TRIFLUOROACETIC ACID-d AS A DEUTERIUM EXCHANGE SOLVENT FOR KETONES

By

BRAHMADEO DEWPRASHAD

Bachelor of Science
University of Guyana
Turkeyen, Guyana
1977

Master of Science
Loughborough University of Technology
Loughborough, England
1979

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Oklahoma State University
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Thesis Approved:

E. Eisenbraun
Thesis Adviser

Paul W. Gene

Subhash Sangaiah

O. E. Rudolph

Norman N. Durham
Dean of Graduate College

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CHAPTER I

INTRODUCTION AND HISTORICAL

Deuterium, hydrogen of mass 2, was discovered by Urey and his coworkers in 1932.[1] Soon others observed that the hydrogen atoms of acetone were exchanged in D_2O and in the presence of an acid or a base.[2-4] The usefulness of this exchange in the study of reaction mechanisms was quickly recognized and the first determination of the primary isotope effect for acetone was carried out.[5] Subsequently, numerous deuterium labelled compounds, including ketones, were synthesized and used in important chemical and biological studies.[6]

Compounds labeled with deuterium have been particularly useful in elucidating reaction mechanisms including isotope effects, delineating mass fragmentation pathways and in NMR studies.[6] In addition, deuterium labeled analogues of drugs have potential as medicinal agents, since the expected isotope effect can influence the rate of metabolism.[7,8]

Deuterium atoms, added to a ketone through α-exchange, generally simplify ^1H NMR spectra. For example, if the α-protons of ketone **1** are replaced by deuterium to give **1-d$_2$**, the α-proton absorption, seen in the spectrum of **1**, would be absent. The

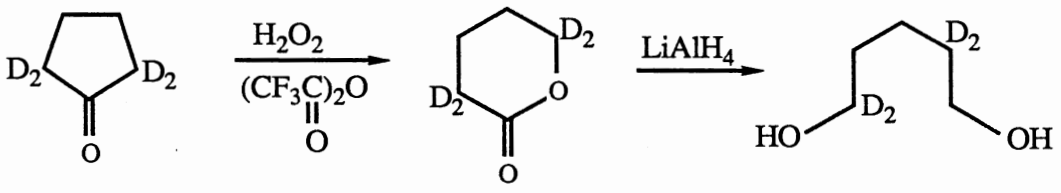
$$\underset{\textbf{1}}{X - CH_2 - CH_2 - CH_2 - \overset{O}{\overset{\|}{C}} - C_6H_5} \rightarrow \underset{\textbf{1-d}_2}{X - CH_2 - CH_2 - CD_2 - \overset{O}{\overset{\|}{C}} - C_6H_5}$$

signal of the β-protons would be changed to a slightly broadened triplet, and the signals resulting from the γ-protons would be unaffected.[9] Actually, each peak of the β-proton triplet is a very closely spaced quintet, but the effect under ordinary resolution is peak broadening. This broadening can be removed by irradiating at the deuterium resonance and

thus a more exact measurement of the proton-proton coupling can be made.[9] These changes in the ^1H NMR spectrum arise from the fact that ^2H has a spin number of 1 and a small coupling constant with protons ($J_{HD} \simeq 0.15\ J_{HH}$).[9] In contrast, the original spectrum consists of a triplet for the α-protons, and a quintet for the β-protons.[9]

In the ^{13}C noise decoupled spectrum, a decrease in the signal and a slight upfield shift is observed for a deuterated carbon.[9] A separate peak may be seen for any residual ^{13}C-H.[9] Additional reasons for the change in the ^{13}C spectrum are the longer T_1 for ^{13}C-D because of decreased dipole-dipole relaxation and the loss of the nuclear Overhauser effect since the resonance frequency of deuterium is not the same as that for proton.

Since the C-D bond is stronger and thus less reactive than the C-H bond, ketones having α-deuterium substitution can be expected to be more stable to exchange than non-labelled ones. Thus, transformations can be carried out which permit retention of deuterium. For example, treatment of cyclopentanone-d_4 (**2-d_4**) with hydrogen peroxide



2-d_4 **3-d_4** **4-d_4**

and trifluoroacetic anhydride leads to the tetradeuterated lactone (**3-d_4**) which in turn can be reduced with lithium aluminium hydride to 1,1,4,4-tetradeuteropentanone-1,5-diol (**4-d_4**).[10] The latter may be converted to other compounds such as dihalides and heterocyclic compounds.

Efficient procedures have been developed for the large scale (kilogram or larger) production of α-deuterated ketones.[11,12] Laboratory-scale synthesis is usually accomplished with an alkali metal carbonate, deuteroxide or alkoxide in a mixture of deuterium oxide and organic solvent (tetrahydrofuran, dioxane or glyme) or in alcohol-o-D.[13] Deuterated mineral acids in deuterium oxide also are used.[13] These laboratory-scale

procedures usually are multiple exchange steps involving a large excess of deuterated solvent and the spent (deuterated) solvent/co-solvent must be separated from the product after each exchange. In addition, a work up involving removal of the deuterated solvent and catalyst and purification of the product must be carried out before NMR studies can be attempted.

An examination of the following procedures illustrate these points for comparison with the use of TFA-d. Cyclohexanone-2,2,6,6-d_4 (**5-d_4**) was made as follows.[14] A mixture of 50 g (0.51 mol) of cyclohexanone (**5**) and 50 mL of deuterium oxide (99.7 atom %D) containing a trace (500 mg) of anhydrous potassium carbonate was stirred at 75° for 12 h. The reaction mixture was then saturated with dry sodium chloride and extracted three times with anhydrous ether. The residue after evaporation of ether was exchanged twice with fresh portions of deuterium oxide and the product (35 g, 70% yield) was purified by distillation.

Ketone **5-d_4** also was made using 45 g (0.46 mol) of cyclohexanone, 80 g (4.0 mol) of deuterium oxide (99.8%), 10 ml of triethylamine and 400 mL of anhydrous dioxane under reflux for 48 h[15]. The deuterium oxide, water, triethylamine and dioxane were removed by distillation. The exchange was repeated four times. The final distillation afforded 27.1 g (58%) of **5-d_4**.

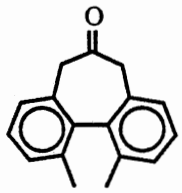
In higher molecular weight ketones, particularly those with adverse steric hindrance or directed enolization, numerous exchange steps are required as described below. For example, phenoxyacetone-d_5 (**6-d_5**) required 18 exchanges.[16] Phenoxyacetone (**6**) (7 g) was placed in a 50-mL flask, the flask was sealed with a rubber septum, deuterium oxide (10 mL) and sodium carbonate (10 mg) were added to the magnetically stirred contents and after 12 h, the deuterium oxide was removed. Fresh deuterium oxide and fresh sodium carbonate were added and the process was repeated 16 times.

In a more recent procedure, 4-pentenophenone-2-d_2 (**7-d_2**)was made by stirring 8.0 g (0.05 mol) of the ketone with 59 mL (1.0 mol) of ethanol-0-d and 0.2 g of metallic

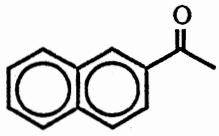
sodium for 24 h, after which time the ethanol-0-d was removed by application of aspirator vacuum.[17] A fresh charge of ethanol-0-d was added and the procedure was repeated twice. The mixture was then neutralized by addition of acetyl chloride. The reaction mixture was concentrated and distilled to give 6.5 g of product (80% yield). It was suggested that for ketones, insoluble in ethanol, an inert cosolvent be added to maintain homogeneity.

Though the workup of this procedure is much less tedious , the progress of the reaction cannot be monitored by use of ^1H NMR on the reaction mixture as the product must be purified, to remove ethanol, before NMR studies are attempted. Also, the procedure uses a large amount of ethanol-0-d (1 mol for 0.05 mol ketone). In addition, provision must be made to prevent back streaming of moisture from the aspirator. This problem may be exacerbated if a cosolvent (as suggested) is used since a longer time would be required to remove the solvents.

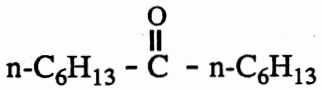
Deuterated aluminum oxide also has been used to effect exchange of α-hydrogens of ketones.[18] Neutral alumina (200 g, activity grade 1) was deuterated with a total of 66 mL D_2O in six exchanges. Deuterium exchange was carried out using 100-200 mg of ketone and 25 g alumina (fresh absorbent being used for a second pass) and eluting with benzene or benzene/hexane. Compounds, **8**, **9**, **10** gave exchanged products as follows:



8



9



10

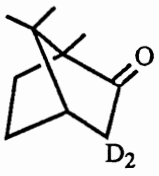
89% d_4 after 1 pass for **8**; 39% d_3, after 2 passes for **9** and 2.5% d_4, after 2 passes for **10** were achieved. Though this procedure is simple, it requires the use of large amounts of anhydrous solvent and it is an inefficient use of deuterium and the extent of incorporation for **9** and **10** is not impressive.

Acid catalysis also is used to effect proton exchange, particularly when the product is base sensitive. Several uses of DCl/D_2O, D_3PO_4/D_2O and D_2O/D_2SO_4 have been reported.[13] For example, 3,5-dimethylcyclohexanone-d_4 (**11-d_4**) was prepared as follows.[19] The ketone, **11**, (100 mg) and 1 g of 10% acidic solution ($DCl/D_3PO_4/D_2O$) were stirred in a sealed flask for 12 h at room temperature. The ketone was extracted with anhydrous ether which was then concentrated and the exchange was repeated with 1 g of fresh acid solution. Isolation of the product ether extraction and distillation gave a product containing 90% d_3, 9.5% d_2 and 0.5% d_1.

