** and *ortho* for **39c**) or two methoxy groups (*para* and *ortho* for **39b**) and then become more reactive than the position that intramolecular cyclization would take place (Fig. 3-1). Thus, intermolecular cyclization can compete with intramolecular cyclizations for 3-arylpropanoic acids **39a**, **39b**, **39c**, 4-arylbutanoic acids **49a**, **49b**, **49c**, and arylacetic acid **55**.

Table 3-1. Indanones and Yields from PPA-Catalyzed Cyclizations of Corresponding 3-Arylpropanoic Acids



1-Indanones	R_1	R_2	R_3	R_4	Yield (%)
60	H	OMe	OMe	H	85
61b	H	OMe	H	OMe	99
62b	H	OMe	OMe	OMe	84
63b	OMe	OMe	H	H	72
64b	OMe	H	H	OMe	87
65b	OMe	OMe	OMe	H	79
66b	OMe	H	OMe	OMe	77
67b	OMe	Me	OMe	H	50

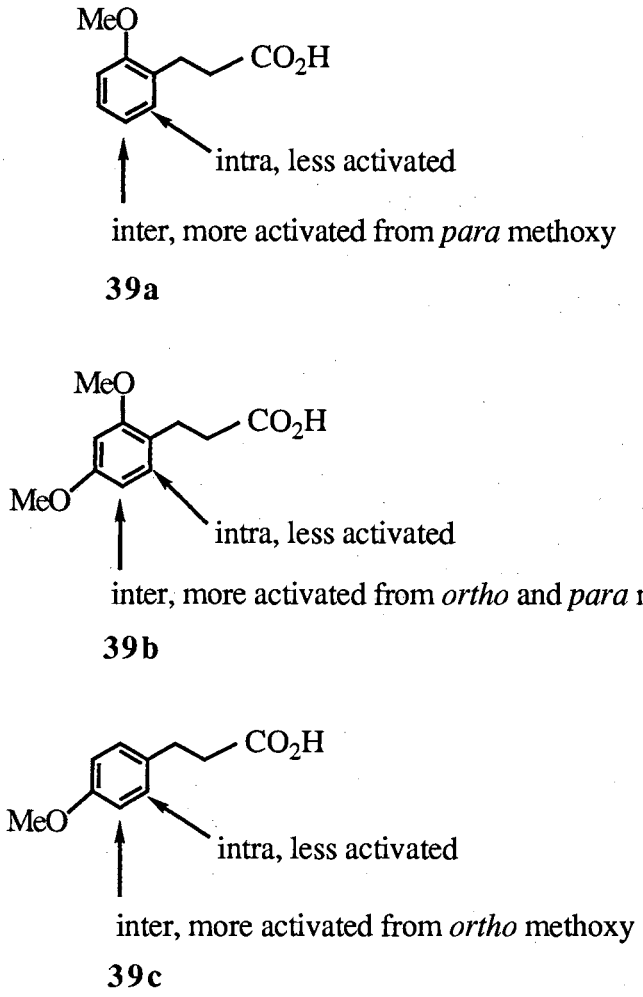


Figure 3-1. The positions of intra- and intermolecular cyclizations and their relative reactivities for **39a**, **39b** and **39c**.

Further investigation showed that the methoxy group adjacent to the side chain plays an important role. Table 3-2 and Table 3-3 give the results of dilution studies. 3-(2-methoxybenzene)propanoic acid (**39a**) and 3-(4-methoxybenzene)propanoic acid (**39c**) were chosen for the dilution study for two reasons. They both have meta-methoxy groups relative to the position that intramolecular cyclization would take place. The difference is that the methoxy group in **39a** is *ortho* (adjacent) to the carboxylic acid side chain and the methoxy group in **39c** is *para* to the carboxylic acid side chain. The second reason is if there are competitive reactions between intra- and intermolecular cyclizations, dilution will

favor the intra-molecular cyclization. The data shown in Tables 3-2 and 3-3 indicate that these two methoxy-substituted benzenepropanoic acids behave very differently in the PPA-catalyzed cyclization reactions. For 3-(4-methoxybenzene)propanoic acid (**39c**) the yields of 6-methoxy-1-indanone (**41c**) increased when the ratio of **39c** to PPA was decreased (Table 3-3). This means that dilution favors intramolecular cyclization of **39c**. But for 3-(2-methoxybenzene)propanoic acid (**39a**) dilution did not significantly increase the intramolecular process (Table 3-2). No matter what conditions were used, decreasing the ratio of acid **39a** to PPA or even using chlorobenzene as co-solvent, a maximum of 2.0% yield of 4-methoxy-1-indanone (**41a**) could be obtained by steam distillation. This provides evidence that methoxy group adjacent to the carboxylic acid side chain can play an important role in the reaction which favors intermolecular cyclization of **39a**.

Table 3-2. Yields of 4-Methoxy-1-indanone (41a) from Varying Ratio of 3-(2-Methoxybenzene)-propanoic Acid (39a) in 500 g of PPA

39a (g)	PhCl (mL)	Yields of **41a** (%)
5.0	100	trace
5.0	200	trace
5.0	400	trace
5.0	800	trace
5.0	0	trace
2.0	0	trace
1.8	0	2.0

Table 3-3. Yields of 6-Methoxy-1-indanone (41c) from Varying Ratio of 3-(4-Methoxybenzene)-propanoic Acid (39c) in 500 g of PPA

39c (g)	Yields of **41c** (%)
28.0	17
15.0	26
5.0	41
2.0	65

In order to explain the fact that a 2-methoxy group, located *ortho* to the carboxylic acid side chain, has an effect on the PPA-catalyzed cyclization, a complex of acylium ion and 2-methoxy group with the positive charge distributed in the whole benzene ring is proposed (Fig. 3-2). The interaction of this positively charged acylium group with the non-bonding oxygen electrons of the adjacent methoxy group has two effects. First, it stabilizes the positive charge so that it can exist long enough to attack an active position and thus the selectivity of the reaction is increased. Second, it renders the aromatic ring more electropositive and hence resistant to the intramolecular cyclization. Both effects favor intermolecular cyclization. That is why 3-(2-methoxybenzene)propanoic acid (**39a**) and 3-(2,4-dimethoxybenzene)propanoic acid (**39b**) undergo intermolecular cyclization to methoxy-substitued [3.3]metacyclophane-1,10-diones (**43a** and **43b**) rather than intramolecular cyclization to 1-indanones. 3-(4-Methoxybenzene)propanoic acid (**39c**) can not form the complex of acylium ion and methoxy group and thus its behavior would be expected to be different. Which reaction, intra- or intermolecular cyclization, is favored depends on the concentration of **39c**. Dilution of **39c** reduces the chance that a molecule of **39c** will meet other molecules of **39c** and intramolecular cyclization is favored. High

concentration of **39c**, however, increases the possibilities for molecules to meet each other and intramolecular cyclization is not favored. This also suggests that the methoxy group adjacent to the carboxylic acid side chain plays a major role in the intermolecular cyclization reaction.

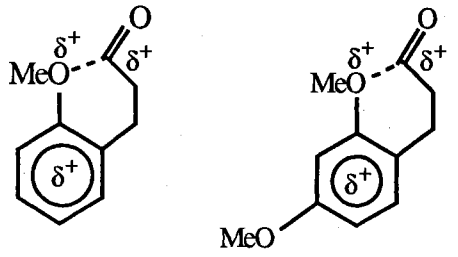
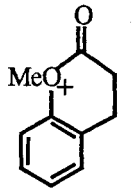
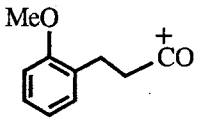
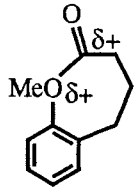
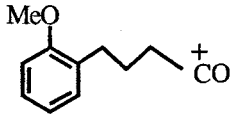


Figure 3-2. Complexes of acylium ions and methoxy groups for intermediate cations **40a** and **40b**.

4-(2-methoxybenzene)butanoic acid (**49a**) and 4-(2,4-dimethoxybenzene)butanoic acid (**49b**) readily cyclize to methoxy-substituted 1-tetralones (**51a**, **51b**) as well as [4.4]metacyclophanediones (**53a**, **53b**). The yields of **51a** and **51b** depend on the ratio of 4-arylbutanoic acids (**49a**, **49b**) to PPA (Table II-1). This indicates that complexes of acylium ion and *ortho* methoxy group are less likely formed during the cyclizations of 4-arylbutanoic acids **49a** and **49b** in PPA. The reason might be the resulting seven-membered ring is less favored than the six-membered ring in forming the complex.

Molecular mechanics calculations were carried out on cations **40a** and **50a** with different conformations, ring conformation A and chain conformation B. The final heat of formation for different conformations, estimated by MOPAC method, are listed in Table 3-4. For cation **40a**, the ring conformation A with the positive charge on the methoxy oxygen, was found to be about 9 kcal more stable than the chain conformation B. This indicates the ring conformation A is more favored than the chain conformation B and probably exists as the major intermediate during the reaction process. For cation **50a**, however, the ring conformation A is about 2 kcal less stable than the chain conformation B

Table 3-4. Final Heat of Formation for the Different Conformations of Intermediate Cations 40a and 50a

Conformations	Final heat of formation (kcal)
 A	135.7
 B	144.1
 A	136.3
 B	134.5

which suggests the chain conformation B of cation **50a** should be the major intermediate during the reaction. These calculated results are consistent with the experimental results that 3-(2-methoxy-benzene)propanoic acid (**39a**) and 3-(2,4-dimethoxybenzene)propanoic acid (**39b**) greatly favor the formation of methoxy-substituted [3.3]metacyclophanediones **43a** and **43b,** but that 4-(2-methoxybenzene)butanoic acid (**49a**) and 4-(2,4-dimethoxy-benzene)butanoic acid (**49b**) cyclize to 1-tetralones (**51a** and **51b**) and methoxy-

substituted [4.4]metacyclophanediones (**53a** and **53b**) depending on the concentration of **49a** and **49b** in PPA.

Figures 3-3 and 3-4 show the cyclization reactions of some 3-arylpropanoic acids which have a 2-methoxy group or 2,4-dimethoxy groups in the aromatic rings. In order to explain the good yields obtained for the 1-indanones, 4,5-dimethoxy (**63b**), 4,7-dimethoxy (**64b**), 4,5,6-trimethoxy (**65b**), 4,6,7-trimethoxy (**66b**), and 4,6-dimethoxy-5-methyl (**67b**), another effect must be considered, that is the other activating groups attached to the aromatic ring. In Figure 3-3, all three 3-arylpropanoic acids (**39a**, **63a** and **64a**) have a 2-methoxy group. The differences are that 3-(2,3-dimethoxybenzene)propanoic acid (**63a**) has one more 3-methoxy group located in a *para* relationship to the cyclized position and 3-(2,5-dimethoxybenzene)propanoic acid (**64a**) has one more 5-methoxy group which is *ortho* to the cyclized position. The yields of 1-indanones (**41a**, **63b** and **64b**) in Figure 3-3 change from 2% to 72% and 87% when the methoxy groups are added to the aromatic ring. In Figure 3-4, all four 3-arylpropanoic acids (**39b**, **65a**, **66a** and **67a**) have 2,4-dimethoxy groups in their aromatic rings. The difference, as compared to **39b**, is that 3-(2,3,4-trimethoxybenzene)propanoic acid (**65a**) has one more 3-methoxy group located in a *para* relationship to the cyclized position, 3-(2,4,5-trimethoxybenzene)propanoic acid (**66a**) has an additional 5-methoxy group located in an *ortho* relationship to the cyclized position, and 3-(2,4-dimethoxy-3-methylbenzene)propanoic acid (**67a**) has one more 3-methyl group which is *para* to the cyclized position. These added methoxy or methyl groups activate the aromatic ring to favor intramolecular cyclization and change the yields of corresponding 1-indanones from none to 79%, 77% and 50%, respectively. This indicates that for a 3-arylpropanoic acid which has 2-methoxy or 2,4-dimethoxy groups, it is necessary to have another activating group to assist intramolecular cyclization to 1-indanones. The stronger the added activating group, the higher the yield of 1-indanones. Good examples are the yields of 4,5,6-trimethoxy-1-indanone

(**65b**, 79%)) and 4,6-dimethoxy-5-methyl-1-indanone (**67b**, 50%). 3-(2,4,5-Trimethoxybenzene)propanoic acid (**66a**) can not form a metacyclophanedione but does cyclize to 4,6,7-trimethoxy-1-indanone (**66b**) in good yield because of the *ortho* influence of the added methoxy group from C-5 of **66a**. Intermolecular reaction can still take place for all these and probably does to account for the decreased yield of **67b** (50%).

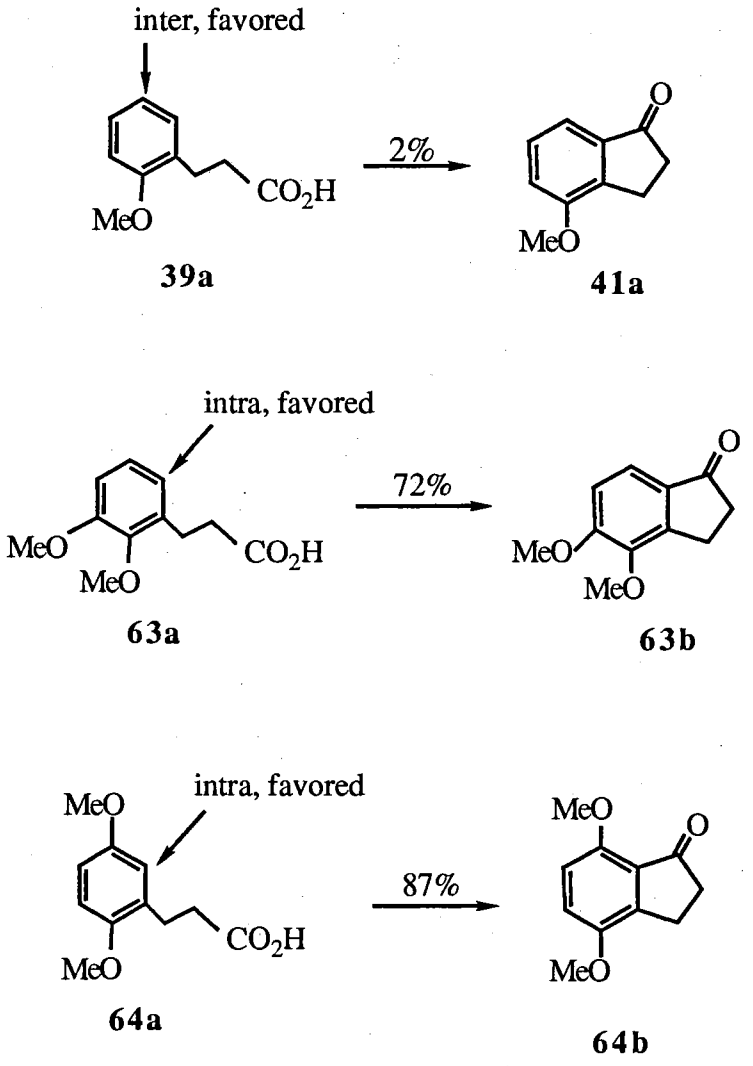


Figure 3-3. Cyclization of 3-arylpropanoic acids having a 2-methoxy group in the aromatic ring.