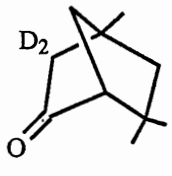
Trifluoroacetic acid-d (TFA-d) has been used, as a catalyst, in rate studies of deuterium exchange in a variety of α-substituted cyclohexanones.[20] Neat TFA-d as a deuterium exchange solvent for the preparation of α-labelled ketones has not been reported. However, TFA-d has been used with D_2O to effect exchange in norbornyl ketones in which incomplete deuteration was achieved with basic catalysts.[21,22,23]

TFA-d (0.1 mol) and D_2O (0.495 mol) and camphor (**12**) (0.01 mol) were heated at 130° in a sealed tube for nine days.[21] The reaction mixture was basified with anhydrous potassium carbonate and extracted with pentane. The extract was dried, filtered and concentrated. The residue was recrystallized from hexane and sublimed to give a product containing 95% d_2. In contrast, only exchange of the exo proton of camphor (**12**) was achieved using NaOD in dioxane.[22]

Thomas et. al. used a base catalyst to prepare deuterium labeled camphor-d_2, **12-d_2**, isofenchone-d_2, **13-d_2** and carvonecamphor-d_2, **14-d_2**.[24] They indicated that



12-d_2

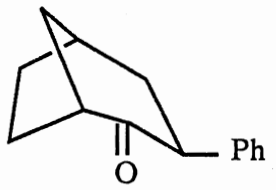


13-d_2

14-d_2

compounds, **12-d_2**, **13-d_2** and **14-d_2** were obtained using the Djerassi and Weinberg camphor-labeling procedure[21]. However, the procedure was not described and yields were not given except 97% d_2 for **12**.

The bicyclic ketone, 3-phenylbicyclo[3.2.1]octan-2-one (**15**) was subjected to



15

TFA-d (10% solution in D_2O) for 24 h at 95°C and only the benzylic proton was exchanged.[24] Experimental details, including work-up procedure, were not given.

TFA-d has properties similar to those of TFA; the latter boils at 72.4 °C and the former at 75 °C.[25, 26] TFA has a pk_a of 0.23 at 25 °C in H_2O[27] and H_0 values of -4.4[28] and -3.1.[29] Such data for TFA-d appear not to be available. TFA is miscible with ether, acetone, ethanol and water[30] and readily dissolves most ketones. Exchange of α-hydrogens of ketones in such an acidic medium were thought to be at such a rate that under mild conditions, fully deuterated ketones could be obtained after a few exchanges. Since TFA-d is devoid of protons, it would facilitate monitoring the exchange process by ^1H NMR on the neat reaction mixture. The volatility of the reagent should lend to its easy removal after each exchange. As such, the use of TFA-d as a deuterium exchange solvent was investigated with a view to developing suitable techniques for its use. Through selection of examples, we also sought the limits of TFA-d as an exchange solvent and an understanding of any possible side reactions during the exchange.

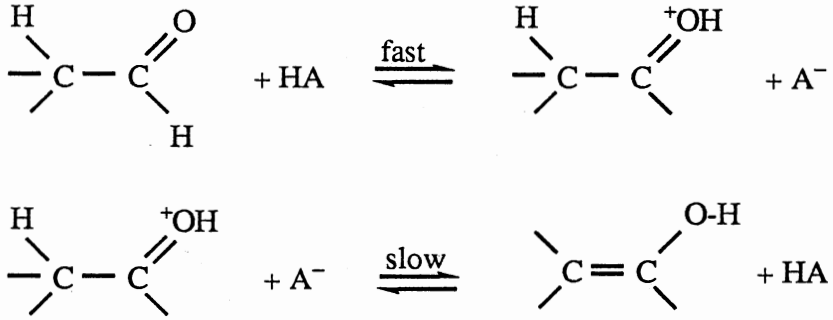
CHAPTER II

RESULTS AND DISCUSSION

Mechanism and Theory

Before the suitability of TFA-d as an exchange solvent can be discussed, an appreciation of the mechanism involved in the exchange process is desirable. Thus, a possible mechanism and some of the factors likely to affect the equilibria of exchange will be described.

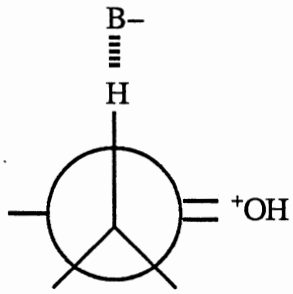
The generally accepted mechanism for acid catalyzed enolization is known as specific acid catalysis and pictures the rate-determining step as deprotonation of the protonated ketone as shown below.[31]



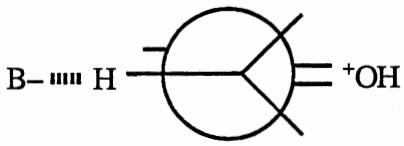
Swain and Rosenberg demonstrated that a base was always necessary for enolization in a strongly acidic medium (94% H_2SO_4); in dilute solutions the hydroxide ion acts as the base.[32]

Two conformations (shown overleaf) of the carbonyl group and the alpha C-H bond have been proposed as being the most favorable for approach of the base.[33,34] Corey and Sneen have proposed α "stereochemical control" for enolization and ketonization reactions.[33] This requires that the α-H removed must be perpendicular to the

direction of the C=O bond, in order to permit a stabilizing delocalization of the σ electrons of the C-α-H bond towards the π orbitals of the carbonyl as shown below for (a).



(a)



(b)

Feather and Gold proposed a trans coplanar arrangement with the C=O bond and the C-α-H bond as shown above for (b). This is an arrangement which leads to minimal steric interactions between the ketone and the base.[34]

The timing of the proton transfer during the acid-catalyzed reaction was examined by Swain et al[35] and by Leinhard and Wang.[36] They concluded that the proton transfer is not concerted with the removal of the α-H, but takes place during a rapid pre-equilibrium step leading to the conjugate acid of the ketone as the true intermediate.

The reaction is considered to be two consecutive bimolecular reactions and the rate (r) is given by:[37]

$$r = k[\text{Ketone}][\text{Acid}][\text{Base}]$$

Therefore for TFA-d

$$r = k[{}^{R}_{R}1{>}C{=}0][CF_3COOD][CF_3COO^-]$$

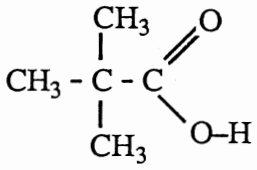
$$\text{and as } [CF_3COO^-] \; \alpha \; [CF_3COOD]$$

$$r = k[{}^{R}_{R}1{>}C{=}0]\,[CF_3COOD]^2$$

This a rate equation implies the dependence of the enolization rate on the pK_a of the acid. Leinhard and Wang[36] found a proportional relationship between the pK_a of various carboxylic acids and their rate of enolization of cyclohexanone. As such, TFA-d catalyzed

enolization of ketones would be expected to be at a much faster rate than that of other carboxylic acids (pK_a of trifluoroacetic acid = 0.23, H_2O, 25°).[27]

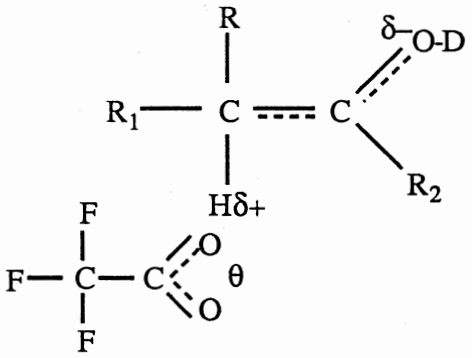
However, additional factors (including structural peculiarities) might lead to unusually high rates of catalysis by some carboxylic acids. For example, Leinhard and Wang found an unexpectedly high rate of enolization of cyclohexanone (**16**) catalyzed by Pivalic acid (**16**), than that expected from its pK_a.



16

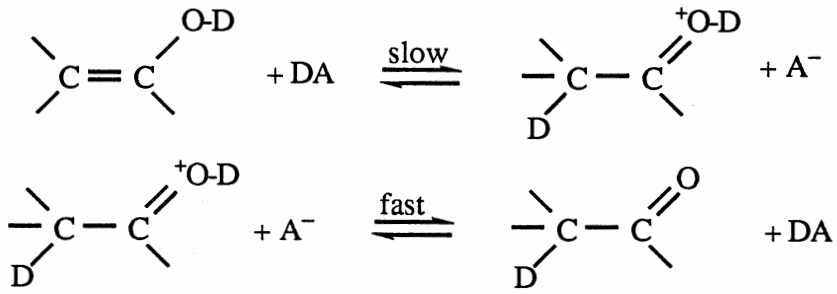
It is believed that the transition state of acid-catalyzed enolization resembles the enol, i.e. the α-transfer is well advanced.[32,35] Since this transfer is still not complete, the position of the transition state may vary with the nature of the substrate, the attacking base or the reaction medium.

The transition state of enolization of ketones catalyzed by TFA-d can be visualized as shown below:



Trifluoroacetic acid has a dielectric constant of 8.6;[38] TFA-d can be expected to have a similar property and acting as a polar protic solvent would stabilize charge separation in the transition state with a resultant enhancement of rate of enolization.

The acid-catalyzed ketonization of the enol is expected to go through a mechanism which is the reverse of enolization[37] as shown below.



The reaction pathways which lead to the incorporation of D can be visualized as shown in Figure 1 for acetone.[37]

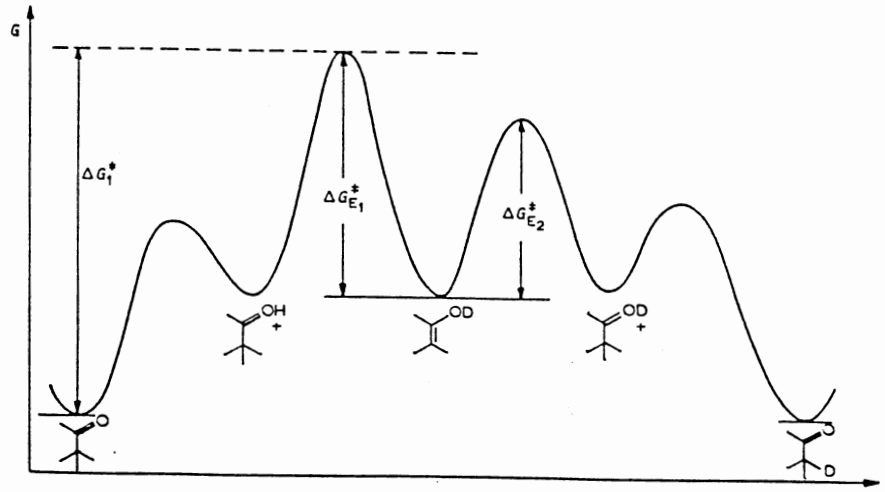


Figure 1. Intermediates in the Acid-Catalyzed Hydrogen-Deuterium Exchange of Acetone on a Free Energy-Coordinate Profile.