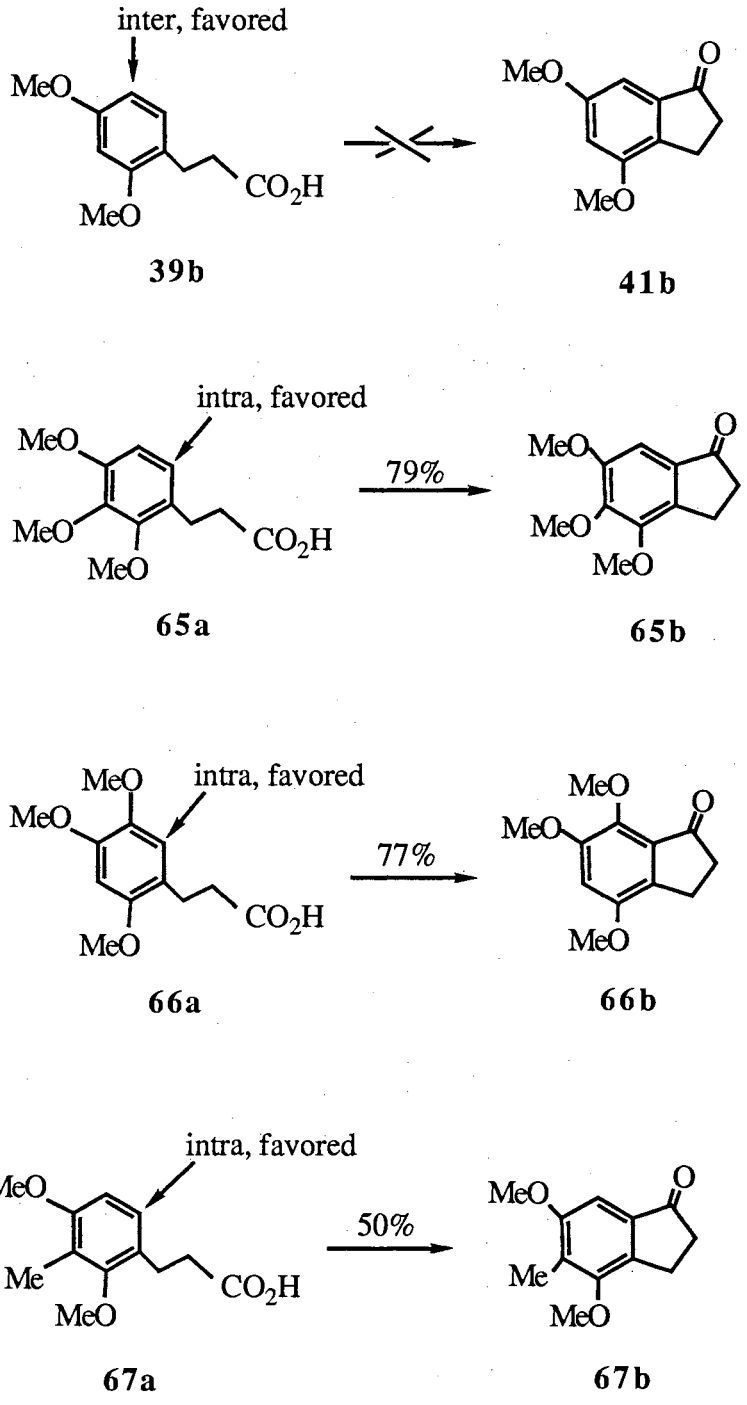
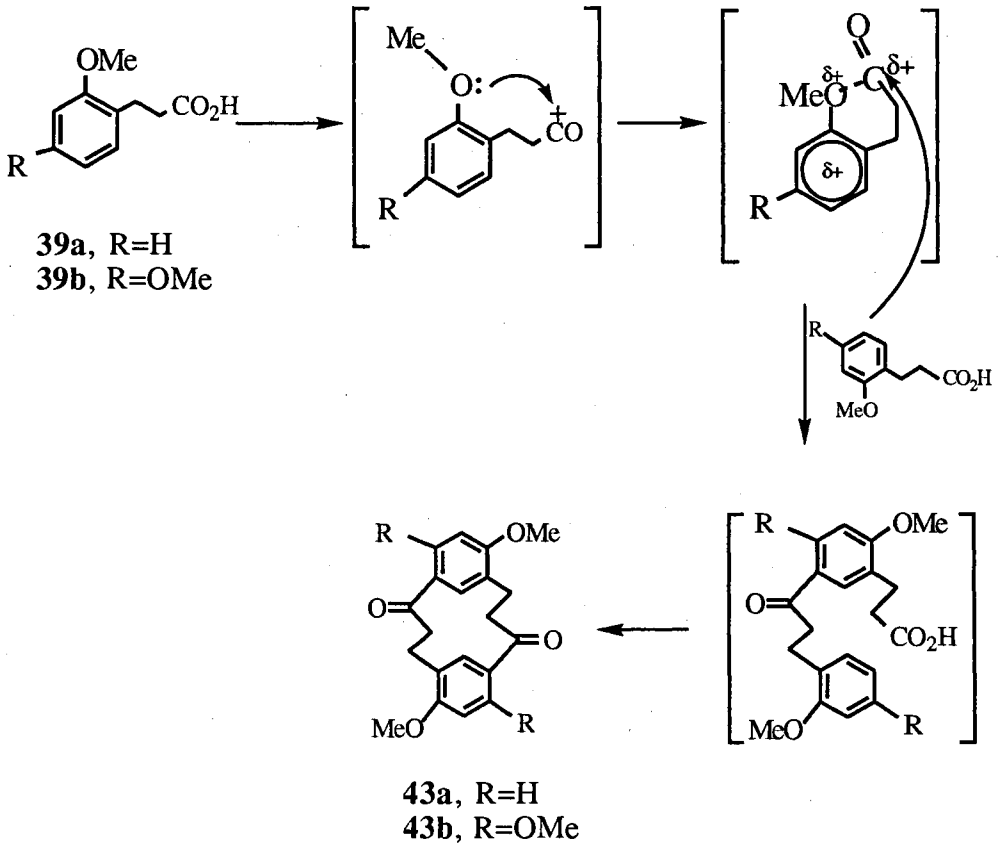


Figure 3-4. Cyclization of 3-arylpropanoic acids having 2,4-dimethoxy groups in the aromatic ring.

Mechanisms for the inter- and intramolecular cyclizations of methoxy-substituted benzenepropanoic acids are proposed below. Scheme 3-1 shows the route for 3-aryl-propanoic acids (**39a** and **39b**) which greatly favor intermolecular cyclization. The first step is to form an acylium ion. Once the acylium ion is formed, it is attacked by the non-bonding oxygen electrons of *ortho* methoxy group and a complex of acylium ion and *ortho* methoxy group is formed. This new cation reacts with the activated position of another molecule, intermolecular cyclization takes place, and methoxy-substituted [3.3]meta-cyclophane-1,10-diones (**43a** and **43b**) are formed.

Scheme 3-1

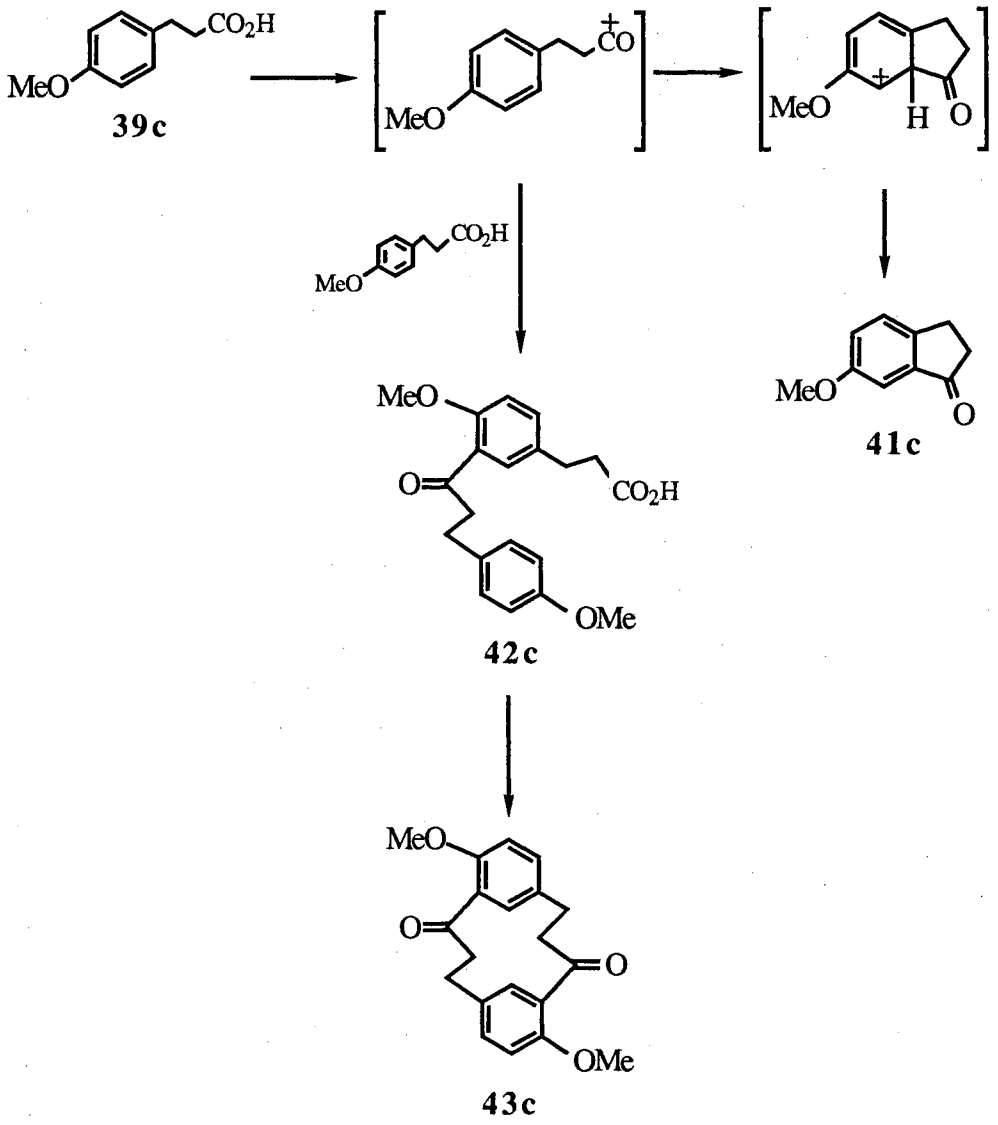


39a, R=H
39b, R=OMe

43a, R=H
43b, R=OMe

Scheme 3-2 shows a mechanism for the cyclization of 3-(4-methoxybenzene)-propanoic acid (**39c**) to 6-methoxy-1-indanone (**41c**) and 7,16-dimethoxy[3.3]meta-cyclophane-1,10-dione (**43c**).

Scheme 3-2



When the acylium ion is formed, there is competition between intra- and intermolecular cyclizations which are controlled by the concentration of 3-(4-

methoxybenzene)propanoic acid (**39c**) in PPA. When the concentration of **39c** is low, there is less opportunity for the acylium ion to meet other molecules of **39c**, the acylium ion cyclizes to intramolecular cyclization product, 6-methoxy-1-indanone (**41c**). If the concentration of **39c** is high, however, there are better chances for the acylium ion to meet other molecules of **39c**, the acylium ion will attack the favored position of the aromatic ring in other molecules of **39c**, and the intermolecular cyclization product, *p*-methoxy-3-(*p*-methoxyhydrocinnamoyl)hydrocinnamic acid (**42c**), is formed. Intermediate keto acid **42c** cyclizes in the terminal ring to form 7,16-dimethoxy[3.3]metacyclophane-1,10-dione (**43c**) because the terminal ring of **42c** remains reactive whereas the remaining ring is deactivated by the attached ketone carbonyl group. The higher the concentration of 3-(4-methoxybenzene)-propanoic acid (**39c**) is, the lower the yield of 6-methoxy-1-indanone (**41c**) can be as shown in Table 3-3.

This argument can also be used to explain what happens during the reaction of 4-(2-methoxybenzene)butanoic acid (**49a**) and 4-(2,4-dimethoxybenzene)butanoic acid (**49b**) in PPA. After the acylium ions are formed, they can either attack the aromatic ring of the same molecule or the aromatic ring of another molecule, resulting in competition between intra- and intermolecular cyclizations. Which reaction, intra- or intermolecular cyclization, is favored depends on the concentrations of **49a** and **49b** in PPA (Table 2-1). When the concentrations of **49a** and **49b** were increased, the yields of 5-methoxy-1-tetralone (**51a**) and 5,7-dimethoxy-1-tetralone (**51b**) which were formed by the intramolecular cyclization decreased, and the yields of the intermolecular cyclization products [6,16-dimethoxy[4.4]metacyclophane-1,11-dione (**53a**) and 6,8,16,18-tetramethoxy[4.4]-metacyclophane-1,11-dione (**53b**) as well as polyones] increased.

Molecular mechanics calculations using MOPAC method were carried out on two keto acid intermediates **42a**, **42b** and *p*-methoxy-3-(*p*-methoxyhydrocinnamoyl)hydrocinnamic acid (**42c**) in order to answer the second question why keto acid **42c** is isolated

but keto acid intermediates **42a** and **42b** did not survive. The most stable conformations estimated by MOPAC are shown in Figure 3-5, Figure 3-6, and Figure 3-7. These figures clearly show that the two benzene rings of all three keto acids, **42a**, **42b**, and **42c**, are not in the same plane and they are not parallel to each other. Instead, they are almost perpendicular to each other. The difference is that the carboxylic acid side chain of **42c** which is located in the remaining ring is far away from the terminal ring (Fig. 3-7), and the carboxylic acid side chains of **42a** (Fig. 3-5) and **42b** (Fig. 3-6) are oriented toward the terminal rings. The distances between C1 and C17 are 7.36 Å, 8.31Å, and 10.42 Å for keto acids **42a**, **42b**, and **42c**, respectively. To cyclize the keto acid **42c** into dione **43c**, the remaining ring must rotate to bring the carboxylic acid side chain close to the terminal ring. For keto acid intermediates **42a** and **42b**, however, the cyclization reaction might take place spontaneously after the keto acid intermediates are formed since their carboxylic acid side chains are already close to the remaining rings. The angles of C3-C4-C5 are flared away from the *ortho* methoxy group for keto acid intermediates **42a** (123.5°) and **42b** (122.8°). For keto acid **42c**, the angle (120.1°) is less and very close to the normal angle (120°) for a sp^2 carbon because no *ortho* methoxy group is present in the melecule. These results suggest that the repulsive interaction between the carboxylic acid side chain and the methoxy group adjacent to the carboxylic acid side chain bends the molecule and brings the carboxylic acid group and remaining ring together for the keto acid intermediates **42a** and **42b**. Here the methoxy group adjacent to the side chain also can play an assisting steric role in the cyclization to [3.3]metacyclophandiones.

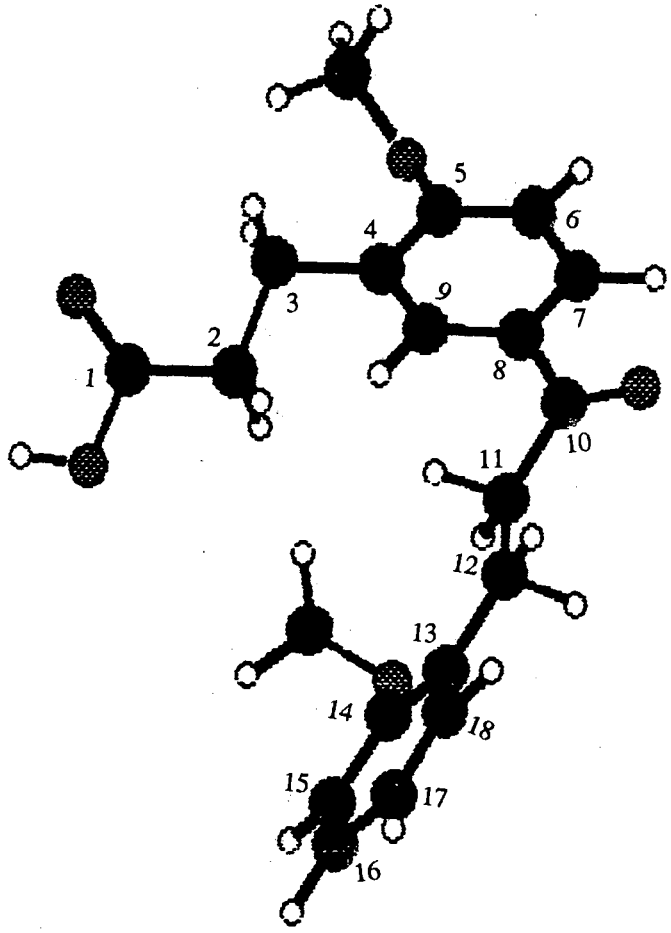


Figure 3-5. The most stable conformation of keto acid **42a** estimated by MOPAC method.

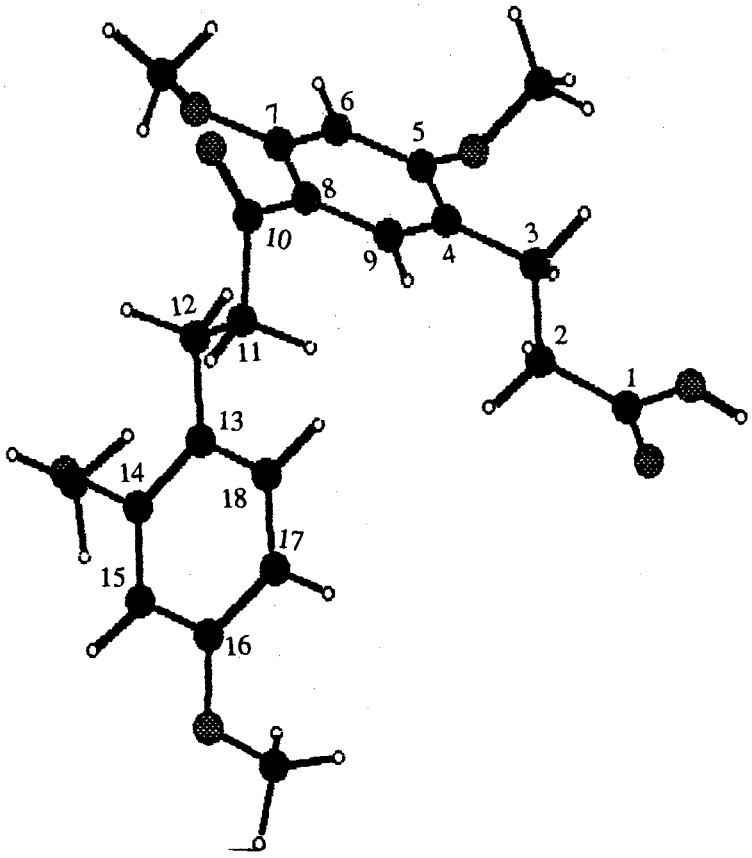


Figure 3-6. The most stable conformation of keto acid **42b** estimated by MOPAC method.

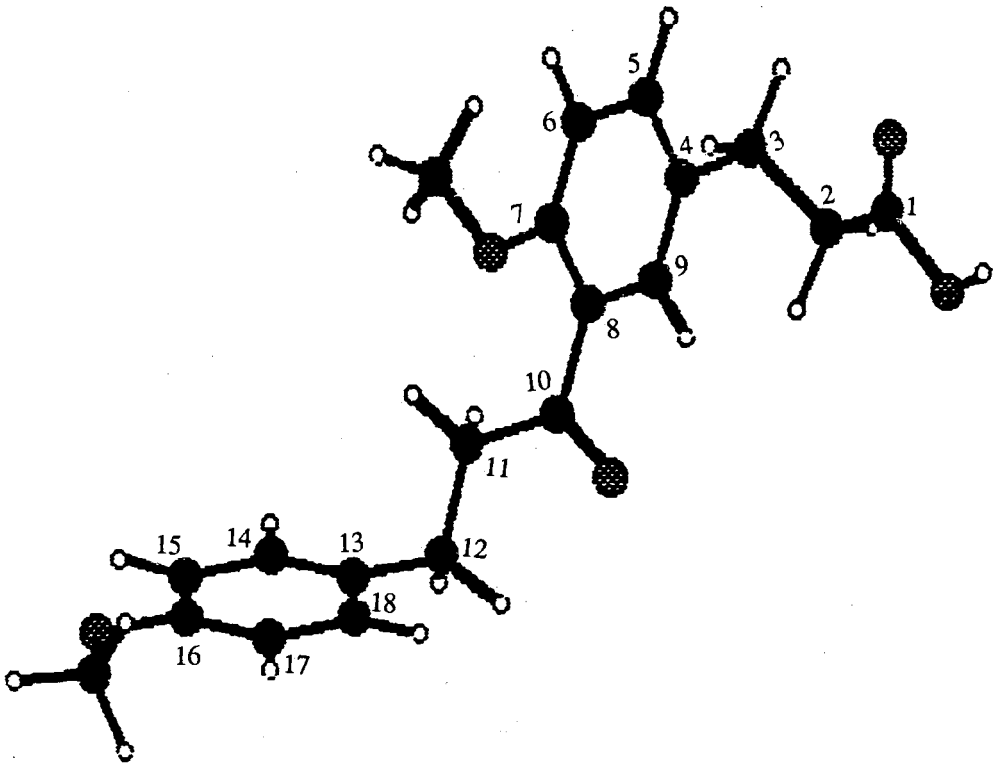


Figure 3-7. The most stable conformation of keto acid **42c** estimated by MOPAC method.

CHAPTER IV

^{17}O NMR STUDY OF METHOXY-SUBSTITUTED 1-INDANONES

The objective of the work in this chapter was to prepare and study a series of methoxy-substituted 1-indanones to learn about the reliability of their substituent effects in the ^{13}C and ^{17}O NMR for use in structure assignment. The current study also was an extension of the earlier ^{13}C and ^{17}O NMR studies of substituent effects of methyl-substituted 1-indanones[124] and to learn more about the effect that crowding (two *ortho* neighbors) has on the ^{13}C and ^{17}O NMR of methoxy-substituted 1-indanones.

The 1-indanones used in this study were purchased [6-methoxy (**41c**), 5,6-dimethoxy (**60**), and 5-methoxy (**72**)] or synthesized as described below. 4-Methoxy-1-indanone (**41a**)[131,132] and 7-methoxy-1-indanone (**73**)[137] were prepared according to literature procedures.

Five methoxy-substituted 3-benzenepropanoic acids [3,4,5-trimethoxy (**62a**), 2,3-dimethoxy (**63a**), 2,5-dimethoxy (**64a**), 2,3,4-trimethoxy (**65a**), and 2,4,5-trimethoxy (**66a**)] were prepared from the corresponding cinnamic acids by catalytic hydrogenation (HOAc, 5% Pd/C, 55psi) and then cyclized in PPA to the substituted 1-indanones [5,6,7-trimethoxy (**62b**), 4,5-dimethoxy (**63b**), 4,7-dimethoxy (**64b**), 4,5,6-trimethoxy (**65b**), and 4,6,7-trimethoxy (**66b**)].

The substituted cinnamic acids [3,5-dimethoxy (**61a**), 2,4-dimethoxy-3-methyl (**67c**), 2,3-dimethyl-4-methoxy (**75a**), 2,5-dimethyl-4-methoxy (**77a**), and 3,5-dimethyl-

4-methoxy (**78a**)] were synthesized by the reaction of malonic acid with the corresponding aldehydes followed by hydrogenation (HOAc, 5% Pd/C, 55psi), and cyclization (PPA) to the corresponding substituted 1-indanones [5,7-dimethoxy (**61b**), 4,6-dimethoxy-5-methyl (**67b**), 4,5-dimethyl-6-methoxy (**75b**), 4,7-dimethyl-6-methoxy (**77b**), and 5,7-dimethyl-6-methoxy (**78b**)].

4,6-Dimethyl-5-methoxy-1-indanone (**76a**) was prepared by transposing the carbonyl group of 5,7-dimethyl-6-methoxy-1-indanone (**78b**). This was accomplished by Wolff-Kishner reduction of **78b** to 4,6-dimethyl-5-methoxy-1-indan (**76b**) and selective chromic acid oxidation of **76b** to 4,6-dimethyl-5-methoxyindan (**76a**).

The 1-indanones [**3**, 3-methyl (**68**), 4-methyl (**69**), 5-methyl (**70**), 6-methyl (**71**), 7-methyl (**37**), 3,7-dimethyl-4-methoxy (**74**), 3,4-dimethyl-7-methoxy (**79**), 4,5-dimethoxy-3,7-dimethyl (**80**), and 5,6-dimethoxy-3,7-dimethyl (**81**)] were available from the earlier studies.[124]

The structural identity of the above 1-indanones rests on their synthesis routes, NMR (^{1}H, ^{13}C, ^{17}O) spectroscopic studies, elemental analyses, and mass spectromeric data. The unsubstituted aromatic carbons of 1-indanones are readily detected from the high intensity of their ^{13}C NMR signals. In addition, the signal for C-5 (*para* to carbonyl) can be identified by a downfield shift as compared to the signal positions of other unsubstituted carbons. This information is particularly useful in distinguishing 1-indanone isomers having one or two unsubstituted aromatic carbons such as the two trimethoxy-1-indanones (**65b**, **66b**) which have a single unsubstituted aromatic carbon signal at 100.60 ppm (C-7) for 4,5,6-timethoxy-1-indanone (**65b**) and 103.33 ppm (C-5) for 4,6,7-timethoxy-1-indanone (**66b**).

Three dimethoxy-1-indanones [5,6-dimethoxy (**60**), 4,5-dimethoxy (**63b**), and 4,7-dimethoxy (**64b**)] provide an interesting series that illustrate the effectiveness of the combined use of ^{1}H, ^{13}C, and ^{17}O NMR data in assigning structures. ^{1}H NMR data

show that aromatic protons of **60** are isolated and appear as two singlets, whereas those of **63b** and **64b** are attached to adjacent carbons, are coupled, and appear as two doublets. The C-7 protons of **60** and **63b** are deshielded by the carbonyl group. The ^{13}C NMR data show the unsubstituted carbons of **64b** have signals at 116.52 ppm (C-5, *para* to carbonyl) and 109.37 ppm (C-6) whereas **60** shows signals at 104.11 ppm (C-4) and 107.50 ppm (C-7) with those of **63b** appearing at 112.30 ppm (C-6) and 120.13 ppm (C-7) for the unsubstituted carbons, respectively. The ^{17}O NMR chemical shift value of the carbonyl groups show that the C-7 of **64b** (δ 521.5 ppm) is substituted whereas the C-7 of **60** (δ 486.1 ppm) and **63b** (δ 493.0) are unsubstituted.

The combined use of ^{13}C and ^{17}O NMR data also was helpful in establishing the structure of **75b** as 4,5-dimethyl-6-methoxy-1-indanone rather than that of the alternative structure 4,7-dimethyl-6-methoxy-1-indanone (**77b**). This is based on the observed ^{17}O NMR value of carbonyl group as 495.4 ppm (calculated 497.7 ppm) for **75b** whereas the alternative structure (**77b**) gives a calculated value of 519.8 ppm (found 521.5 ppm). The ^{13}C NMR spectrum of **75b** gave a high intensity signal at 100.62 ppm for the unsubstituted carbon (C-7) and unsubstituted carbon signal for **77b** appears at 117.73 ppm (C-5).

Tables 4-1 and 4-2 show the ^{17}O NMR chemical shift values of the carbonyl oxygen for 26 1-indanones. Large changes in chemical shift of the carbonyl group are observed for the 1-indanones depending on the type and location of the substituents (Fig. 4-1). As compared to 1-indanone (**3**) with ^{17}O signal of carbonyl group at 505.0 ppm, the ^{17}O chemical shift for methyl substitution on the aromatic ring ranges from 499.0 ppm with the methyl group at C5 for **70** to 520.4 ppm with methyl group at the C7 for **37**, a range of 31.4 ppm. A similar comparison with methoxy substitution at C5 and C7 again shows these positions to be the most sensitive to the substitution and produce the greatest range of chemical shifts. The values are 486.2 ppm and 519.2 ppm for methoxy groups at

C5 for **72** and C7 for **73**, respectively. This is a range of 33.0 ppm. Introduction of a methoxy group into the aromatic ring produces shielding changes of 19.1 ppm (C5) and 0.8 ppm (C6), consistent with electronic influences for the C5 methoxy group of **72** and C6 methoxy group of 6-methoxy-1-indanone (**41c**). Not surprisingly, of these the largest chemical shift of the carbonyl group comes from a methoxy group at position 5 where the electron release from the methoxy group is the greatest. This is a much greater upfield shift than that of a methyl group (6.3 ppm[124]) at the same position.

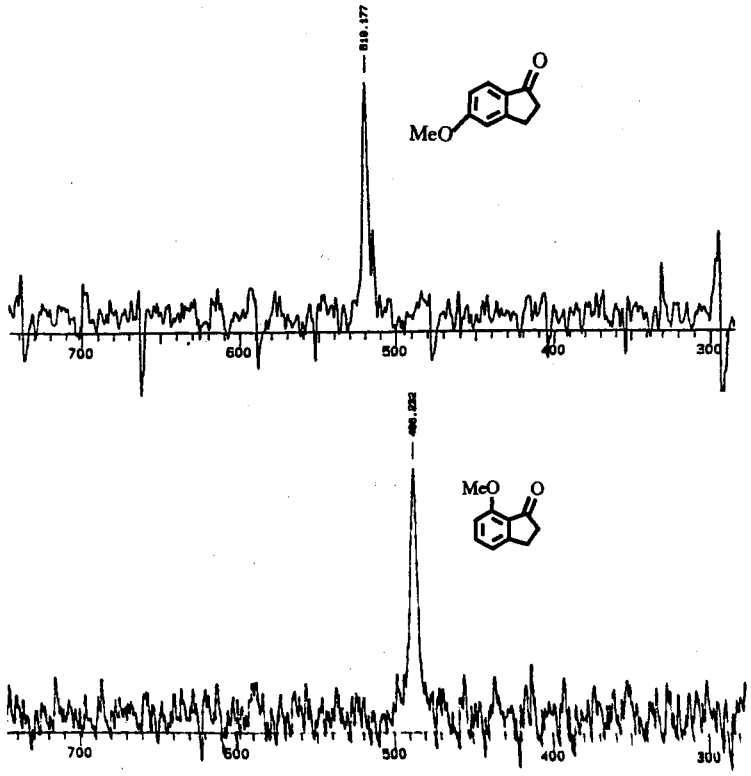
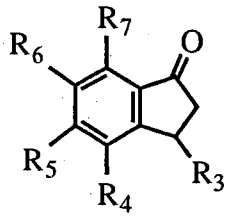


Figure 4-1. The ^{17}O NMR spectra of 5-methoxy-1-indanone (**74**) and 7-methoxy-1-indanone (**75**) in acetonitrile at 75 °C (water as external standard).