The completeness of the reaction, leading to deuterium exchange, depends upon the differences between the free energies of activation of the enol $\Delta G^{\neq}_{E_1}$ and $\Delta G^{\neq}_{E_2}$. These two energies are related to the experimental protonation and deuteration rate constants of the enol by the classical relationships[37] $\Delta G^{\neq}_{E_1} = -RT \ln \left(\frac{kT}{h}\right) k^{H}_{exp}$ and $\Delta G^{\neq}_{E_2} = -RT \ln \left(\frac{kT}{h}\right) k^{D}_{exp}$.

The ratio k^H and k^D representing the specific protonation and deuteration rate constants of the enol, and [H] and [D] the concentrations of H and D atoms in the medium.

The ratio k^H/k^D is equal to the primary isotope effect for the transfer of a proton, 7±2, depending upon the system under consideration.

Though the mechanism for the TFA-d catalyzed deuterium exchange of ketones has not been delineated, the specific acid catalysis mechanism seems plausible and the results of this study will be discussed in light of this mechanism.

The effectiveness of TFA-d as an exchange solvent for ketones can be ascribed to acidity resulting in a high concentration of D^+ and CF_3COO^-, stabilization of the enol transition state by hydrogen (deuterium) bonding and association with TFA-d and finally high solubility of ketones in this solvent permitting a homogeneous exchange system using small amounts of TFA-d.

Investigation of Experimental Conditions for Exchange of a Series of Ketones

TFA-d was selected as the exchange solvent after it was determined that its rate of exchange of ketones **17**, **19**, **24**, **25** and **28** at room temperature was much faster than when TFA-d/D_2O (1:1), CD_3COOD/D_2O (1:1) or CD_3COOD/TFA-d/D_2O (1:1:1) was used.

In order to determine the exchange conditions for a range of structural types of ketones in TFA-d, exchange was attempted with ketones **2, 5, 12** and **18-42**, in quantities of 0.25-0.70 mmol. The exchange was monitored by ^1H NMR on the reaction mixture. The extent of exchange was verified by ^1H and ^{13}C NMR and mass spectroscopy on the deuterated product. The results are summarized in Table 1.

Ketone, **17**, a dione, exchanges on addition of TFA-d to a sample in an NMR tube. The ready exchange of this compound is understandable due to the stability of the intermediate enol (as a result of intermolecular hydrogen bonding) as shown below for **17E**.

Table I

Exchange Conditions for α-Carbonyl Protons in TFA-d

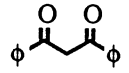
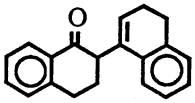
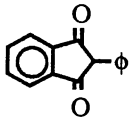
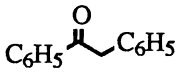
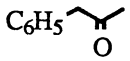
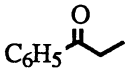
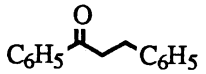
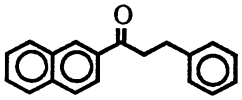
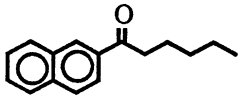
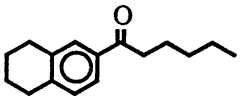
Ketone Structure	No.	Exchange Conditions A[a]	B[b]	C[c]	No. of Exchanges	% Exchanged[d]
	**17**	√			1	>95
	**18**	√			1	>95(α,y)
	**19**		√		1	>95
	**20**		√		1	>95
	**21**		√		1	85(CH_2) 30(CH_3)
	21		√		4	>95
	**22**		√		4	>95
	**23**		√		3	>95
	**24**		√		3	>95
	**25**		√		4	>95
	**26**		√		4	>95

Table I (Continued)

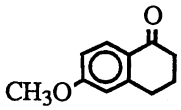
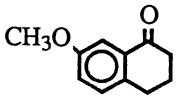
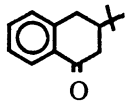
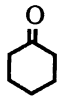
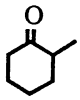
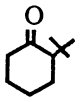
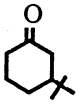
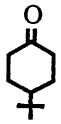
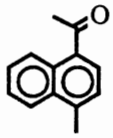
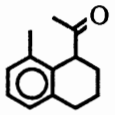
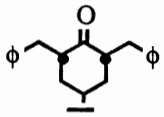
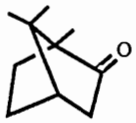
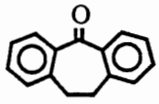
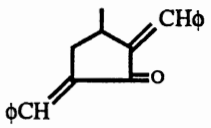
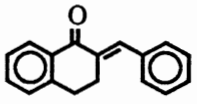
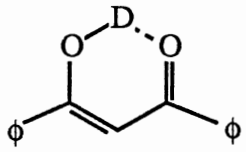
Ketone Structure	No.	Exchange Conditions A[a]	B[b]	C[c]	No. of Exchanges	% Exchanged[d]
	**27**		√		4	>95
	**28**		√		4	>95
	**29**		√		4	>95
	**2**		√		4	>95
	**30**		√		4	>95
	**5**		√		4	>95
	**31**		√		4	>95
	**32**		√		4	>90
	**33**		√		4	>90
	**34**		√		4	>90
$n-C_5H_{11}-\overset{\overset{\cdot\cdot}{O}}{\overset{\|}{C}}-CH_3$	**35**		√		5	>95

Table I (Continued)

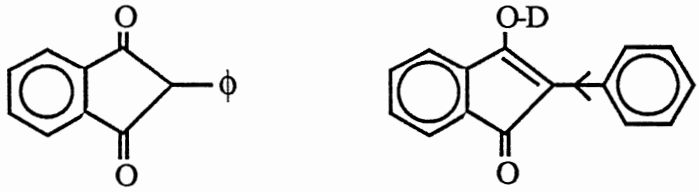
Ketone Structure	No.	Exchange Conditions A[a]	B[b]	C[c]	No. of Exchanges	% Exchanged[d]
$n-C_4H_9-\overset{\overset{O}{\|\|}}{C}-C_2H_5$	**36**		√		5	>95
	**37**		√		4	>95
	**38**		√ √		4	75(CH_3) 10(CH)
	**39**		√		3	>95
	**12**			√	3	>95
	12		√		4	0
	**40**			√	3	0
	**41**			√	3	0
	**42**		√		3	0

[a]Addition of TFA-d to NMR Tube (Experimental, A). [b]Stirring with TFA-d for 18-20h (Experimental, B). [c]Refluxing with TFA-d for 68 h (Experimental, C). [d]Estimated by ^1H NMR. √: Exchange effected by condition indicated



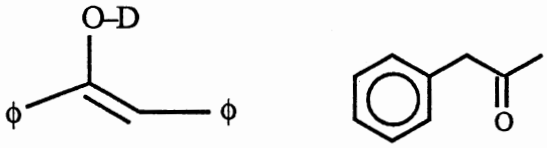
17E

Ketone **19**, a five membered ring dione with a 2-phenyl substituent, has a geometry which does not permit an internally stabilized enol intermediate as for **17E** and as such does not exchange as rapidly. However the enol (**19E**) is stabilized by carbonyl and phenyl substituents. Exchange was complete within 18 h of stirring in a single treatment.



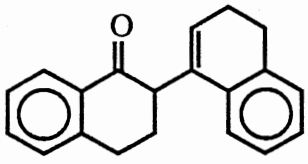
19 **19E**

Ketone **20**, with benzylic α-hydrogens, exchanged under similar conditions. Stabilization of the enol intermediate **20E** is enhanced by the two phenyl substituents.



20E **21**

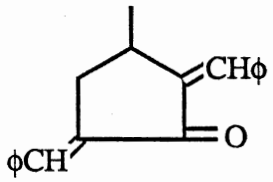
The methylene (benzylic) protons of ketone **21** exchanged under the same conditions but longer stirring and a fresh charge of reagent were needed to effect exchange of the terminal (methyl) protons. Ketones **15-35** required 2-4 additional charges of TFA-d and periods of stirring.



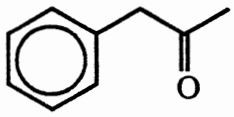
18

Ketone **18**, exchanged only the alpha and the vinylic hydrogens (as shown by ^1H NMR) on addition of TFA-d in a NMR tube after 3 h. However, exchange under condition B results in some exchange of the β-carbonyl hydrogens and the allylic hydrogens.

In d-camphor (**12**), exchange could not be affected by stirring at room temperature and as such reflux was used. In ketone **41**, NMR evidence indicated that there was no migration of exocyclic double bonds when this ketone was stirred in TFA-d. In addition, exchange was not effected in compound **41**, even with reflux.



41



21

Dibenzosuberone (**40**) did not undergo exchange even when heated at reflux for 9 days. This being an indication that TFA-d could be used to effect exchange of α–carbons without exchange of aromatic or benzylic protons not adjacent to a carbonyl group.

The relative rate of exchange of the benzylic and terminal methyl protons of ketone **21** was investigated with the intent of demonstrating that the disparity in the rate of exchange of these two groups would allow preferential deuterium incorporation at the benzylic position and also to highlight some of the considerations that need to be made when selecting the exchange time and relative concentration of ketone and TFA-d.