As a consequence of *ortho* and *para* arrangement of the methoxy group for the isomeric indanones 5-methoxy-1-indanone (**72**) and 7-methoxy-1-indanone (**73**), the

carbonyl groups of the two compounds are in electronically equivalent environments. Therefore, the 33.0 ppm downfield shift noted for the ^{17}O NMR signal of carbonyl of **73** relative to **72** can be confidently attributed to steric interaction. This shift is significantly greater than 21 ppm shift difference noted for the introduction of a methyl group in the 7-position of 1-indanone and very close to the 36.0 ppm shift difference observed on introduction of a *tert*-butyl group in the 7-position of 1-indanone.[124]

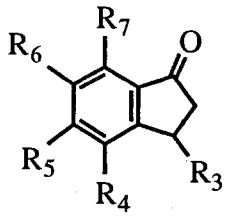
Table 4-1. ^{17}O NMR Chemical Shifts of the Carbonyl Group and Shift Increments for Mono-Substituted 1-Indanones



Indanone	R_3	R_4	R_5	R_6	R_7	δ (C=O)	Δ δ*
3	H	H	H	H	H	505.3	
68	Me	H	H	H	H	507.7	2.4
69	H	Me	H	H	H	504.8	-0.5
70	H	H	Me	H	H	499.0	-6.3
71	H	H	H	Me	H	504.1	-1.2
37	H	H	H	H	Me	520.4	15.1
41a	H	OMe	H	H	H	505.7	0.4
72	H	H	OMe	H	H	486.2	-19.1
41c	H	H	H	OMe	H	504.5	-0.8
73	H	H	H	H	OMe	519.2	13.9

*Δ δ = δ (C=O) - 505.3

Table 4-2. ^{17}O Chemical Shifts of Carbonyl Groups for Substituted 1-Indanones



Indanone	R_3	R_4	R_5	R_6	R_7	δ obs	δ calcd	$\Delta\delta$*
74	Me	OMe	H	H	Me	523.9	523.0	0.9
75b	H	Me	Me	OMe	H	495.4	497.7	-2.3
76a	H	Me	OMe	Me	H	498.2	484.5	13.7
77b	H	Me	H	OMe	Me	521.5	519.8	1.7
78b	H	H	Me	OMe	Me	515.9	513.3	2.6
79	Me	Me	H	H	OMe	523.9	521.1	2.8
63b	H	OMe	OMe	H	H	493.0	486.4	6.6
80	Me	OMe	OMe	H	Me	508.5	504.1	4.4
64b	H	OMe	H	H	OMe	521.5	519.6	1.9
67b	H	OMe	Me	OMe	H	500.2	498.6	1.6
60	H	H	OMe	OMe	H	486.1	485.4	0.7
81	Me	H	OMe	OMe	Me	504.5	502.9	1.6
61b	H	H	OMe	H	OMe	501.6	500.1	1.5
65b	H	OMe	OMe	OMe	H	497.0	485.8	11.2
66b	H	OMe	H	OMe	OMe	522.7	518.8	3.9
62b	H	H	OMe	OMe	OMe	506.5	499.3	7.2

*$\Delta\delta = \delta$obs - δcalcd

The substituent shift values seem to be additive for the 1-indanones that contain non-crowded methoxy groups such as 5,6-dimethoxy (**60**), 5,7-methoxy (**61b**), 4,7-dimethoxy (**64b**), 3,7-dimethyl-4-methoxy (**74**), and 4,7-dimethyl-6-methoxy (**77b**) as shown in Table 4-2, considering the error from the 400 MHz NMR instrument as + and - 1.0 ppm.

For substitution in the aromatic portion of the ring system, the ^{17}O NMR chemical shifts of carbonyl group may be predicted from the shift increments (Table 4-1). For example, by using additivity of substituent effects, a value of 485.4 ppm [505.3+(-19.1)+(-0.8)] is predicted for the carbonyl group of 5,6-dimethoxy-1-indanone (**60**), and 486.1 ppm is the value observed. Furthermore, additivity of substituent effects is noted when substitution occurs on both the aliphatic and aromatic portions of the ring systems. For example, the predicted value of carbonyl group for 3,7-dimethyl-4-methoxy-1-indanone (**74**) is 523.0 ppm (505.3+2.4+14.9+0.4), and the observed value is 523.9 ppm. Not unexpectedly, the prediction of ^{17}O NMR chemical shift of carbonyl group based upon additivity of substituent effect is less secure for the case in which crowded methoxy groups, especially a crowded 5-methoxy group, are involved. For example, the calculated value is 485.8 ppm for the carbonyl group of 4,5,6-trimethoxy-1-indanone (**65b**) and the observed value is 497.0 ppm. The calculated and observed ^{17}O chemical shift values for the carbonyl groups are listed in Table 4-2.

Table 4-3 shows the chemical shift values for methoxy oxygens. There is a large upfield chemical shift of the methoxy signal resulting from one and/or two *ortho* neighbors. For example, ^{17}O chemical shift value of 4-methoxy oxygen for 4-methoxy-1-indanone (**41a**) is 46.6 ppm in comparison with the value of 13.5 ppm for 4,5-dimethoxy-1-indanone (**63b**) which has an added *ortho* methoxy group. The ^{17}O chemical shift of 5-methoxy oxygen for 5-methoxy-1-indanone (**72**) is 60.9 ppm, but 53.2 ppm for 5,6-dimethoxy-1-indanone (**60**) which has one *ortho* methoxy group, 25.7 ppm for 4,6-dime-

Table 4-3. ^{17}O NMR Chemical Shifts of Methoxy Oxygens

1-Indanones	4-OMe	5-OMe	6-OMe	7-OMe
4-Methoxy (**41a**)	46.6			
5-Methoxy (**72**)		60.9		
6-Methoxy (**41c**)			49.6	
7-Methoxy (**73**)				57.6
3,7-Dimethyl-4-methoxy (74)	42.5			
4,5-Dimethyl-6-methoxy (**75b**)			48.0	
4,6-Dimethyl-5-methoxy (**76**)		25.7		
4,7-Dimethyl-6-methoxy (**77b**)			42.2	
5,7-Dimethyl-6-methoxy (**78b**)			17.2	
3,4-Dimethyl-7-methoxy (**79**)				53.7
4,5-Dimethoxy (**63b**)	13.5	48.3		
4,5-Dimethoxy-3,7-dimethyl (**80**)	11.0	47.7		
4,7-Dimethoxy (**64b**)	36.9			46.1
4,6-Dimethoxy-5-methyl (**67b**)	21.7		51.3	
5,6-Dimethoxy (**60**)		53.2	39.7	
5,6-Dimethoxy-3,7-dimethyl (**81**)		53.6	6.7	
4,5,6-Trimethoxy (**65b**)	13.5	15.6	40.5	
4,6,7-Trimethoxy (**66b**)	31.0		39.6	32.6
5,6,7-Trimethoxy (**62b**)		55.3	2.7	21.5

thyl-5-methoxy-1-indanone (**76**) which has two *ortho* methyl groups, and 15.6 ppm for 4,5,6-trimethoxy-1-indanone (**65b**) which has two *ortho* methoxy groups. For the 6-methoxy oxygen, the differences of ^{17}O chemical shifts between 6-methoxy-1-indanone

(**41c**, 49.6 ppm) and multi-substituted indanones [5,6-dimethoxy-1-indanone (**60**) 39.7 ppm, 5,7-dimethyl-6-methoxy-1-indanone (**78b**) 17.2 ppm, 5,6-dimethoxy-3,7-dimethyl-1-in-danone (**81**) 6.7 ppm, and 5,6,7-trimethoxy-1-indanone (**62b**) 2.7 ppm].are also significant. For the 7-methoxy oxygen, 57.6 ppm is the value of 7-methoxy-1-indanone (**73**). When 5,6,7-trimethoxy-1-indanone (**62b**) has one more *ortho* methoxy group, the ^{17}O chemical shift changes to 21.5 ppm. All these results suggest that ^{17}O chemical shifts can be used to help to distinguish the crowded and non-crowded methoxy groups in 1-indanones . When the methoxy group is crowded it may be out of the benzene plane and the electronic influence of the ketone carbonyl group on the methoxy group will be reduced.

Molecular mechanics calculations were carried out on the 1-indanone (**3**), 7-methyl-1-indanone (**37**) and 7-methoxy-1-indanone (**73**). The carbonyl group and the aromatic ring were found to be coplanar for **3** (0.03°) and **37** (0.23°); however, a small torsion angle rotation (2.86°) was predicted for **73**. These calculations clearly indicate that torsion angle change is not a major contributor to the large downfield shifts observed for the hindered 1-indanones. As observed in other systems,[123] the C-C=O bond angle, estimated by the MOPAC method, for the hindered compounds are flared away from the substituent in the more hindered systems; for example, compare 127.0° for **3**, 127.5° for **37** and 127.8° for **73**. These results suggest that van der Waals interactions should play an important role in determining the chemical shifts for the hindered 1-indanones.

In order to test for a relationship between repulsive van der Waals energy and ^{17}O chemical shifts it is necessary to study systems in which steric interactions with the carbonyl group is probable. Several substituted 1-indanones in Table 4-1 and 4-2 meet this requirement such as 7-methyl (**37**), 5,7-dimethoxy (**61b**), 5,6,7-trimethoxy (**62b**), 4,7-dimethoxy (**64b**), 4,6,7-trimethoxy (**66b**), 7-methoxy (**73**), 3,7-dimethyl-4-methoxy (**74**), 4,7-dimethyl-6-methoxy (**77b**), 5,7-dimethyl-6-methoxy (**78b**), 3,4-dimethyl-7-

methoxy (**79**), 4,5-dimethoxy-3,7-dimethyl (**80**), and 5,6-dimethoxy-3,7-dimethyl (**81**). However, to simplify comparisons, isomers that have substituents located at electronically equivalent positions and that do not have additional steric interactions, other than the substituent-carbonyl one, should be studied.[124] The isomeric pairs **37**, **70** and **72**, **73** in Table 4-1 meet these criteria. As noted above, downfield shifts of 21 and 33 ppm, respectively, are observed on comparison of these isomeric pairs.

Using the method previously employed by our group,[123,124] we took the difference in total van der Waals energy for the hindered and unhindered isomers (Table 4-4), for example 5-methoxy-1-indanone (**72**) and 7-methoxy-1-indanone (**73**), and correlated this energy with the chemical shift difference between the hindered compound (**73**) and the parent of the series (1-indanone **3**, 505.3 ppm). Figure 4-2 shows a plot of

Table 4-4. Estimated Local van der Waals Energy and ^{17}O Chemical Shifts of 1-Indanone Pairs

1-Indanones	van der Waals energy (kcal)	$\delta_{C=O}$ (ppm)
5-Methyl (**70**)	2.7226	499.0
7-Methyl (**37**)	3.2465	520.4
5-Methoxy (**72**)	2.9317	486.2
7-Methoxy (**73**)	3.2436	519.2
3,3-Dimethyl-5-t-butyl (**82**)	5.0427	505.0
3,3-Dimethyl-7-t-butyl (**38**)	8.1997	541.0

the data obtained from the methyl-, t-butyl- and methoxy-1-indanone pairs. This plot further demonstrates that a reasonable relationship exists between repulsive van der Waals energies and ^{17}O chemical shifts. These results provide additional support for the conclusion that repulsive van der Waals interactions are important in determining downfield NMR chemical shifts of many nuclei in hindered systems.[121,122]

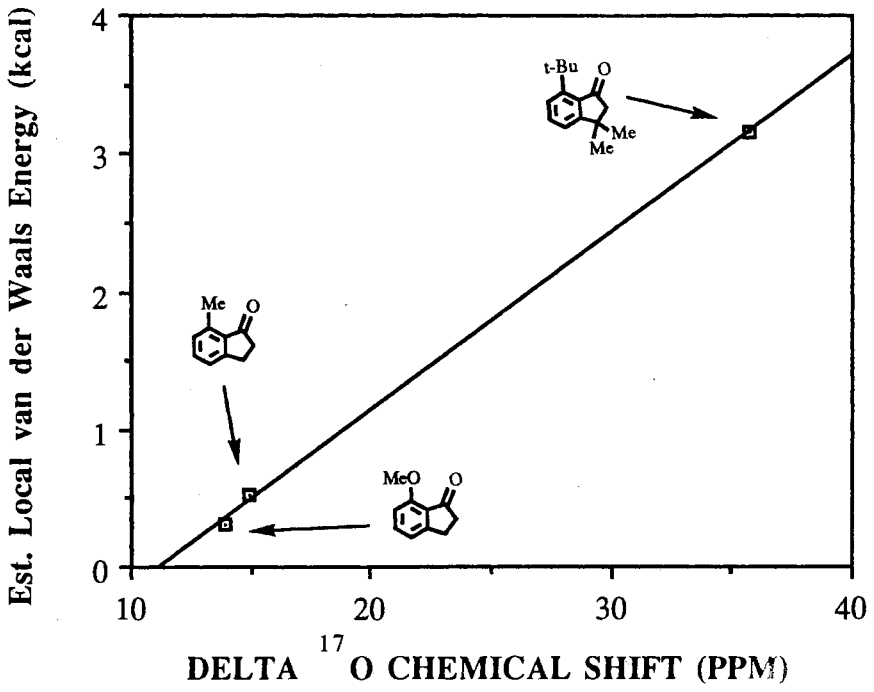


Figure 4-2. Relationship between estimated repulsive van der Waals interactions and ^{17}O chemical shift difference values.

CHAPTER V

CONCLUSIONS AND FUTURE WORK

PPA-catalyzed cyclizations of 3-(2-methoxybenzene)propanoic acid (**39a**), 3-(2,4-dimethoxybenzene)propanoic acid (**39b**), 3-(4-methoxybenzene)propanoic acid (**39c**), 4-(2-methoxybenzene)butanoic acid (**49a**), 4-(2,4-dimethoxybenzene)butanoic acid (**49b**), 4-(4-methoxybenzene)butanoic acid (**49c**) and 2-methoxybenzeneacetic acid (**55**) were investigated. It was found that in the cyclization of methoxy-substituted arylpropanoic and arylbutanoic acids in PPA, either intra- or intermolecular reaction can take place depending on the number and position of methoxy groups. Arylpropanoic acids (**39a** and **39b**) greatly favor the formation of 5,14-dimethoxy[3.3]-metacyclophane-1,10-dione (**43a**) and 5,7,14,16-tetramethoxy[3.3]metacyclophane-1,10-dione (**43b**). Arylpropanoic acid **39c** and arylbutanoic acids (**49a** and **49b**), however, form both monomeric products such as 6-methoxy-1-indanone (**41c**), 5-methoxy-1-tetralone (**51a**), and 5,7-dimethoxy-1-tetralone (**51b**) and dimeric products such as 7,16-dimethoxy[3.3]metacyclophane-1,10-dione (**43c**), 6,16-dimethoxy[4.4]metacyclophane-1,11-dione (**53a**), and 6,8,16,18-tetramethoxy[4.4]metacyclophane-1,11-dione (**53b**). For 2-methoxybenzeneacetic acid (**55**), 2-methoxy-5-(*o*-methoxybenzeneacetyl)benzeneacetic acid (**57**) was the major product and 4,12,20-trimethoxy[2.2.2]-metacyclophane-1,9,17-trione (**59**) was also obtained.

Identification of the above compounds solved a long standing question of why 3-(2-methoxybenzene)propanoic acid (**39a**) failed to give 4-methoxy-1-indanone (**41a**) in PPA[125] and why 5,7-dimethoxy-1-tetralone (**51b**) was extremely difficult to prepare from

49b.[136] This work also provides a one-step synthesis of several methoxy-substituted [3.3]metacyclophanediones and [4.4]metacyclophanediones.

Several research areas are obviously interesting for future work: First, the separation, purification and identification of polyones from the sublimation residues of 6,16-dimethoxy[4.4]metacyclophane-1,11-dione (**53a**) and 6,8,16,18-tetramethoxy[4.4]-metacyclophane-1,11-dione (**53b**) need to be investigated to obtain and study additional large ring compounds. Second, the reactions of 2,4-dimethoxybenzeneacetic acid (**83**) and 4-methoxybenzeneacetic acid (**84**) in PPA should be investigated in order to finish the arylacetic acid series and to compare the influence of the position of the methoxy group on the formation of keto acid intermediates such as 2-methoxy-5-(*o*-methoxybenzeneacetyl)-benzeneacetic acid (**57**) and cyclic polyones such as 4,12,20-trimethoxy[2.2.2]meta-cyclophane-1,9,17-trione (**59**). Third, some other arylpropanoic acids such as 3-(2-methoxybenzene)butanoic acid (**85**) and 3-(2-methoxybenzene)-3-methylbutanoic acid (**86**) could be included in the future studies to investigate how added methyl groups at C-3 would affect the cyclization of **85** and **86** in PPA. There is the possibility that repulsive interactions between methoxy and methyl groups would favor the intramolecular cyclization to form 4-methoxy-3-methyl-1-indanone (**87**) and 3,3-dimethyl-4-methoxy-1-indanone (**89**). Or if it does not go that way, two new compounds, 5,14-dimethoxy-3,12-dimethyl[3.3]metacyclophane-1,10-dione (**88**) and 5,14-dimethoxy-3,3,12,12-tetra-methyl[3.3]metacyclophane 1,10-dione (**90**) could result.