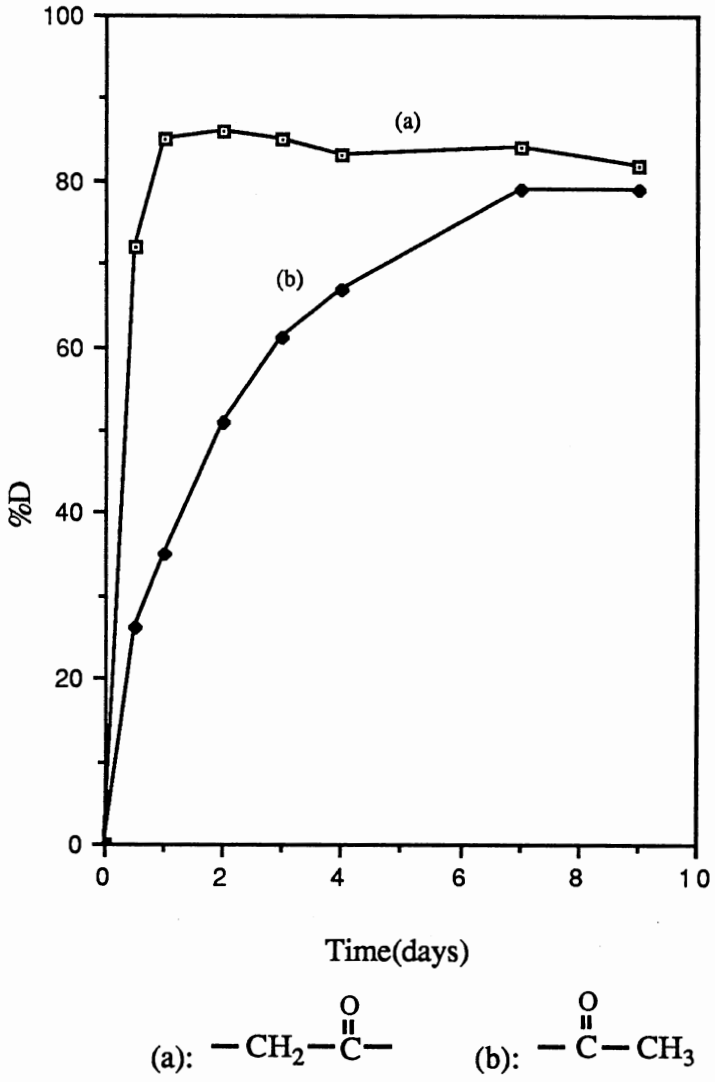
Eight mmol of ketone **21** and 6.2 mL (80 mmol) of TFA-d were stirred for varying periods of time. The percent deuterium exchange found are listed in Table II and these data were used to plot Figure 2. As shown in Figure 2, maximum exchange of benzylic protons was achieved within 24 h. However, the terminal methyl protons exchanged at a much slower rate with a maximum reached by the 7th day. A higher percentage of deuterium incorporation at the benzylic position would be possible with the use of shorter exchange time and additional number of exchanges or a larger amount of the reagent. The terminal

Table II

Relative Rates of Exchange of Protons of Methyl Benzyl Ketone (**21**) in TFA-d

Time (days)	% D [a]	
	$-CH_2-\overset{O}{\overset{\|}{C}}-$	$-\overset{O}{\overset{\|}{C}}-CH_3$
0	0	0
0.5	72	26
1	85	35
2	86	51
3	85	61
4	83	67
7	84	79
9	82	79

[a] %D estimated by ^1H NMR.



(a): $-CH_2-\overset{\overset{O}{\|}}{C}-$ (b): $-\overset{\overset{O}{\|}}{C}-CH_3$

Figure 2. Relative Rates of Exchange of Protons of Methyl Benzyl Ketone (**21**) in TFA-d

methyl protons exchange at a much slower rate and the use of much larger amounts of TFA-d would still necessitate several exchanges. Although more economical use of deuterium would be made if longer exchange times were used, complete exchange would be achieved in an inconveniently long time. Side reactions (e.g. aldol), though negligible under the conditions used, might increase. Additional factors to be considered in choosing the exchange conditions are the number of exchangable protons and the solubility of the ketone in TFA-d. Solubility can limit the minimum amount of exchange solvent that can be used.

With these factors to consider, attempts were made to prepare a variety of α–labelled ketones.

Preparation of α–Labelled Ketones

α–Exchange of ketones **9, 34** and **43-47** was done on a preparative scale. The experimental conditions and results are given in Table III. The procedure used to prepare these ketones (detailed in Experimental section) has several advantages over traditional methods of exchange.

The exchange process is much less tedious than other methods of exchange since there is no need for extractive isolation of the product. All of the introduced reagent (TFA-d) is easily aspirated as TFA or TFA-d leaving the exchanged product as a residue. Earlier methods necessitate extraction into an anhydrous solvent and separation of spent D_2O after each exchange. The necessity of avoiding H_2O during these isolation procedures add greatly to the inconvinience of the extractive processes. As an additional advantage, the deuterated ketone in the current procedure can be directly distilled from the reaction flask using a Kugelrohr apparatus.

The progress of the exchange was followed by ^1H and ^{13}C NMR of the neat reaction mixture with TFA-d serving as the NMR solvent. This will be discussed in more detail in the section entitled 'TFA-d as a NMR Solvent for Ketones'. Again, the direct

Table III

Preparation of α-Labelled Ketones Using TFA-d

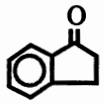
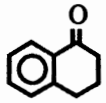
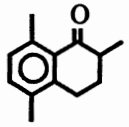
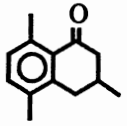
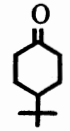
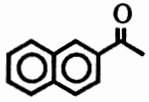
Ketone			TFA-d		Pot Residue	Product	%d[b]					
Structure	No.	g (mmol)	mL (mmol)	Number of exchanges[a]	g (%)	g (%)	d_0	d_1	d_2	d_3	d_4	d_5
$n\text{–}C_6H_{13}\text{–}\overset{\overset{O}{\|}}{C}\text{–}CH_3$	**43**	5.12 (40)	12 (154)	7	0.153 (3.0)	4.133 (81)	0.00	0.00	0.00	0.00	2.98	97.02
	**44**	5.280 (40)	12 (154)	4	0.247 (4.7)	4.233 (81)	3.95	0.00	95.42	0.64[c]	0.00	0.00
	**45**	5.840 (40)	12 (154)	4	0.177 (3.0)	5.610 (95)	3.16	3.95	92.53	0.37[c]	0.00	0.00
	**46**	7.62 (40)	12 (154)	4	0.032 (0.4)	7.17 (94)	4.36	95.59	0.00	0.04[c]	0.00	0.00
	**47**	1.880 (10)	12 (154)	4	0.070 (3.7)	184 (97)	0.00	5.53	94.47	0.00	0.00	0.00

Table III (Continued)

Ketone Structure	TFA-d No.	g (mmol)	mL (mmol)	Number of exchanges[a]	Pot Residue g (%)	Product g (%)	%d d_0	d_1	d_2	d_3	d_4	d_5
	**34**	6.160 (40)	12 (154)	5	0.210 (3.4)	4.320 (68)	0.00	0.00	0.00	9.61	90.39	0.00
	**9**	6.80 (40)	12 (154)	5	0.148 (2.2)	6.302 (93)	0.82	0.33	4.47	94.18	0.00	0.20[c]

[a]Stirring for 20 h at RT as described under E of Experimental. [b]The program does not permit calculating beyong d_5. [c]Normally this represents surplus deuterium incorporated at positions other than at alpha.

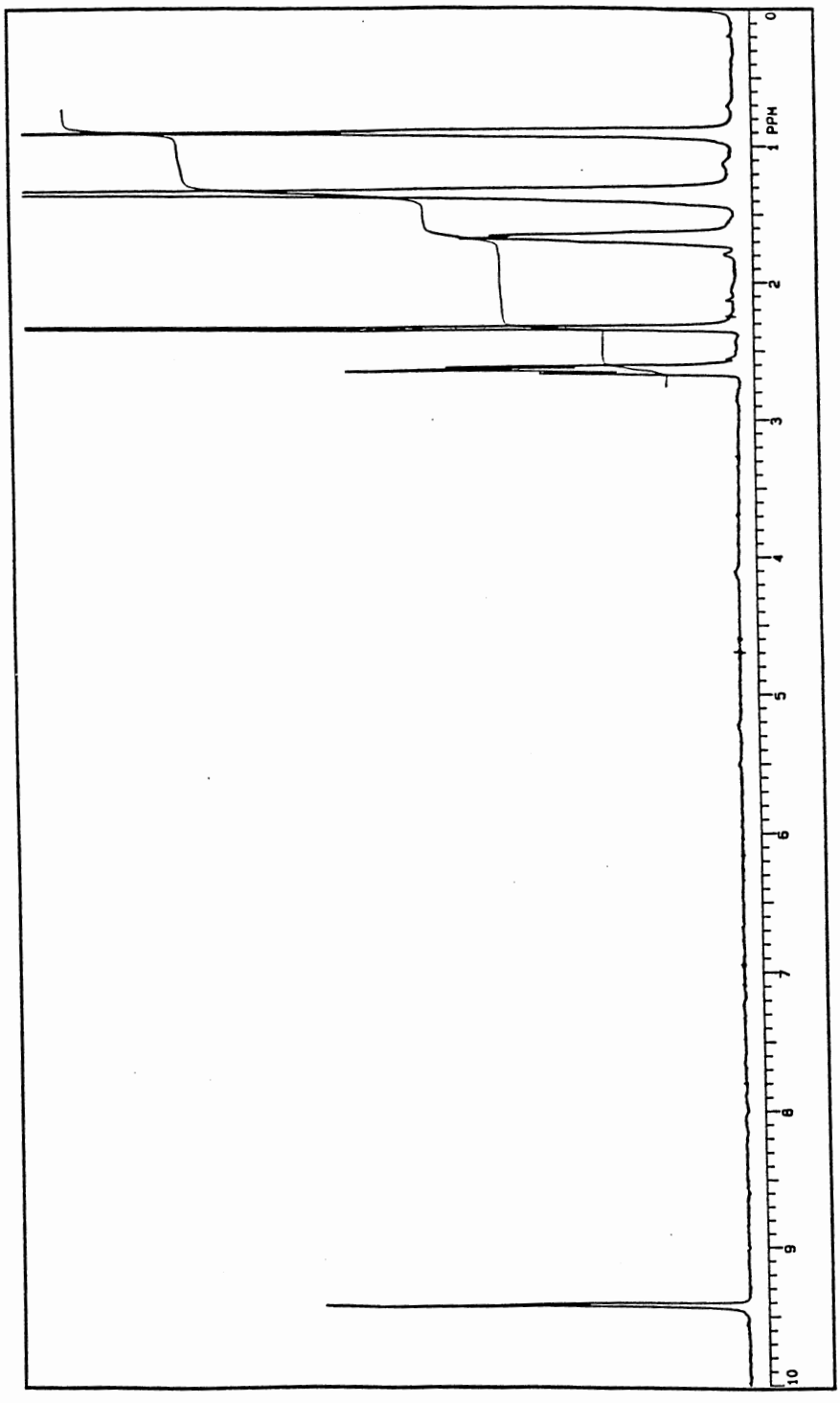
monitoring with NMR is a distinct advantage as compared to extractive isolation and analysis after each exchange.