CHAPTER VI

EXPERIMENTAL SECTION

Procedures for NMR and MS Studies. ^{1}H NMR and ^{13}C NMR spectra were measured on a Varian XL-300 NMR spectrometer at 300 and 75 MHz. Chemical shifts were reported in ppm or δ values downfield from TMS using $CDCl_3$ as solvent. ^{17}O NMR were run on a Varian XL-400 NMR spectrometer at 54 MHz equiped with a 10 mm broad band probe at 75 ^{o}C. The molar concentration of sample was held constant at 0.5 M (1.5 x molecular weight mg in 3 mL anhydrous CH_3CN). Chemical shifts are reported downfield from water as an external reference with instrument settings of SW=44052.9 Hz, AT=0.023 sec, PW=40 μsec, D1=0 sec, and CT=40000-132329. Liquid secondary ion mass spectrometry (LSIMS) analyses were performed on a VG Analytical ZAB2-SE high resolution mass spectrometer tuned to a resolution of 1000 (FWHM definition) and operated at 8 KV accelerating voltage with acesium ion gun at a potential of 35 KV. Data were acquired over the mass range of 100-1000 using a scan time of 15 seconds. The matrix consisted of thioglycerol with 1% trifluoroacetic acid. The high resolution mass spectrometry (HRMS) analyses were also performed on VG Analytical ZAB2-SE mass spectrometer. The HRMS employed an electron energy of 70 eV and a 80 KV accelerating potential. The instrument was tuned to a resolution of 10000 (FWHM) and data were acquired over the range of 50-500 Daltons at 15 sec/scan. Direct-probe (DP) electron impact (EI) MS data were obtained using a VG Analytical TS-250 mass spectrometer operating at 4 KV accelerating potential and 70 eV electron energy. The

instrument was tuned to 500 resolution (FWHM) and acquisition was at 2 sec/scan from 50-500 Daltons.

Reactions With PPA Using a Waring Blendor. PPA (500g, Stauffer Chemical Co.) was weighed into a 1-qt, water-jacketed, stainless-steel, Waring Blendor vessel attached, using a size-reduction adapter, to a 3 hp Waring Blendor base.[130] Stirring was initiated cautiously at low speed setting of the Blendor and further controlled with an auxilliary 20 amp Variac. The voltage was gradually increased to 70 V and held at this voltage until the temperature of the PPA rose to about 50 °C. A test run with PPA alone showed that stirring friction warms the PPA. Cooling water was passed through the base of the vessel, as needed, to aid in maintaining the selected reaction temperature and to protect the bearing of the impeller. The acid for cyclization (2 g or 5 g) was added in portions during 1-2 min and the voltage was reduced (to 50-60 V) to maintain a reaction temperature of 70-80 °C. Stirring was continued for 30 min (except for one 60 min run of **42**) and color changes from pale yellow to orange or red were observed. As expected, darker colors are observed at higher temperatures. The stirrer was stopped, crushed ice was added until the vessel was at least 3/4 full. Stirring was cautiously resumed to hydrolyze the PPA with more ice added as needed. The hydrolyzed mixture was transferred to a large (at least 5 L) separatory funnel and 3-4 L of water was added. The products were extracted (CH_2Cl_2, 4 x 500 mL) and the combined extracts were washed with water (3 x 500 mL) and then brine (500 mL). The water layer was neutralized with sodium carbonate or alkali before disposal. The dried ($MgSO_4$) extract was distilled to recover CH_2Cl_2. The residue, on stream distillation and extraction, gave the 1-indanone products **41a** and **41c** in Schemes 2-1, 2-2. The pot residue from steam distillation was disolved in CH_2Cl_2, extracted repeatedly with saturated $NaHCO_3$ solution to remove keto acid, dried, and stripped of solvent to yield the nonvolatile products shown in Schemes 2-1

and 2-2. The bicarbonate extract was acidified and the precipitated **42c** was isolated by extraction with CH_2Cl_2.

For the larger cycliacylation runs, it was convenient to filter the reaction mixture through a bed of filter aid (Dicalite or Celite) and wash the filter cake thoroughly with water and with saturated $NaHCO_3$ solution. If keto acid or starting acid is present, the product and Dicalite are first thoroughly mixed with saturated $NaHCO_3$ solution in a blender. The filter cake, dried under an infrared heat lamp and then under vacuum, was extracted with CH_2Cl_2 in a modified Soxhlet extractor to obtain the neutral product(s).

Procedure for Wolff-Kishner Reduction of 43a and 43c to 44a, 43b to 44b, and 45 to 46. These reductions were carried out following an earlier procedure[133] using a small-scale version of a stainless-steel vessel and stainless-steel condenser. The samples of **43a**, **43b**, **43c** and **45** (1.77, 2.19, 1.73 and 0.93 g), diethylene glycol (250 mL), KOH (10 g) and hydrazine hydrate (25 ml) were added and the reduction mixture was heated at reflux under a nitrogen atmosphere for 60 min. The products were isolated and remethylated[134] using dimethyl sulfate (2.5, 5.3, 3.0 and 3.0 mL), sodium hydroxide (0.80, 1.68, 0.80 and 1.0 g), tetrabutylammonium bromide (0.43, 0.90, 0.43 and 0.50 g), water (10 mL) in refluxing CH_2Cl_2 (100 mL) to give **44a**, **44b**, and **46**. The yields are given below.

Single Crystal X-ray Diffraction. Single crystals of **43a** (0.15 x 0.15 x 0.17 mm) and **44b** (0.15 x 0.20 x 0.20 mm), grown from acetonitrile, were mounted on a Syntex P3 automated diffractometer. Unit cell dimentions were determined by least squares refinement of the best angular positions for 15 independent reflections ($2q>20^o$) during normal alignment procedures using molybdenum radiation (l=71069 Å). Data [1031, **43a**, and 5081, **44b**, independent points after removal of redundant (**43a** and **44b**) and space group forbidden data, **43a**] were collected at room temperature using a variable scan rate, a q-2q scan mode and a scan width of 1.2^o below Ka_1 and 1.2^o above

Ka_2 to a maximum 2q value of 45.0°. Backgrounds were measured at each side of the scan for a combined time equal to the total scan time. The intensities of three standard reflections were remeasured after every 97 reflections. As the intensities of these reflections showed less than 5% variation, corrections for decomposition were deemed unnecessary. Data were corrected for Lorentz, polarization, centering, and background effects. Observed reflections [676, **43a**, and 2164, **44b**, points (I>3.0 s I)] were used for solution of carbon and oxygen positions by direct methods using MULTAN80. Refinment of scale factor, positional, and anisotropic thermal parameters for these atoms were carried out to convergence. Hydrogen atoms were located from a difference Fourier synthesis. Hydrogen positional parameters with fixed isotropic thermal parameters were included in final cycles of least squares refinement but not subjected to refinement. Final refinement [function minmized,] led to a final factor, R = 4.8% **43a** and 7.6% **44b**. Scattering factors were taken from Cromer and Mann. In the final stage of refinement, a weight of 1/s (F) was used. Rw= 6.2%, **43a** and 9.6% **44b**.

4-Methoxy-1-indanone (41a): mp 104.5-105.5 °C (lit.[131] 102-103 °C); ^{1}H NMR δ 2.66 (m, 2 H), 3.02 (m, 2 H), 3.90 (s, 3 H), 7.02 (m, 1 H), 7.33 (m, 2 H,); ^{13}C NMR δ 22.51, 36.13, 55.45, 114.73, 115.27, 128.83, 138.61, 144.05, 157.09, 207.19; ^{17}O NMR (CH_3CN) δ 46.6 (OMe), 505.7 (CO).

6-Methoxy-1-indanone (41c):[138] ^{1}H NMR δ 2.72 (m, 2 H), 3.07 (m, 2 H), 3.83 (s, 3 H), 7.18 (m, 2 H), 7.37 (d, 1 H, *J* = 9.0 Hz); ^{13}C NMR δ 25.11, 36.99, 55.58, 104.88, 124.02, 127.36, 138.22, 147.98, 159.36, 207.03; ^{17}O NMR (CH_3CN) δ 49.6 (OMe), 504.5 (CO).

***p*-Methoxy-3-(*p*-methoxyhydrocinnamoyl)hydrocinnamic acid (42c):** 0.67 g (14%) from 5.0 g of **39c** in 500 g PPA; mp 121.5-122.5 °C (lit.[127] 119-120.5 °C); ^{1}H NMR δ 2.66 (t, 2 H, *J* = 8.1 Hz), 2.93 (m, 4 H), 3.26 (t, 2 H, *J* = 8.1 Hz), 3.78 (s, 3 H), 3.85 (s, 3 H), 6.87 (m,3 H), 7.16 (d, 2 H, *J* = 8.4 Hz), 7.32 (dd, 1 H, *J* = 8.4,

2.4 Hz), 7.51 (d,1 H, J = 2.4 Hz), 10.86 (s, 1 H); ^{13}C NMR δ 29.52, 29.67, 35.60, 45.72, 55.27, 55.62, 111.79, 113.84, 128.20, 129.39, 130.03, 132.39, 133.35, 133.74, 157.24, 157.83, 178.76, 202.01; HRMS (+EI) calcd for $C_{20}H_{22}O_5$ 342.1467, found 342.1467; EIMS m/z (rel. intensity) 342 (30), 269 (17), 207 (100), 134 (10), 121 (60); Anal. calcd: C, 70.16; H, 6.48. Found: C,70.16; H, 6.51.

5,14-Dimethoxy[3.3]metacyclophane-1,10-dione (43a): 0.83 g (46%) from 2.0 g of **39a** in 500 g PPA; mp 234-235 °C; ^{1}H NMR δ 2.96 (broad s, 8 H), 3.82 (s, 6 H), 6.59 (d, 2 H, J = 8.4 Hz), 6.89 (d, 2 H, J = 2.1 Hz), 7.38 (dd, 2 H, J = 8.4, 2.1 Hz); ^{13}C NMR δ 27.75, 40.36, 55.59, 109.89, 127.69, 128.25, 132.05, 134.45, 160.14, 203.34; HRMS (+EI) calcd for $C_{20}H_{20}O_4$ 324.1362, found 324.1533; EIMS m/z (rel. intensity) 324 (100), 295 (5), 161 (76), 145 (17), 91 (10); Anal. calcd: C, 74.05; H, 6.22. Found: C, 74.34; H, 6.37.

5,7,14,16-Tetramethoxy[3.3]metacyclophane-1,10-dione (43b): 0.90 g (49%) from 2.0 g of **39b**; mp 279-280 °C; ^{1}H NMR δ 2.83 (t, 4 H, J = 6.3 Hz), 3.05 (m, 4 H), 3.76 (s, 6 H), 3.82 (s, 6 H), 6.08 (s, 2 H), 6.49 (s, 2 H); ^{13}C NMR δ 29.13, 41.25, 55.46, 55.79, 94.40, 120.06, 124.30, 135.25, 158.30, 160.51, 206.42; HRMS (+EI) calcd for $C_{22}H_{24}O_6$ 384.1573, found 384.1566; EIMS m/z (rel. intensity) 384 (100), 355 (10), 191 (41), 164 (), 91 (5); Anal. calcd: C, 68.73; H, 6.29. Found: C, 68.44; H, 6.02.

7,16-Dimethoxy[3.3]metacyclophane-1,10-dione (43c): 0.60 g (14%) from 5.0 g of **39c** in 500 g PPA; mp 181-182 °C; ^{1}H NMR δ 2.84 (t, 4 H, J = 6.5 Hz), 3.04 (t, 4 H, J = 6.5 Hz), 3.76 (s, 6 H), 6.35 (d, 2 H, J = 2.4 Hz), 6.60 (d, 2 H, J = 8.4 Hz), 7.07 (dd, 2 H, J = 8.4, 2.4 Hz); ^{13}C NMR δ 33.14, 44.11, 55.63, 111.23, 131.27, 131.53, 131.86, 132.79, 155.88, 207.06; HRMS (+EI) calcd for $C_{20}H_{20}O_4$ 324.1360, found 324.1360; EIMS m/z (rel. intensity) 324 (100), 295 (5), 161 (55), 149 (15), 90 (15); Anal. calcd for C, 74.05; H, 6.22. Found: C, 74.40; H, 6.30.

5,14-Dimethoxy[3.3]metacyclophane (44a): 1.15 g (70%) from 1.77 g of **43a**, 1.05 g (65%) from 1.73 g of **43c**; mp 136-137 °C; ^{1}H NMR δ 2.02 (m, 2 H), 2.65 (m, 8 H), 3.27 (s, 6 H), 6.32 (d, 2 H, J = 8.1 Hz), 6.63 (dd, 2 H, J = 8.1, 2.1 Hz), 6.72 (d, 2 H, J = 2.1 Hz); ^{13}C NMR δ 27.98, 31.98, 35.86, 55.35, 110.16, 125.94, 128.00, 132.77, 135.80, 154.97; HRMS (+EI) calcd for $C_{20}H_{24}O_2$ 296.1776, found 296.1793; EIMS m/z (rel. intensity) 296 (100), 161 (15), 147 (30), 135 (15), 121 (11); Anal. calcd: C, 81.04; H, 8.16. Found: C, 81.05; H, 8.32.

5,7,14,16-Tetramethoxy[3.3]metacyclophane (44b): 1.25 g (88%) from 2.19 g of **43b**; mp 200-201 °C; ^{1}H NMR δ 2.01 (m, 4 H), 2.65 (broad s, 8 H), 3.68 (s, 12 H), 6.01 (s, 2 H), 6.64 (s, 2 H); ^{13}C NMR δ 25.14, 31.80, 55.51, 95.26, 120.55, 137.08, 155.98; HRMS (+EI) calcd for $C_{22}H_{26}O_4$ 356.1988, found 356.2016; EIMS m/z (rel. intensity) 356 (100), 191 (5), 177 (10), 165 (15), 91 (8); Anal. calcd: C, 74.13; H, 7.92. Found: C, 73.93; H, 7.83.

5,7,14,16,23,25-Hexamethoxy[3.3.3]metacyclophane-1,10,18-trione (45): 0.19 g (10%) from 2.0 g of **39b**; mp 236-237 °C; ^{1}H NMR δ 2.91 (t, 6 H, J = 6.2 Hz), 3.22 (m, 6 H), 3.90 (s, 18 H), 6.37 (s, 3 H), 7.27 (s, 3 H); ^{13}C NMR δ 23.21, 41.96, 55.48, 55.61, 94.39, 119.98, 121.92, 131.30, 159.09, 161.88, 199.53; +LSIMS calcd for $C_{33}H_{36}O_9$ 576, found M+H 577.

5,7,14,16,23,25-Hexamethoxy[3.3.3]metacyclophane (46): 0.73 g (84%) crude yield from 0.93 g of **45**, 52% yield after extraction through acidic/basic alumina with toluene; mp 144-146 °C; ^{1}H NMR δ 1.97 (m, 6 H), 2.55 (t, 12 H, J = 7.6 Hz), 3.84 (s, 18 H), 6.46 (s, 3 H), 7.02 (s, 3 H); ^{13}C NMR δ 27.29, 30.16, 55.73, 95.64, 122.20, 130.71, 156.32; HRMS (+EI) calcd for $C_{33}H_{42}O_6$ 534.2981, found 534.2977; EIMS m/z (rel. intensity) 534 (10), 296 (20), 202 (45), 69 (68), 57 (100); Anal. calcd: C, 74.13; H, 7.92. Found: C, 74.28; H, 7.92.

5,14-Dihydroxy[3.3]metacyclophane (47): 3.4 g (82%) from 5.0 g of **43a**; mp 183-185 °C; ^{1}H NMR δ 2.03 (m, 4 H), 2.67 (m, 8 H), 6.26 (d, 2 H, *J* = 8.1 Hz), 6.61 (dd, 2 H, *J* = 8.1, 2.1 Hz), 6.77 (d, 2 H, *J* =2.1 Hz); ^{13}C NMR δ 27.87, 31.90, 35.99, 114.33, 125.39, 126.12, 132.82, 136.17, 150.68; HRMS (+EI) calcd. for $C_{18}H_{20}O_2$ 268.1463, found 268.1463; EIMS m/z (rel. intensity) 268 (100), 147 (20), 134 (46), 122 (25), 91 (17).

5,14-Diacetoxy[3.3]metacyclophane (48): 0.25 g (96%) crude yield from 0.20 g of **47**, 91% yield after extraction through neutral alumina with ether; mp 128-129 °C; ^{1}H NMR δ 2.00 (m, 4 H), 2.24 (s, 6 H), 2.62 (t, 4 H, *J* = 5.4 Hz), 2.69 (t, 4. H, *J* = 5.4 Hz), 6.54 (d, 2 H, *J* = 8.4 Hz), 6.72 (dd, 2 H, *J* = 8.4, 2.1), 6.79 (d, 2 H, *J* = 2.1 Hz); ^{13}C NMR δ 20.92, 27.76, 32.09, 35.89, 121.46, 126.74, 130.96, 136.04, 137.84, 146.41, 169.34; HRMS (+EI) calcd. for $C_{22}H_{24}O_4$ 352.1664, found 352.1659; EIMS m/z (rel. intensity) 352 (17), 310 (40), 268 (100), 134 (25), 84 (25).

5-Methoxy-1-tetralone (51a): 0.48 g (28%) from 2.0 g of **49a** in 500 g PPA; m p 89.5-90.5 °C (85-90 °C from Aldrich); ^{1}H NMR δ 2.11 (m, 2 H), 2.63 (m, 2 H), 2.9 (t, 2 H, *J* = 6.3), 3.87 (s, 3 H), 7.02 (d, 1 H, *J* = 7.5 Hz), 7.27 (t, 1 H, *J* = 7.8 Hz), 7.66 (d, 1 H, *J* = 6.9 Hz); ^{13}C NMR δ 22.55, 22.81, 38.85, 55.69, 114.25, 118.76, 126.72, 133.55, 133.65, 156.77, 198.68; HRMS (+EI) calcd. for $C_{11}H_{15}O_2$ 176.0837, found 176.0836; EIMS m/z (rel. intensity) 176 (100), 161 (17), 148(37), 120(28), 90(26).

5,7-Dimethoxy-1-tetralone (51b): 0.38 g (20%) crude yield from 2.0 g of **49b** in 500 g PPA, 14% yield after extraction through neutral alumina with light petrulium ether; mp 70.5-71 °C (lit.[136] bp 167 °C/0.01mm); ^{1}H NMR δ 2.08 (pent, 2 H, *J* = 6.3 Hz), 2.62 (t, 2 H, *J* = 6.3 Hz), 2.81 (t, 2 H, *J* = 6.3 Hz), 6.62 (d, 1 H, *J* = 2.4 Hz), 7.13 (d, 1 H, *J* = 2.4 Hz); ^{13}C NMR δ 22.39, 22.74, 38.95, 55.56, 55.70, 99.75, 103.99,

127.05, 133.84, 157.88, 158.77, 198.61; HRMS (+EI) calcd for $C_{12}H_{14}O_3$ 206.0943, found 206.0945.

6,16-Dimethoxy[4.4]metacyclophane-1,11-dione (53a): 0.53 g (30%) from 2.0 g of **49a** in 500 g PPA; m p 255-256 °C; ^{1}H NMR δ 2.21 (m, 4 H), 2.66 (m, 8 H), 3.92 (s, 9 H), 6.97 (d, 2 H, *J* = 8.7 Hz), 7.53 (d, 2 H, *J* = 2.4 Hz), 8.00 (dd, 2 H, J = 8.7, 2.4 Hz); ^{13}C NMR δ 24.37, 28.82, 34.10, 55.61, 110.74, 128.21, 128.88, 129.24, 132.22, 161.93, 200.92; RHMS (+EI) calcd. for $C_{22}H_{24}O_4$ 352.1674, found 352.1674; EIMS m/z (rel. intensity) 352 (36), 176 (100), 162 (11), 151 (10), 113 (8).

6,8,16,18-Tetramethoxy[4.4]metacyclophane-1,11-dione (53b): 1.0 g (54%) from 2.0 g of **49b** in 500 g PPA; mp 306-308 °C; ^{1}H NMR δ 2.11 (m, 4 H), 2.56 (m, 4 H), 2.87 (m, 4 H,), 3.89 (s, 6 H), 3.91 (s, 6 H), 6.36 (s, 2 H), 6.78 (s, 2 H); ^{13}C NMR δ 24.29, 29.41, 43.11, 55.48, 55.53, 55.56, 55.62, 94.55, 94.60, 120.56, 121.80, 132.44, 158.92, 161.71, 202.01, 202.75; HRMS (+EI) calcd. for $C_{24}H_{28}O_6$ 412.1886, found 412.1892; EIMS m/z (rel. intensity) 412 (40), 206 (100), 191 (27), 151 (25) 57(37).

6,16-Dimethoxy[4.4]metacyclophane (54a): 0.71 g (88%) from 0.90 g of **53a**; m p 148-150 °C; ^{1}H NMR δ 1.51 (m, 8 H), 2.49 (m, 4 H), 2.64 (m, 4 H), 3.79 (s, 6 H), 6.12 (d, 2 H, *J* = 2.1 Hz), 6.71 (d, 2 H, *J* = 8.1 Hz), 6.89 (dd, 2 H, *J* = 8.1, 2.1 Hz); ^{13}C NMR δ 26.17, 26.40, 27.85, 33.91, 55.64, 109.71, 127.31, 127.97, 130.16, 133.94, 156.02; HRMS (+EI) calcd. for $C_{22}H_{28}O_2$ 324.2089, found 324.2089; EIMS (rel. intensity) 324 (60), 162 (100), 147 (30), 134 (52), 91 (32).

6,8,16,18-Tetramethoxy[4.4]metacyclophane (54b): 0.39 g (90%) from 0.50 g of **53b**; mp 172-174 °C; ^{1}H NMR δ 1.54 (s, broad, 8 H), 2.54 (s, broad, 8 H), 3.81 (s, 12 H), 6.42 (s, 2 H), 6.59 (s, 2 H); ^{13}C NMR δ 26.39, 26.77, 55.91, 95.54, 122.03, 129.75, 156.33; HRMS (+EI) calcd. for $C_{24}H_{32}O_4$ 384.2300, found 384.2300; EIMS m/z (rel. intensity) 384 (10), 270 (25), 97 (30), 71 (64), 57 (100).

2-Methoxy-5-(*o*-methoxybenzeneacetyl)benzeneacetic acid (57): 1.1 g (58%) from 2.0 g of **55** in 500 g PPA; mp 165-166 °C; ^{1}H NMR δ 3.69 (s, 2 H), 3.78 (s, 3 H), 3.88 (s, 3 H), 4.22 (s, 2 H), 6.89 (m, 3 H), 7.21 (m, 2 H), 7.92 (d, 1 H, *J* = 2.1 Hz), 8.02 (dd, 1 H, *J* =8.7, 2.4 Hz); ^{13}C NMR δ 35.67, 39.57, 55.39, 55.81, 109.92, 110.57, 120.65, 122.51, 123.89, 128.28, 129.81, 130.42, 130.98, 131.75, 157.13, 161.31, 176.53, 196.46; HRMS (+EI) calcd. for $C_{18}H_{18}O_5$ 314.1154, found 314.1153; EIMS m/z (rel. intensity) 314 (15), 193 (100), 149 (12), 91 (24), 77 (12).

4,12,20-Trimethoxy[2.2.2]metacyclophane-1,9,17-trione (59): 0.20 g (10%) from 2.0 g of **55** in 500 g PPA; mp 219-220 °C; ^{1}H NMR δ 3.85 (s, 9 H), 4.03 (s, 6 H), 6.87 (d, 2 H, *J* = 8.7 Hz), 7.54 (d, 2 H, *J* = 2.1 Hz), 7.79 (dd, 2 H, *J* = 8.7, 2.1 Hz); ^{13}C NMR δ 41.59, 55.77, 110.97, 124.09, 129.65, 129.90, 132.06, 161.25, 196.94; +LSIMS calcd. for $C_{27}H_{24}O_6$ 444, found M+H 445.

5,6-Dimethoxy-1-indanone (60):[138] ^{1}H NMR δ 2.66 (m, 2 H), 3.05 (m, 2 H), 3.91 (s, 3 H), 3.97 (s, 3 H), 6.90 (s, 1 H), 7.17 (s, 1 H); ^{13}C NMR δ 25.57, 36.51, 56.06, 56.21, 104.11, 107.50, 129.86, 149.35, 150.43, 155.38, 205.68; ^{17}O NMR (CH_3CN) δ 39.7 (OMe), 53.2 (OMe), 486.1 (CO).

5,7-Dimethoxy-1-indanone (61b): mp 98-99 °C (lit.[139] 98-99 °C); ^{1}H NMR δ 2.65 (t, 2 H), 3.03 (t, 2 H), 3.88 (s, 3 H), 3.91 (s, 3 H), 6.31 (s, 1 H), 6.49 (s, 1 H); ^{13}C NMR δ 25.94, 36.95, 55.73, 55.77, 97.41, 101.64, 119.44, 159.36, 160.46, 166.96, 203.16; ^{17}ONMR (CH_3CN) δ 62.3 (OMe), 501.6 (CO).

5,6,7-Trimethoxy-1-indanone (62b): mp 111-112 °C (lit.[20] 111-113 °C); ^{1}H NMR δ 2.65 (m, 2 H), 3.03 (m, 2 H), 3.85 (s, 3 H), 3.95 (s, 3 H), 4.04 (s, 3 H), 6.69 (s, 1 H); ^{13}C NMR δ 25.70, 37.21, 56.28, 61.38, 61.92, 103.81, 122.86, 140.66, 151.54, 153.26, 159.69, 203.10; ^{17}O NMR (CH_3CN) δ 2.7 (OMe), 21.5 (CO), 55.3 (OMe), 506.5 (CO).

4,5-Dimethoxy-1-indanone (63b): mp 73-74.5 °C (lit.[20] 74-75 °C); ^{1}H NMR δ 2.66 (m, 2 H), 3.10 (m, 2 H), 3.92 (s, 3 H), 3.95 (s, 3 H), 6.97 (d, 1H, *J* = 8.4 Hz), 7.50 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR δ 22.48, 36.41, 56.23, 60.32, 112.30, 120.13, 131.15, 145.44, 147.87, 157.53, 205.39; ^{17}O NMR (CH_3CN) δ 13.5 (OMe), 48.3 (OMe), 493.0 (CO).

4,7-Dimethoxy-1-indanone (64b): mp 124.5-125 °C (lit.[140] 124.5-125 °C); ^{1}H NMR δ 2.66 (m, 2 H), 2.98 (m, 2 H), 3.85 (s, 3 H), 3.90 (s, 3 H), 6.73 (d, 2 H, *J* = 8.7 Hz), 6.98 (d, 2 H, *J* = 8.7 Hz); ^{13}C NMR δ 22.26, 36.74, 55.80, 55.97, 109.37, 116.52, 126.26, 145.96, 150.41, 151.73, 205.03; ^{17}O NMR (CH_3CN) δ 36.9 (OMe), 46.1 (OMe), 521.5 (CO).

4,5,6-Trimethoxy-1-indanone (65b): mp 82-84 °C (lit.[141] 80-81 °C); ^{1}H NMR δ 2.66 (m, 2 H), 3.05 (m, 2 H), 3.89 (s, 3 H,), 3.96 (s, 3 H), 3.97 (s, 3 H), 7.03 (s, 1 H); ^{13}C NMR δ 22.40, 36.14, 56.23, 60.60, 61.08, 100.60, 132.53, 141.56, 147.64, 150.04, 154.24, 205.96; ^{17}O NMR (CH_3CN) δ 13.5 (OMe), 15.6 (OMe), 40.5 (OMe), 497.0 (CO).

4,6,7-Trimethoxy-1-indanone (66b): mp 124.5-125 °C; ^{1}H NMR δ 2.64 (m, 2 H), 2.90 (m, 2 H), 3.87 (s, 3 H), 3.89 (s, 3 H), 3.91 (s, 3 H), 6.73 (s, 1 H); ^{13}C NMR δ 21.43, 37.03, 55.75, 57.22, 61.72, 103.33, 130.25, 135.73, 140.12, 152.10, 152.32, 204.69; ^{17}O NMR (CH_3CN) δ 31.0 (OMe), 39.6 (OMe), 522.7 (CO); HRMS (+EI) calcd for $C_{12}H_{14}O_4$ 222.0892, found 222.0895; Anal. calcd: C, 64.85; H, 6.30. Found: C, 64.85; H, 6.30.

4,6-Dimethoxy-5-methyl-1-indanone (67b): mp 99-101 °C (lit.[49] 99-101 °C); ^{1}H NMR δ 2.22 (s, 3 H), 2.69 (t, 2 H), 3.10 (t, 2 H), 3.58 (s, 3 H), 3.86 (s, 3 H), 6.98 (s, 1 H); ^{13}C NMR δ 9.79, 22.72, 36.33, 55.90, 60.08, 99.17, 127.67, 136.36, 139.98, 155.87, 158.94, 206.57; ^{17}O NMR (CH_3CN) δ 21.7 (OMe), 51.3 (OMe), 500.2 (CO).

5-Methoxy-1-indanone (72):[138] ^{1}H NMR δ 2.67 (m, 2 H), 3.09 (m, 2 H), 3.88 (s, 3 H), 6.90 (m, 2 H), 7.69 (d, 1 H, J = 9 Hz); ^{13}C NMR δ 25.87, 36.43, 55.63, 109.73, 115.28, 125.32, 130.42, 158.18, 165.24, 205.30; ^{17}O NMR (CH_3CN) δ 60.9 (OMe), 486.2(CO).

7-Methoxy-1-indanone (73): mp °C (lit. [137] 102-103 °C); ^{1}H NMR δ 2.67 (m, 2 H), 3.08 (m, 2 H), 3.95 (s, 3 H), 6.78 (d, 1H,J = 8.1 Hz), 7.01 (δ, 1H, J = 7.5 Hz), 7.52 (t, 1H,J = 8.1 Hz); ^{13}C NMR δ 25.56, 29.71, 36.76, 55.75, 108.80, 118.45, 125.21, 136.39, 157.97, 158.16, 204.85; ^{17}O NMR (CH_3CN) δ 57.6 (OMe), 519.2 (CO).

3,7-Dimethyl-4-methoxy-1-indanone (74): mp 48-50 °C (lit.[49] 48-50 °C); ^{1}H NMR δ 1.35 (d, 3 H, J = 7.2 Hz), 2.25 (dd, 1 H, J = 18.9, 2.1 Hz), 2.54 (s, 3 H), 2.87 (dd, 1 H, J = 18.9, 7.8 Hz), 3.45 (m, 1 H), 3.86 (s, 3 H), 6.91 (δ, 1 H, J = 8.4 Hz), 7.04 (d, 1 H, J = 8.1 Hz); ^{13}C NMR δ 17.50, 20.67, 30.18, 46.06, 55.37, 115.15, 129.58, 130.29, 134.94, 148.74, 155.22, 207.80; ^{17}O NMR δ 42.5 (OMe), 523.9 (CO).