Another advantage of TFA-d, as an exchange solvent, is that there are minimal side reactions. A comparison of the ^1H NMR spectra of 2-octonone (**43**) at the beginning (Spectrum 1) and at the end (Spectrum 2) of the exchange process indicate complete exchange with no side reactions. The ^1H and ^{13}C NMR of the reaction mixture and fully deuterated product (before distillation) of the other ketones, also, did not show additional signals. The mass spectral data showing the percentage of deuterated product and the weight of the pot residue give the same indication. These are presented in Table III.

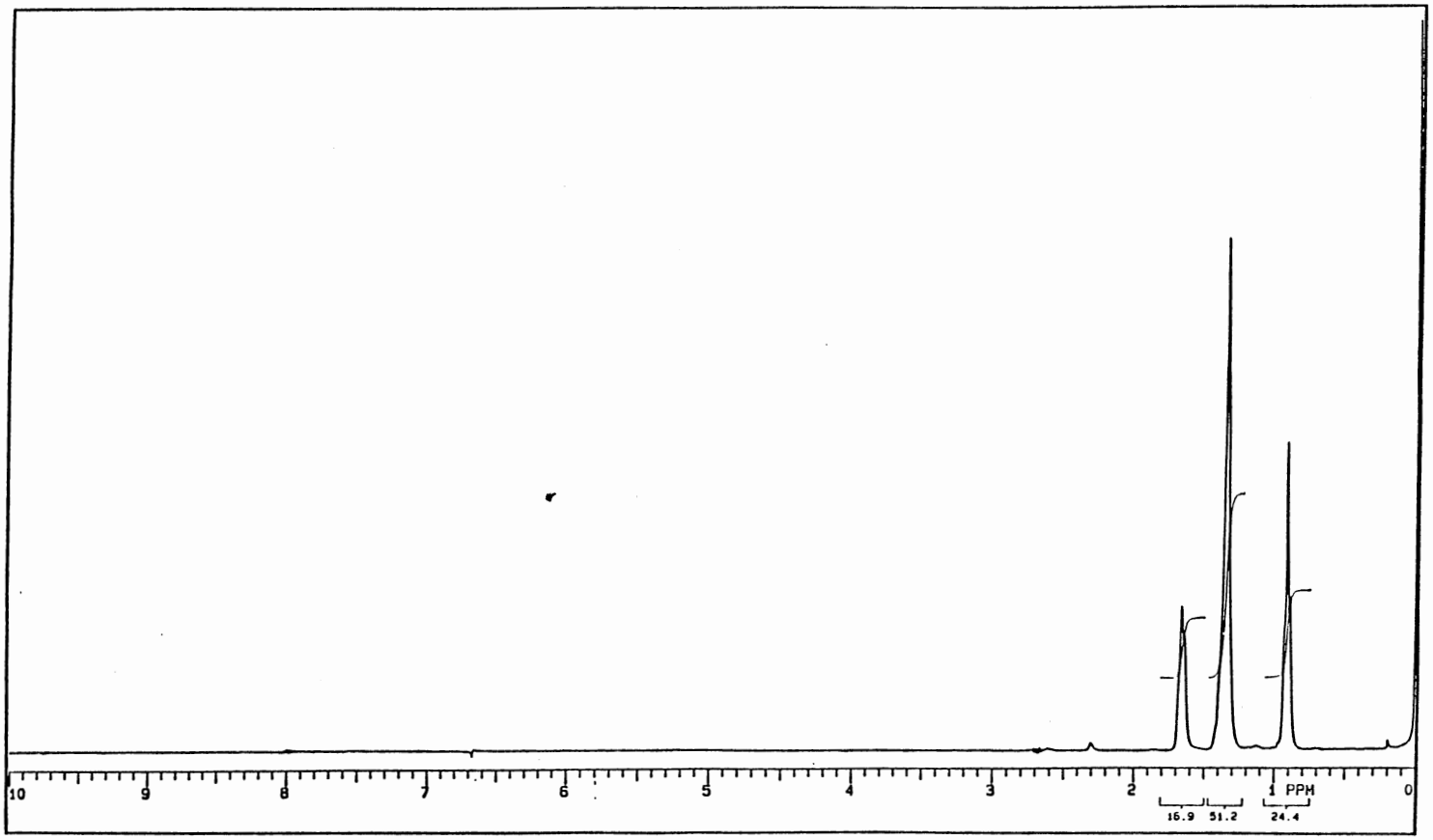
In base catalyzed methods of exchange, aldol products are significant. For example, cyclohexanone -2,2,6,6-d_4 (**5-d4**) was made in 70% yield[14] and 58% yield[15] via base-catalyzed exchange. Aldol condensation contributed to the low yields. In another exchange, 4-pentenophenone-2-d_2 (**7-d2**) was prepared in only 80% yield by stirring in ethanol-0-d and sodium metal at room temperature.[17]

Very little pot residue (<5%) was obtained after Kugelrohr distillation of the residue of each of the ketones in Table III. In addition, yields of 93-97% of labelled compound was obtained for ketones **9**, **45**, **46** and **47**. However, the lower molecular weight ketones **34** and **44** show some loss of product, as a result of prolonged aspiration to remove spent TFA-d/TFA. The yields were 68% and 81% respectively. Addition of a condenser to the flask during aspiration of 2-octonone (**43**) resulted in a yield increase from 65 to 81%.

The deuterium used in exchange reactions usually originates from D_2O. The use of TFA-d as an exchange solvent makes available, for exchange, all of the deuterium of D_2O.



Spectrum 1. ^{1}H NMR (TFA-d) of 2-Octanone (43).



Spectrum 2. ^{1}H NMR (TFA-d) of 2-Octanone-d_5 (**43-d_5**).

This is possible as the TFA-d is made from interacting the anhydride and D_2O with all of the available deuterium converted to TFA-d as indicated below:

$$\left(CF_3C\right)_2O + D_2O \rightarrow 2\ CF_3COOD \rightleftharpoons 2D^+ + 2\ CF_3COO^-$$

In base or mineral acid-catalyzed exchange, using D_2O as deuterium source, for each equivalent of deuterium available (as D^+) an equivalent amount of the isotope is incorporated in deuteroxide anion (and not available for exchange) as shown below.

$$D_2O \rightleftharpoons D^+ + OD^-$$

Thus TFA-d, as an exchange solvent for ketones, provides more efficient use of the isotope than when D_2O is used with a mineral acid or a base. For example, 2-octanone (**43**) which required the most number of exchanges in this study, was exchanged with TFA-d in ratio of 27 mole reagent (from 13.5 mol D_2O) per mol ketone (as calculated from Table III). In contrast, cyclohexanone was deuterated via base catalysis and D_2O as solvent source in the ratios of 174 and 150 mol D_2O per mol ketone.[14,15]

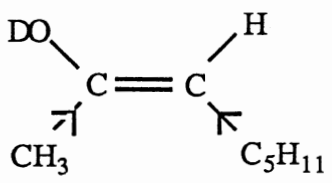
The commercial TFA-d (99.5% d) at \$130/mol[39] is too expensive for routine use as an exchange solvent. However, since TFA-d may readily be prepared by mixing equimolar quantities of TFA anhydride (99+%, \$28/mol[39]) and D_2O (99.8% \$10/mol[39]) the TFA-d cost becomes \$19/mol which compares favorably with that of ethyl alcohol-d and D_2O.

As shown in Table III, the five α–protons of 2-octanone were exchanged to 99% using 7x12 mL TFA-d per 40 mmol ketone. This procedure compares favorably with the base-catalyzed exchange of the two α–protons of 4-pentenophenone (**7**) done on a similar scale using 50 mmol ketone and 3x59 mL ethyl alcohol-d.[17]

Although 2-octanone (**43**) required 7 exchanges, most of the other ketones studied required 4-5 exchanges. Literature reports show that alicyclic ketones have a slower rate of acid and base catalyzed exchange than cyclic ones.[37] We observed that the α–CH_3 of 2-octanone exchanged at a somewhat faster rate than the α–methylene. ^1H NMR studies

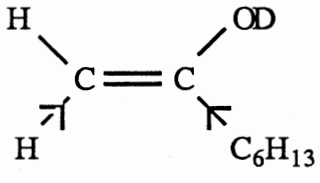
showed that exchange of the latter was completed one day earlier than the former. Similar observations have been reported for the DCl catalyzed exchange of 2-butanone (**52**).[40]

A comparison of the enol intermediates for exchange at these sites, indicates greater stabilization of the enol (possibly as a result of hyperconjugation) arising from α–methylene (**43E1**) than from terminal α–methyl (**43E2**) enolization as indicated below.



more stable

43E1



43E2

TFA-d catalyzed exchange, at room temperature, was found to be slower than base catalyzed exchange which usually is carried out in refluxing solvent. As expected, refluxing in TFA-d increased the rate of exchange. However, this is not recommended for all ketones and the reasons will be discussed in the section entitled 'Investigation of Possible Side Reactions of Ketones in TFA-d'.