4,5-Dimethyl-6-methoxy-1-indanone (75b): mp 142-144 °C (lit.[49] 142-144 °C); ^{1}H NMR δ 2.22 (s, 3 H), 2.24 (s, 3 H), 2.66 (t, 2 H), 2.93 (t, 2 H), 3.84 (s, 3 H), 7.03 (s, 1 H); ^{13}C NMR δ 12.67, 14.97, 24.66, 36.44, 55.64, 100.62, 133.54, 134.82, 134.88, 147.45, 157.65, 207.35; ^{17}ON MR (CH_3CN) δ 48.0 (OMe), 495.4 (CO).

4,6-Dimethyl-5-methoxy-1-indanone (76): mp 102.5-103 °C; ^{1}H NMR δ 2.27 (s, 3 H), 2.32 (s, 3 H), 2.68 (m, 2 H), 2.97 (m, 2 H), 3.77 (s, 3 H), 7.48 (s, 1 H); ^{13}C NMR δ 11.61, 16.46, 24.63, 36.48, 59.90, 123.38, 128.17, 131.16, 132.66, 154.48, 162.39, 206.47; ^{17}O NMR δ 25.7 (OMe), 497.4 (CO); HRMS (+EI) calcd. for $C_{12}H_{14}O_2$ 190.0994, found 190.0990.

4,7-Dimethyl-6-methoxy-1-indanone (77b): mp 163-164 °C (lit.[49] 162-164 °C); ^{1}H NMR δ 2.31 (s, 3 H), 2.50 (s, 3 H), 2.66 (t, 2 H), 2.88 (t, 2 H), 3.84 (s, 3 H),

6.92 (s, 1 H); ^{13}C NMR δ 9.65, 17.91, 23.23, 37.44, 56.37, 117.73, 123.89, 132.89, 134.84, 146.25, 156.83, 208.76; ^{17}ONMR (CH_3CN) δ 42.2 (OMe), 521.5 (CO).

5,7-Dimethyl-6-methoxy-1-indanone (78b): mp 73.5-74.5 °C; ^{1}H NMR δ 2.35 (s, 3 H), 2.58 (s, 3 H), 2.65 (t, 2 H), 2.99 (t, 2 H), 3.71 (s, 3 H), 7.10 (s, 1 H); ^{13}C NMR δ 10.90, 17.16, 24.67, 37.44, 60.08, 125.86, 130.83, 133.92, 138.57, 151.53, 156.26, 207.65; ^{17}O NMR (CH_3CN) δ 17.2 (OMe), 515.9 (CO); HRMS (+EI) calcd for $C_{12}H_{14}O_2$ 190.0994, found 190.0992); Anal. calcd: C, 75.76; H, 7.42. Found: C, 75.91; H, 7.42.

3,4-Dimethyl-7-methoxy-1-indanone (79): mp 76-77 °C(lit.[61] 77 °C); ^{1}H NMR δ 1.30 (d, 3 H, J = 7.2 Hz), 2.27 (dd, 1 H, J = 17.1, 1.5 Hz), 2.33 (s, 3 H), 2.91 (dd, 1 H, J = 18.6, 7.8 Hz), 3.41 (m, 1 H), 3.92 (s, 3 H), 6.73 (d, 1 H, J = 8.4 Hz), 7.32 (d, 1 H, J = 8.1 Hz); ^{13}C NMR δ 17.17, 21.31, 31.84, 46.49, 55.71, 109.23, 123.87, 126.57, 137.71, 156.13, 160.50, 204.74; ^{17}O NMR (CH_3CN) δ 53.7 (OMe), 523.9 (CO).

4,5-Dimethoxy-3,7-dimethyl-1-indanone (80): mp 64.5-65.5 °C; ^{1}H NMR δ 1.39 (d, 3 H, J = 7.2 Hz), 2.24 (dd, 1 H, J = 18.9, 2.7 Hz), 2.59 (s, 3 H), 2.88 (dd, 1 H, J = 18.6, 7.8 Hz), 3.48 (m, 1 H), 3.88 (s, 3 H), 3.93 (s, 3 H), 6.68 (s, 1 H); ^{13}C NMR δ 18.27, 21.33, 30.23, 46.47, 56.05, 60.57, 114.05, 127.57, 135.45, 143.69, 152.98, 157.10, 205.79; ^{17}O NMR (CH_3CN) δ 11.0 (OMe), 47.7 (OMe), 508.5 (CO); HRMS (+EI) calcd for $C_{13}H_{16}O_3$ 220.1100, found 220.1095; Anal calcd: C, 70.89; H, 7.32. Found: C, 70.52; H, 7.21.

5,6-Dimethoxy-3,7-dimethyl-1-indanone (81): mp 72-73 °C; ^{1}H NMR δ 1.36 (d, 3H, J = 7.2 Hz), 2.22 (dd, 1 H, J = 18.6, 3.3 Hz), 2.56 (s, 3 H), 2.87 (dd, 1 H, J = 18.6, 7.5 Hz), 3.28 (dt, 1 H, J = 3.3, 7.2 Hz), 3.77 (s, 3 H), 3.96 (s, 3 H), 6.80 (s, 1 H); ^{13}C NMR δ 10.73, 21.60, 32.02, 46.23, 55.86, 60.36, 104.72, 127.45, 131.59, 146.78, 158.09, 158.53, 205.70; ^{17}O NMR (CH_3CN) δ 6.7 (OMe), 53.6

(OMe), 504.5 (CO); HRMS (+EI) calcd for $C_{13}H_{16}O_3$ 220.1100, found 220.1099; Anal. calcd: C, 70.89; H, 7.32. Found: C, 71.12; H, 7.33.

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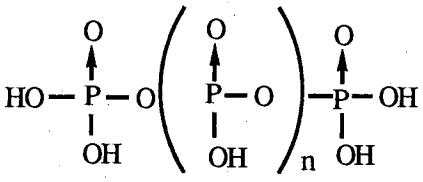
APPENDIX A

GLOSSARY OF STRUCTURES



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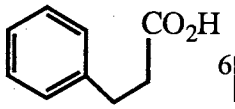

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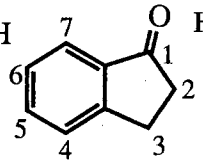

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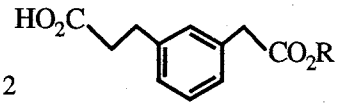

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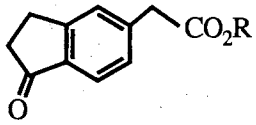

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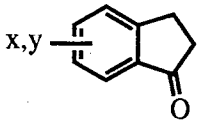

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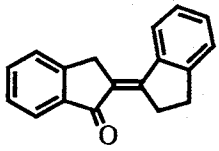

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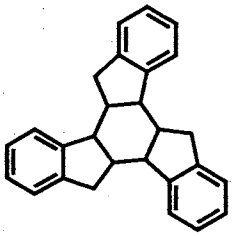

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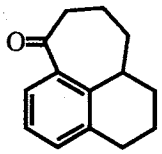

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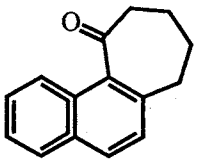

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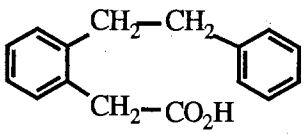

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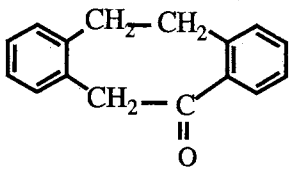

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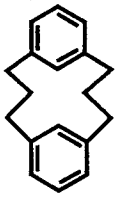

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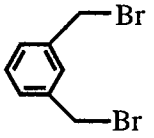

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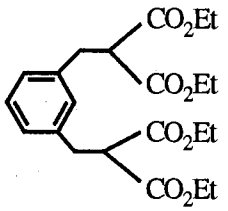

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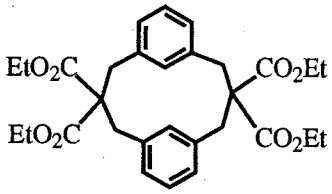

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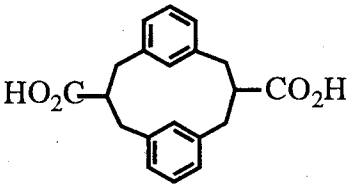

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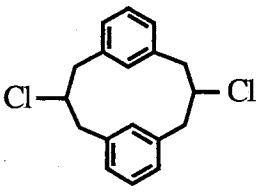

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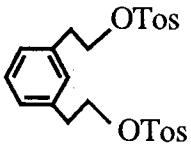

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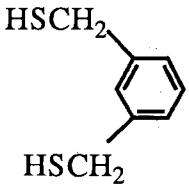

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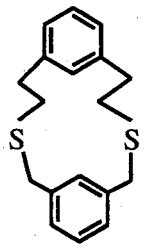

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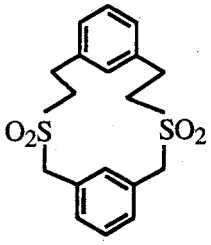

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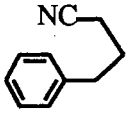

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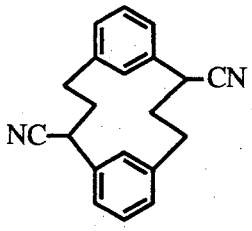

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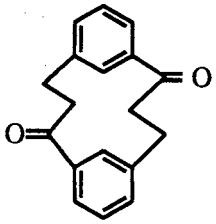

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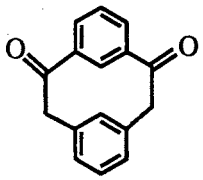

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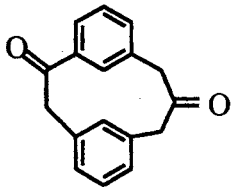

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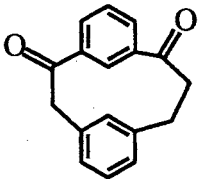

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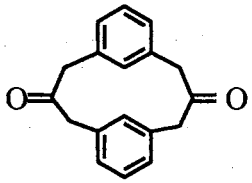

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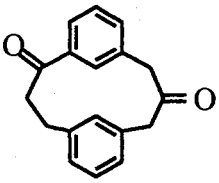

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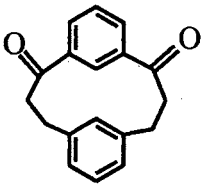

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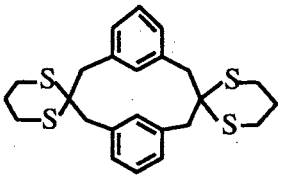

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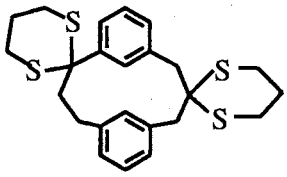

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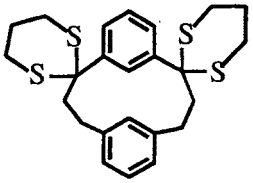

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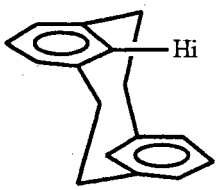

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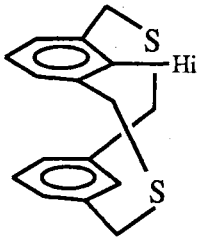

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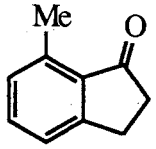

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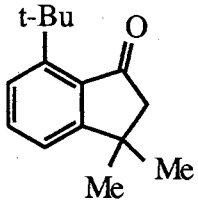

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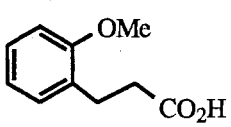

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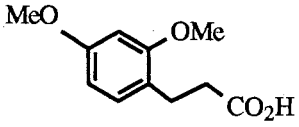

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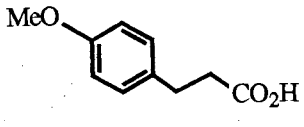

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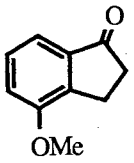

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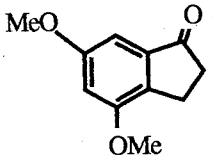

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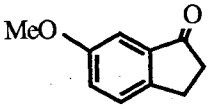

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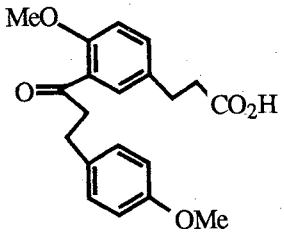

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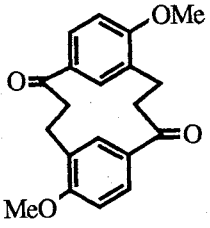

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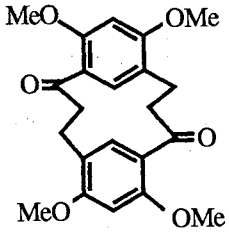

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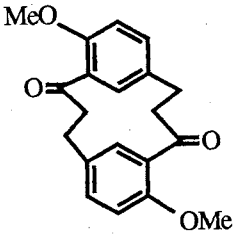

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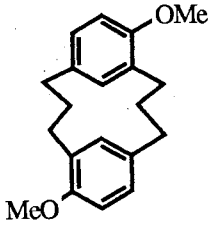

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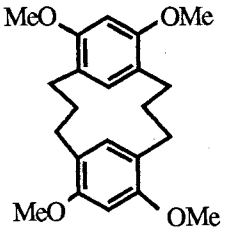

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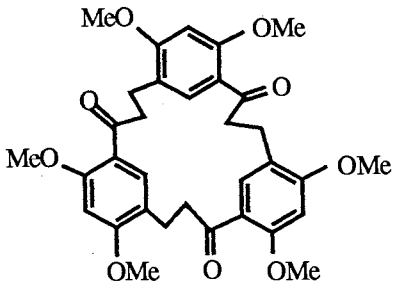

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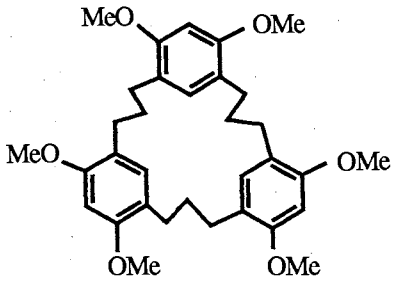

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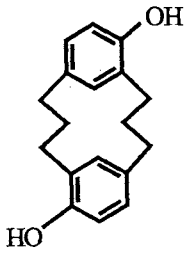

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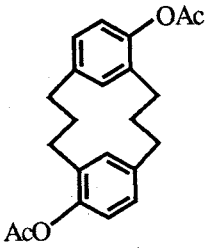

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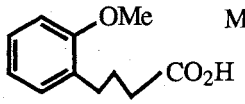

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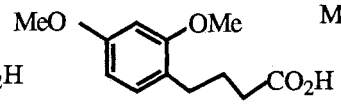

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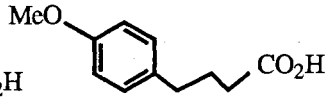

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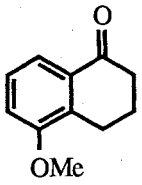

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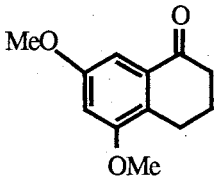

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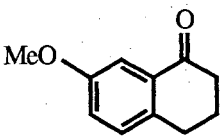

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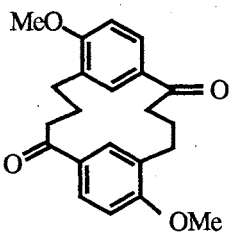

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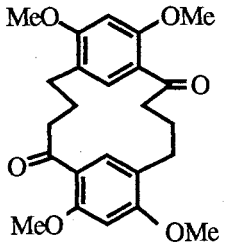

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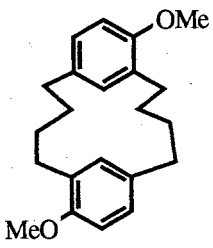

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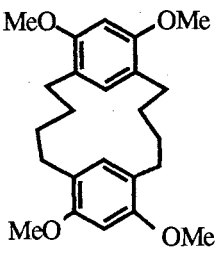

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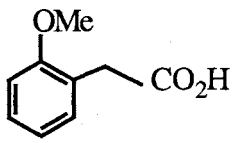

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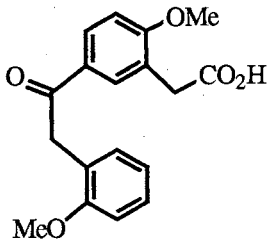

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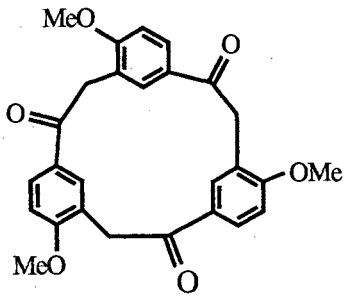

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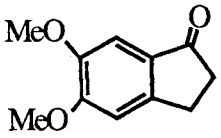

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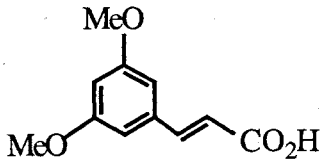

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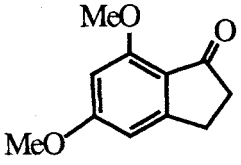

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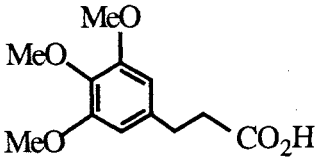

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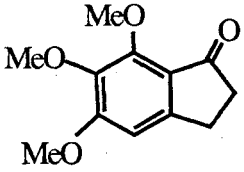

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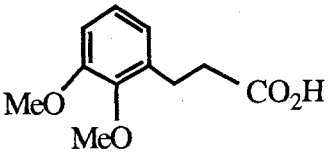

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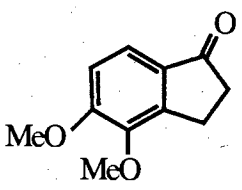

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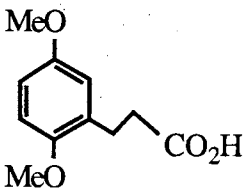

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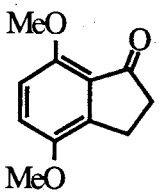

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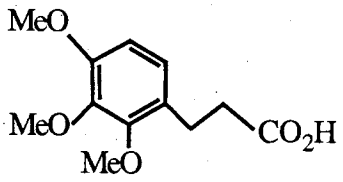

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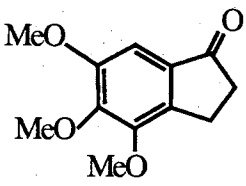

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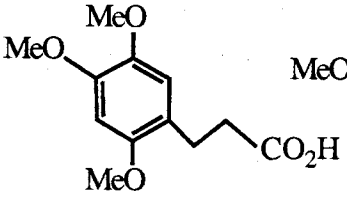

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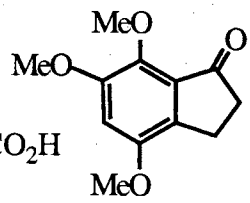

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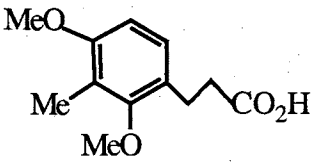

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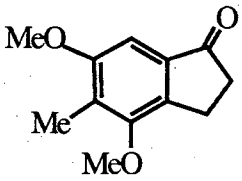

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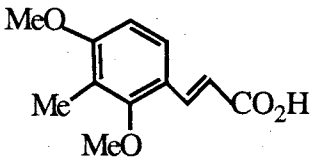

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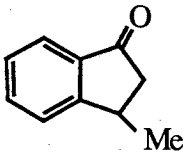

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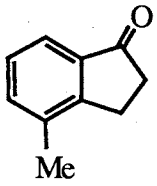

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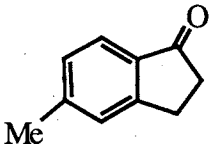

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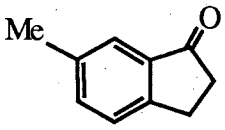

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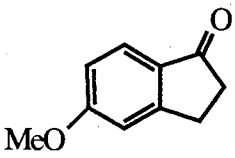

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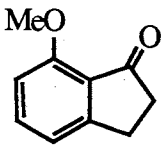

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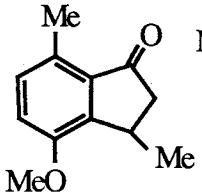

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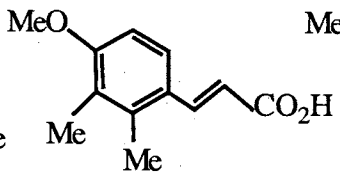

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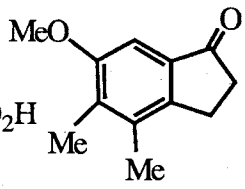

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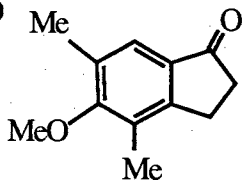

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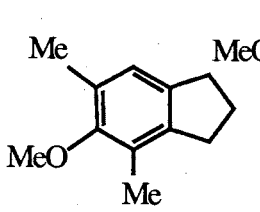

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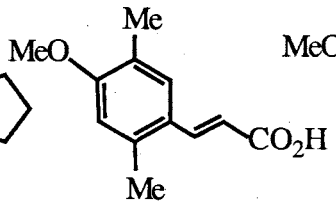

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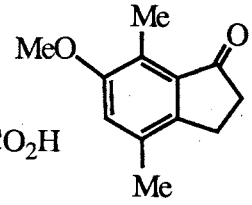

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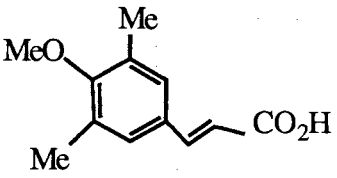

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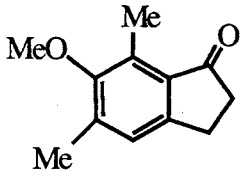

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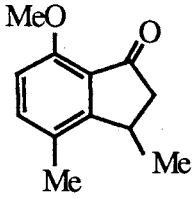

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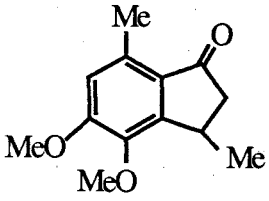

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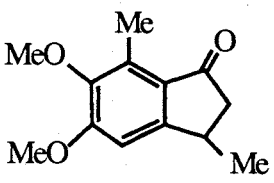

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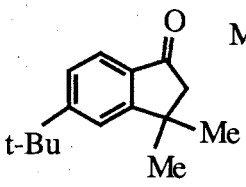

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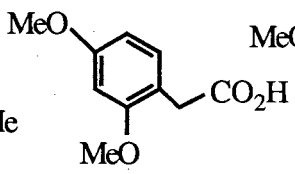

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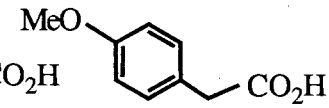

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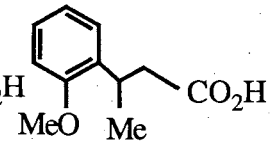

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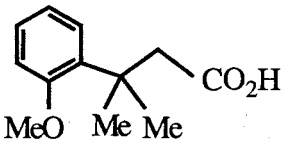

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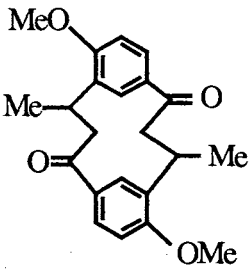

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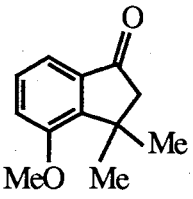

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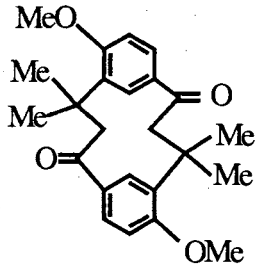

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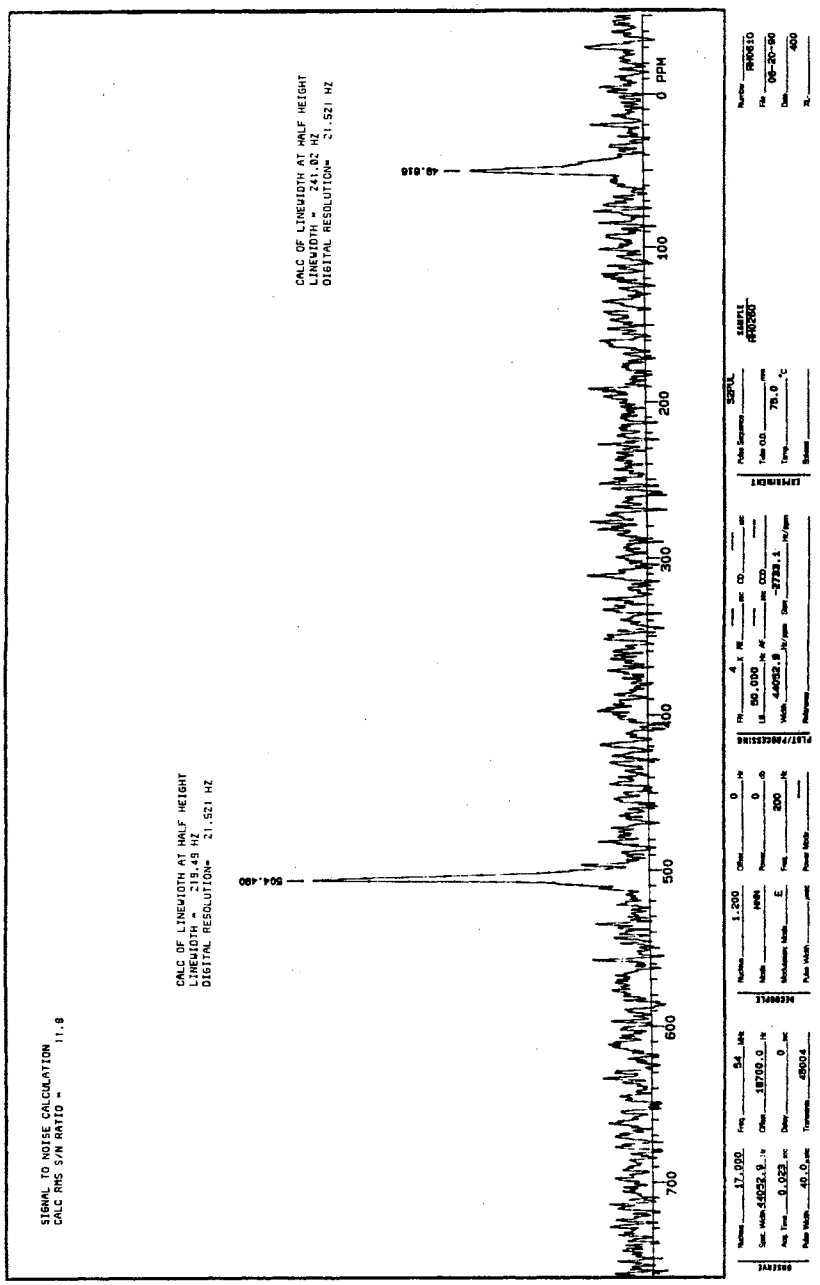
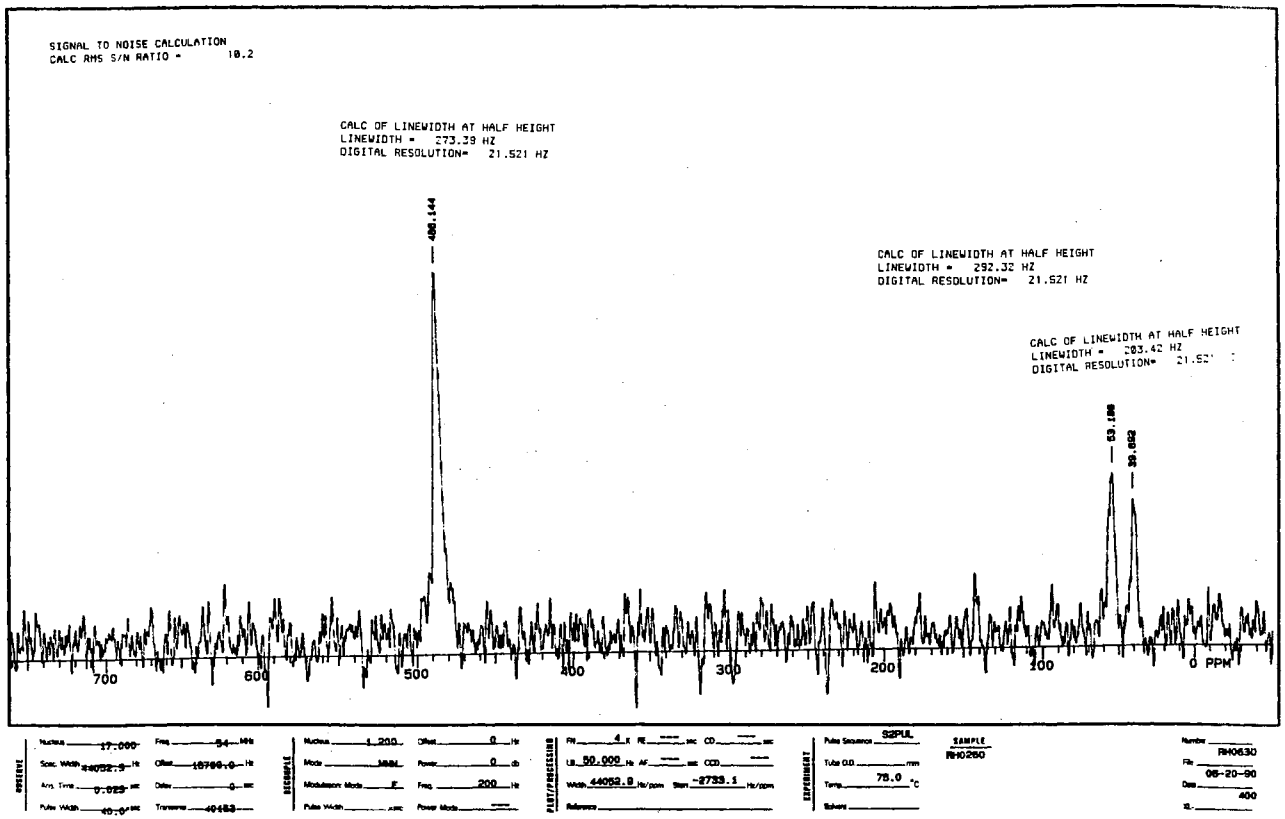
APPENDIX B

SELECTED ^{17}O NMR SPECTRA



^{17}O NMR spectrum of 6-methoxy-1-indanone (**41c**).



^{17}O NMR spectrum of 5,6-dimethoxy-1-indanone (**60**).

VITA

Juan Zhang

Candidate for the Degree of

Doctor of Philosophy

Thesis: POLYPHOSPHORIC-ACID CATALYZED CONVERSION OF METHOXY-SUBSTITUTED ARYLPROPANOIC AND ARYLBUTANOIC ACIDS TO DERIVATIVES OF METACYCLOPHANEDIONES, 1-INDANONES, AND 1-TETRALONES

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