Steric Effects in TFA-d Catalyzed Exchange of Ketones

Several ketones in which steric factors might lead to peculiarities in the exchange process were selected for study. These are listed in Table IV with the experimental conditions and exchange results.

Exchange at a chiral α–carbon of a cis or trans ketone can be expected to result in epimerization as a deuteron generally may approach either face of the enol.

Exchange of *cis*-2,6-dibenzyl-4-t-butylcyclohexanone (**39**) resulted, as expected, in a mixture of cis and trans products in the ratio of 80:20.

Exchange of 3,17-androstanedione (**48**) was studied. After seven exchanges, ^{13}C signals at δ 44.57 and 38.06 disappeared indicating complete exchange of two of the

Table IV

TFA-d Catalyzed Exchange in Ketones-Steric Effects

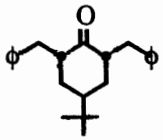
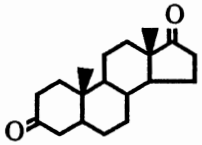
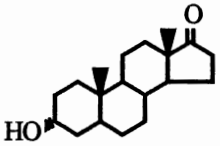
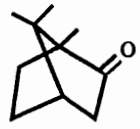
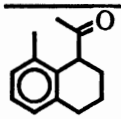
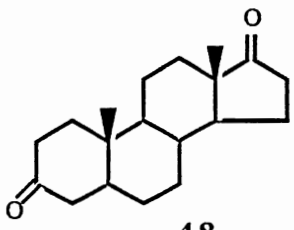
Ketone			TFA-d	Exchange(s)		Pot Residue	Product	%d					
Structure	No.	g (mmol)	mL (mmol)	condition[a]	# of	g (%)	g (%)	d_0	d_1	d_2	d_3	d_4	d_5
	**39**	3.34 (10)	6 (77)	RT 1 day (E)	4			0.00	0.00	99.41	0.59	0.00	0.00
	**48**	2.87 (10)	8 (103)	RT 1 day (E)	9								
	**49**	0.145 (0.5)	3 (39)	RT 2 days (E)	3 4			4.81 6.37	93.68 93.63	0.00 0.00	0.00 0.00	0.00 0.00	1.51 0.00
	**12**	6.096 (40)	14 (180)	Reflux 3 days(F)	3	0.105 (1.7)	5.125 (1.84)	1.95	4.96	93.09	0.00	0.00	0.00

Table IV (Continued)

Ketone			TFA-d	Exchange(s)		Pot Residue	Product	%d					
Structure	No.	g (mmol)	mL (mmol)	condition[a]	# of	g (%)	g (%)	d_0	d_1	d_2	d_3	d_4	d_5
	**38**	1.88 (10)	6 (77)	RT 1 day (E)	4	0.064 (3.4)	1.789 (94)	1.16	11.82	37.16	39.62	10.03	0.21

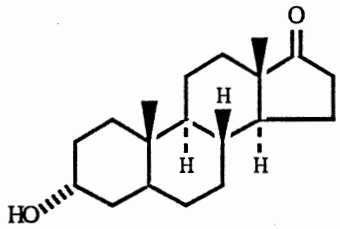
[a]Described in E or F as indicated in Experimental



48

α–carbons (as can be seen from Spectra 3 and 4). However, the signal at δ 35.81, though diminishing in intensity, persisted even after two additional exchanges. Mass spectral data indicated a product mixture consisting of d_5:d_6 (3:1); exact calculations were not possible since the program used to calculate deuterium incorporation could not calculate for greater than d_5.

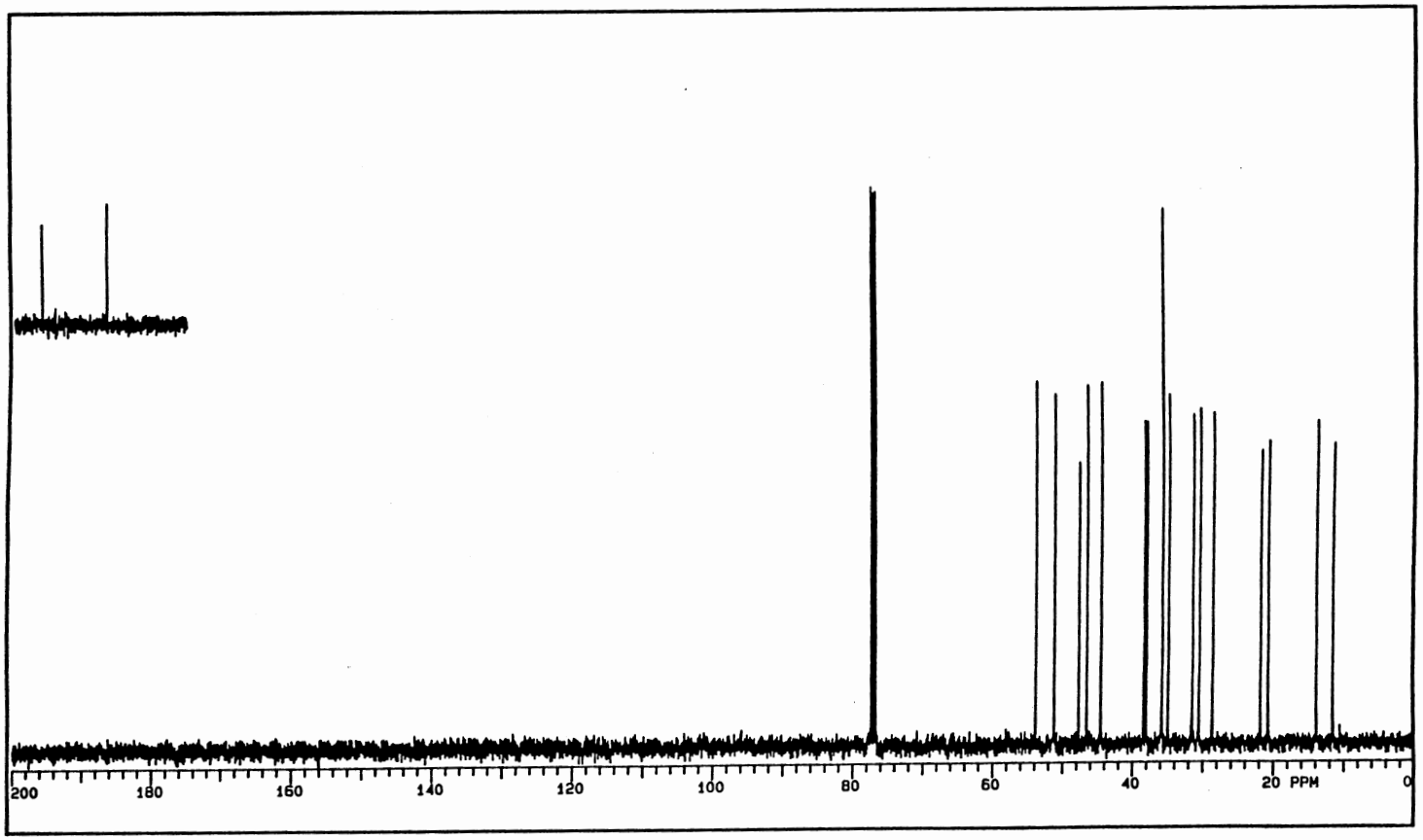
In order to locate the non-exchangeable site of **48** and in order to investigate whether a hydroxyl group survives the exchange conditions, exchange was attempted on 5 α–androstan-3α–ol-17-one (androsterone) (**49**). In view of the slower exchange rate



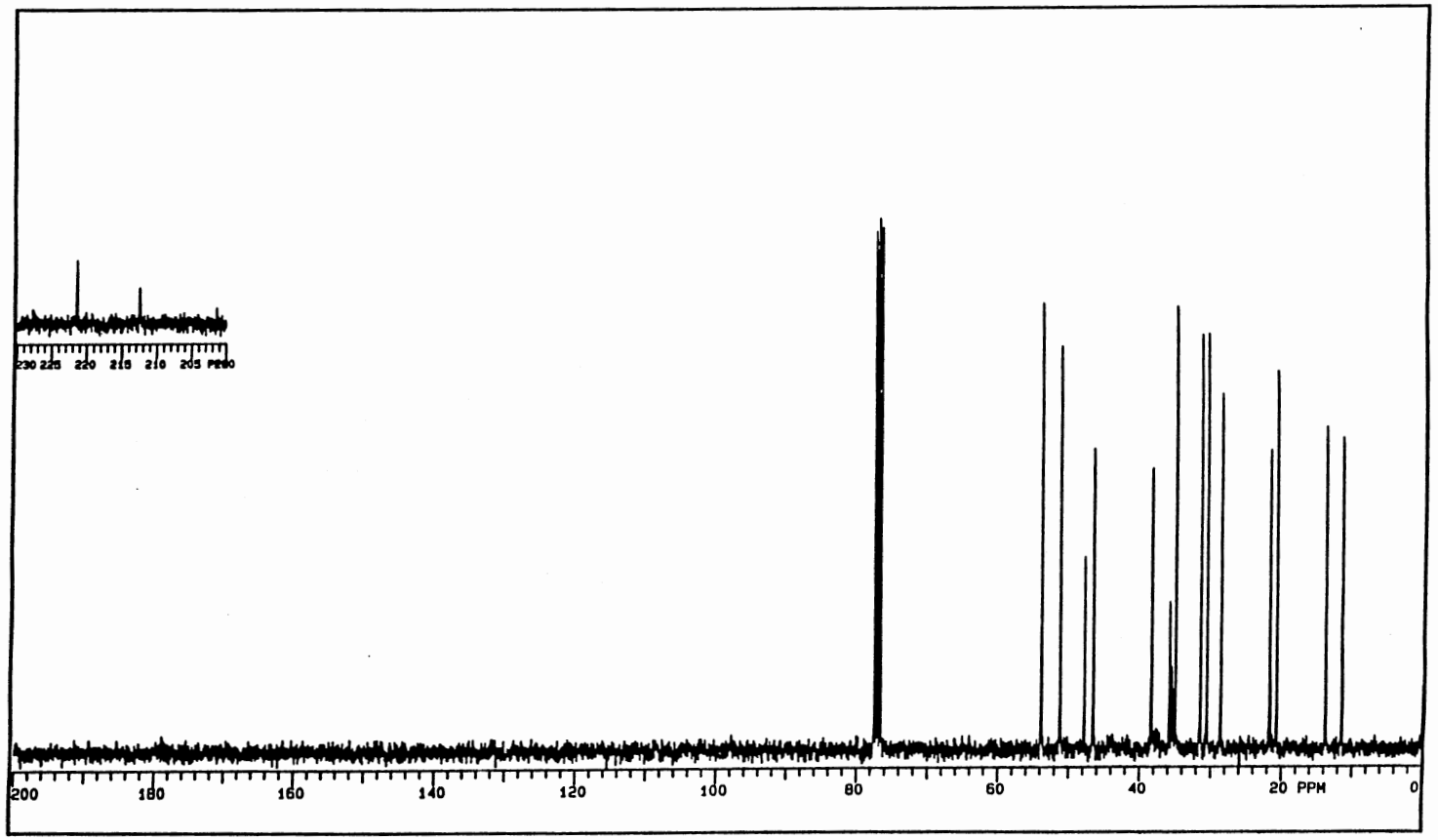
49

found for the previous example, conditions were modified and exchange was attempted using 0.5 mmol of the steroid in 3 mL TFA-d and stirring for 2 days. After 3 exchanges (6 days) the product had 93.68% d, and 0.00% d_2. An additional exchange (2 days) did not result in more deuterium incorporation. ^{13}C NMR indicated that there was some exchange at the carbon corresponding to δ 35.79. Since there was incomplete exchange at the carbon corresponding to δ 35.81 of androstanedione (**48**) it can be concluded that these two steroids preferentially exchange one of the α–carbonyl protons of the cyclopentanone ring.

In order to explain such selectivity, the conformation of ketone **49** was considered. In the rigid steroid system, the cyclopentanone ring is not capable of pseudorotation, as

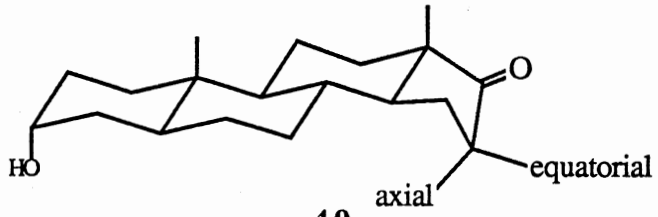


Spectrum 3. ^{13}C NMR ($CDCl_3$) of 3,17-Androstanedione (48).



Spectrum 4. ^{13}C NMR ($CDCl_3$) of 3,17-Androstanedione (48) after Seven Exchanges.

such the α–carbonyl protons are fixed, one each in the equatorial and axial orientation as shown below.

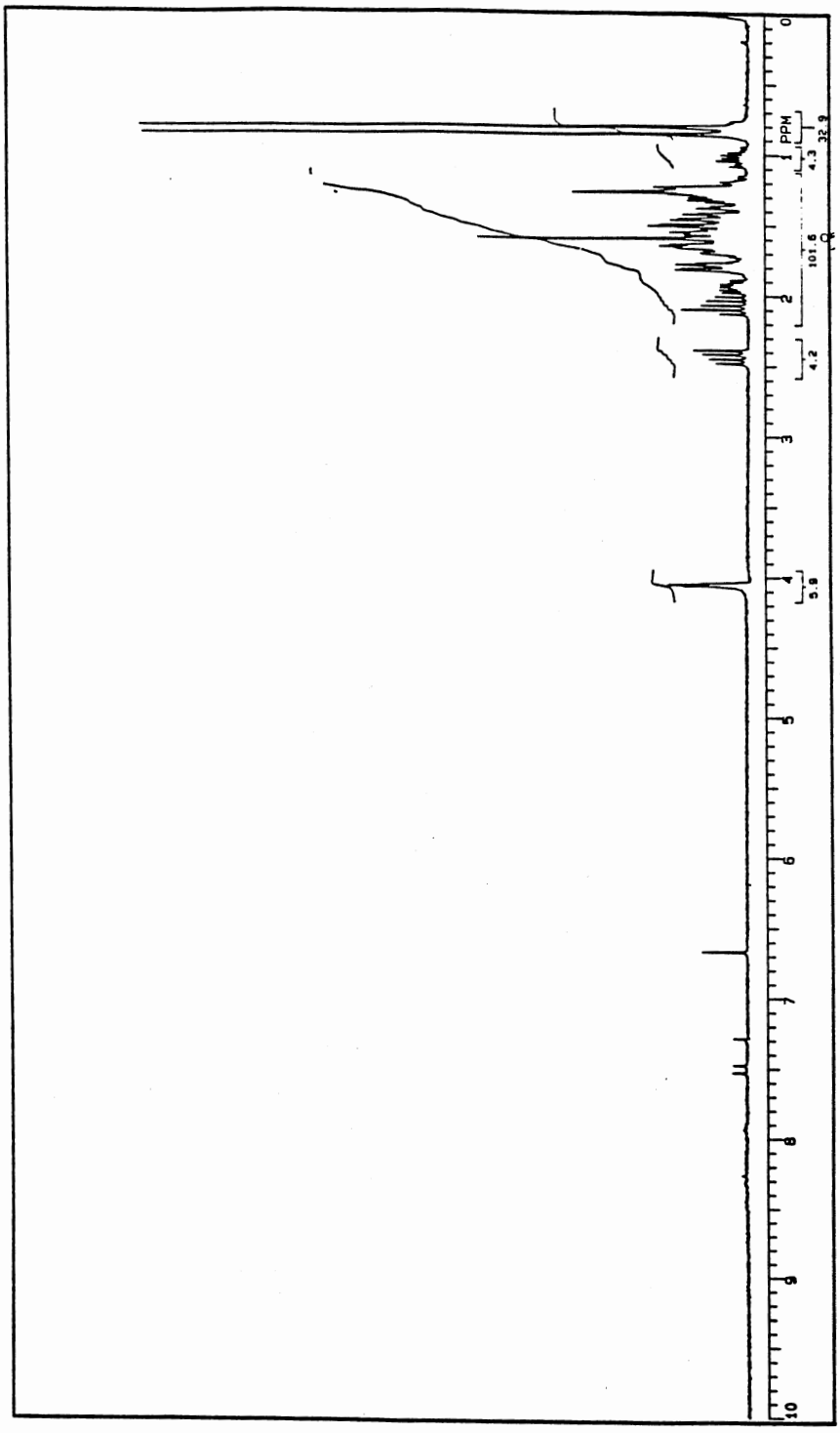


49

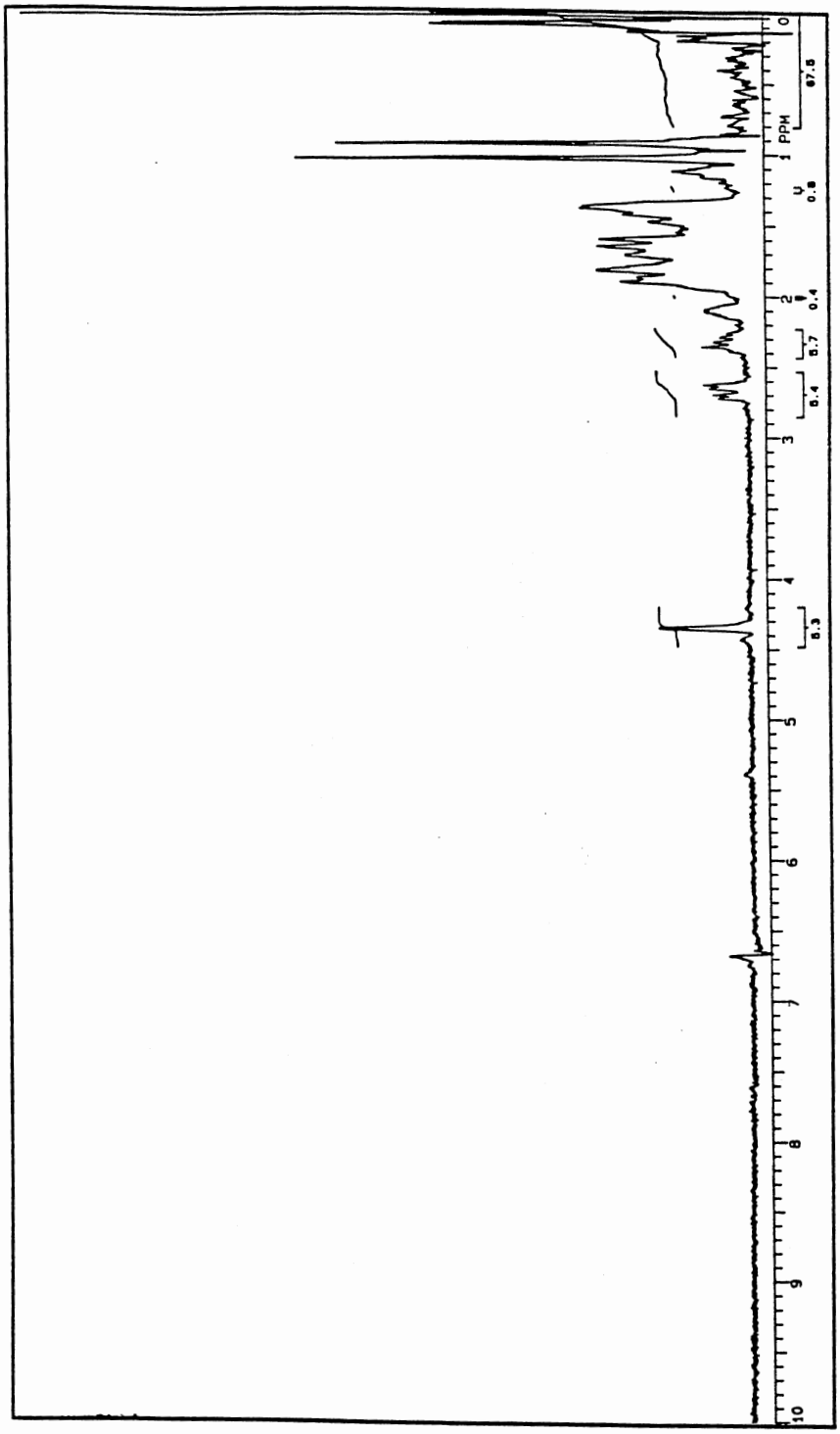
NMR evidence (Spectra 5, 6 and 7) indicates that the proton, α to the carbonyl group, with signal at δ 2.25-2.40 of spectrum 6 is exchanged.

The α–carbonyl protons of **49** are easily identified since the signals in $CDCl_3$ appear at δ 2.38-2.50 (m, 1), 2.00-2.15 (m, 1) whereas in TFA-d these signals are deshielded to δ 2.60-2.75 (m, 1), 2.25-2.40 (m, 1). A 2D NMR study in $CDCl_3$ and in TFA-d indicates that both of these protons are bound to a single carbon. The upfield signals disappear after exchange whereas the downfield signals persist and appear at δ 2.45 (d, 1) in $CDCl_3$ and 2.65 (d, 1) in TFA-d. The 2D NMR study in $CDCl_3$ (Spectra 8 and 9) and in TFA-d indicates that this proton is attached to the carbon at which exchange had occurred.

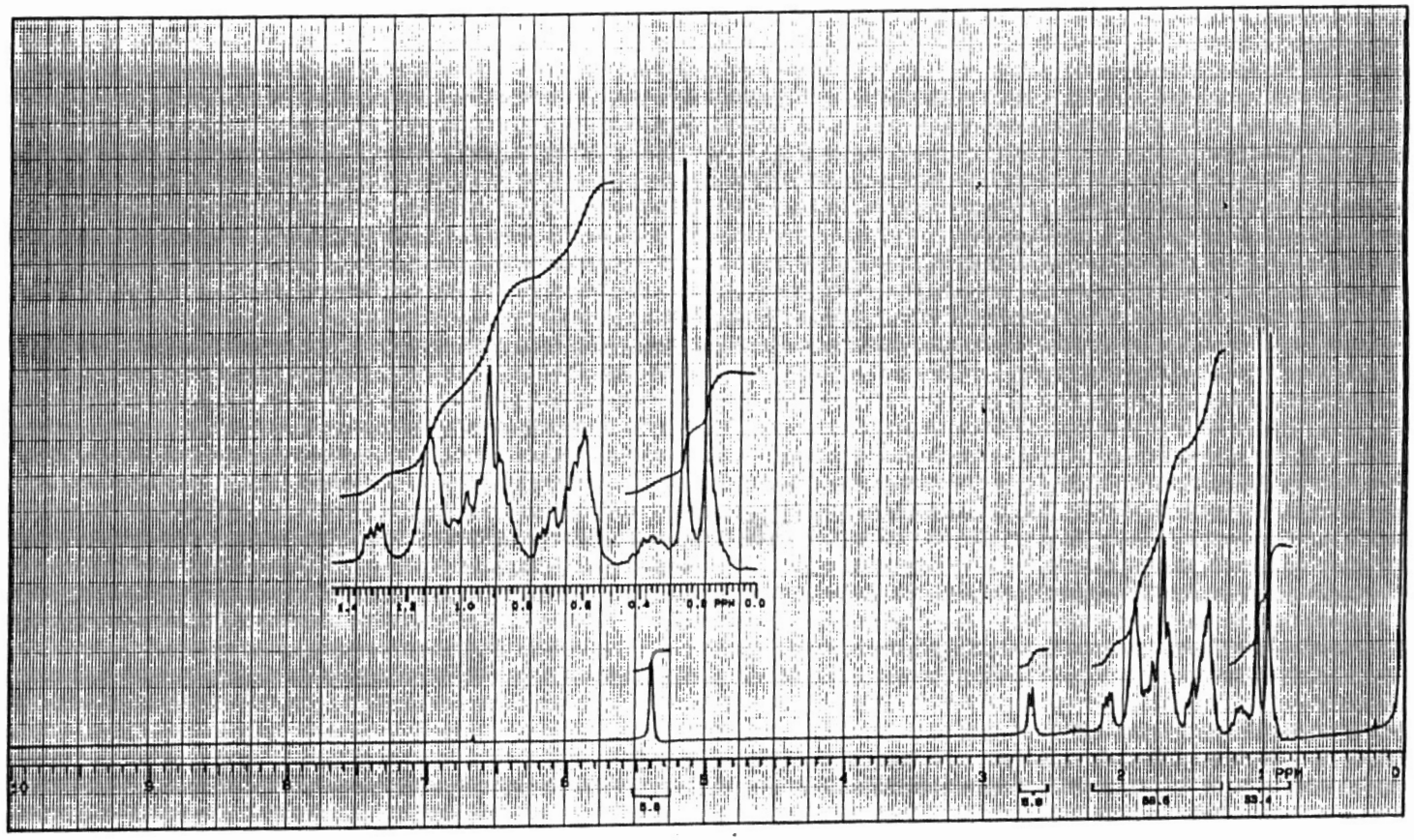
Examination of a Dreiding model of **49** showed that the equatorial proton is near the plane of the carbonyl with the axial proton being perpendicular. As such, the axial proton would be more readily exchanged as interaction of the unshared electrons of the carbonyl π system is bonding when the unshared electron pair is in the axial position and non bonding when the unshared pair is equatorial. This is illustrated on page 38 and is an application of the Corey mechanism shown on page 8.



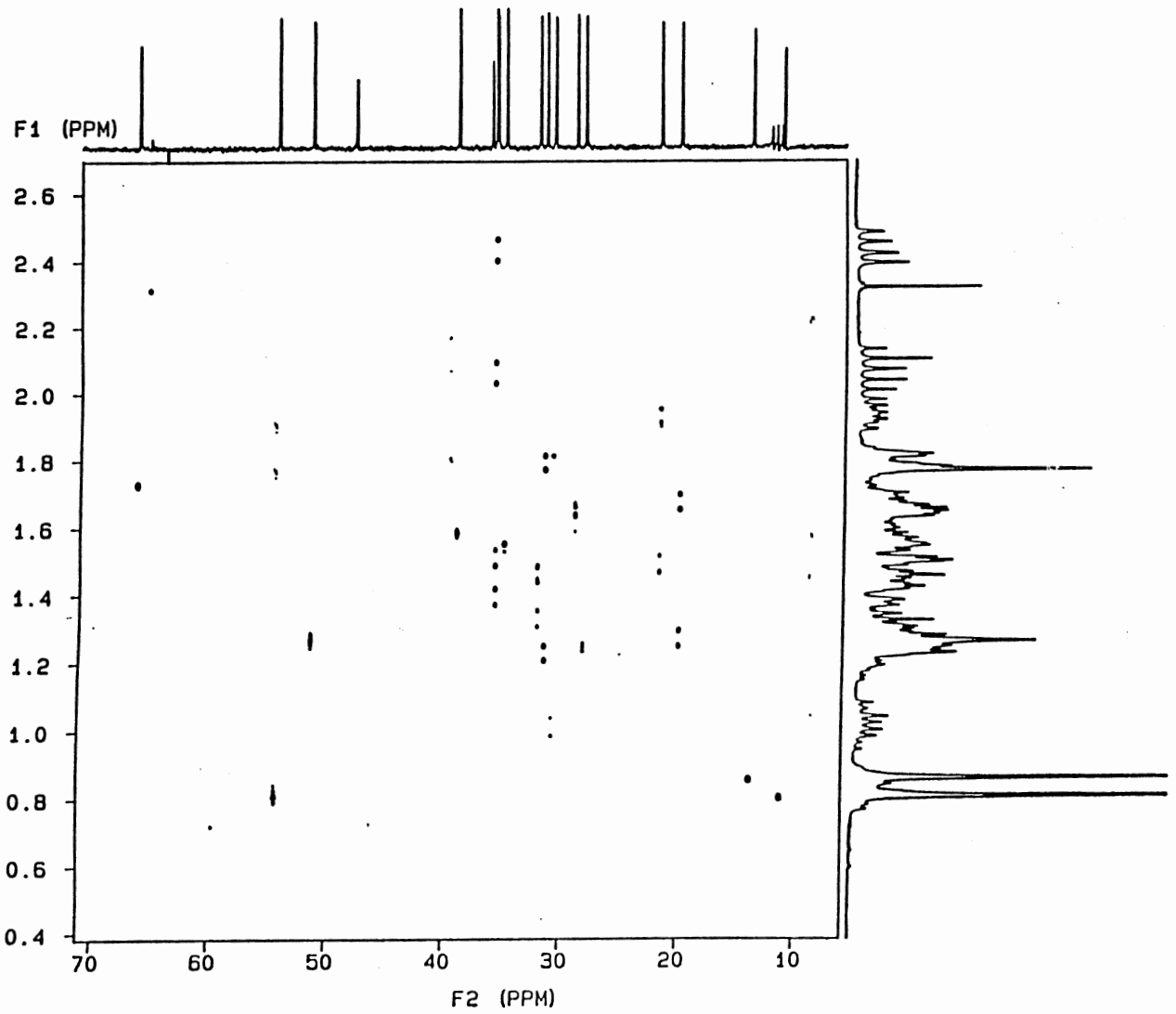
Spectrum 5. ^{1}H NMR ($CDCl_3$) of Androsterone (49).



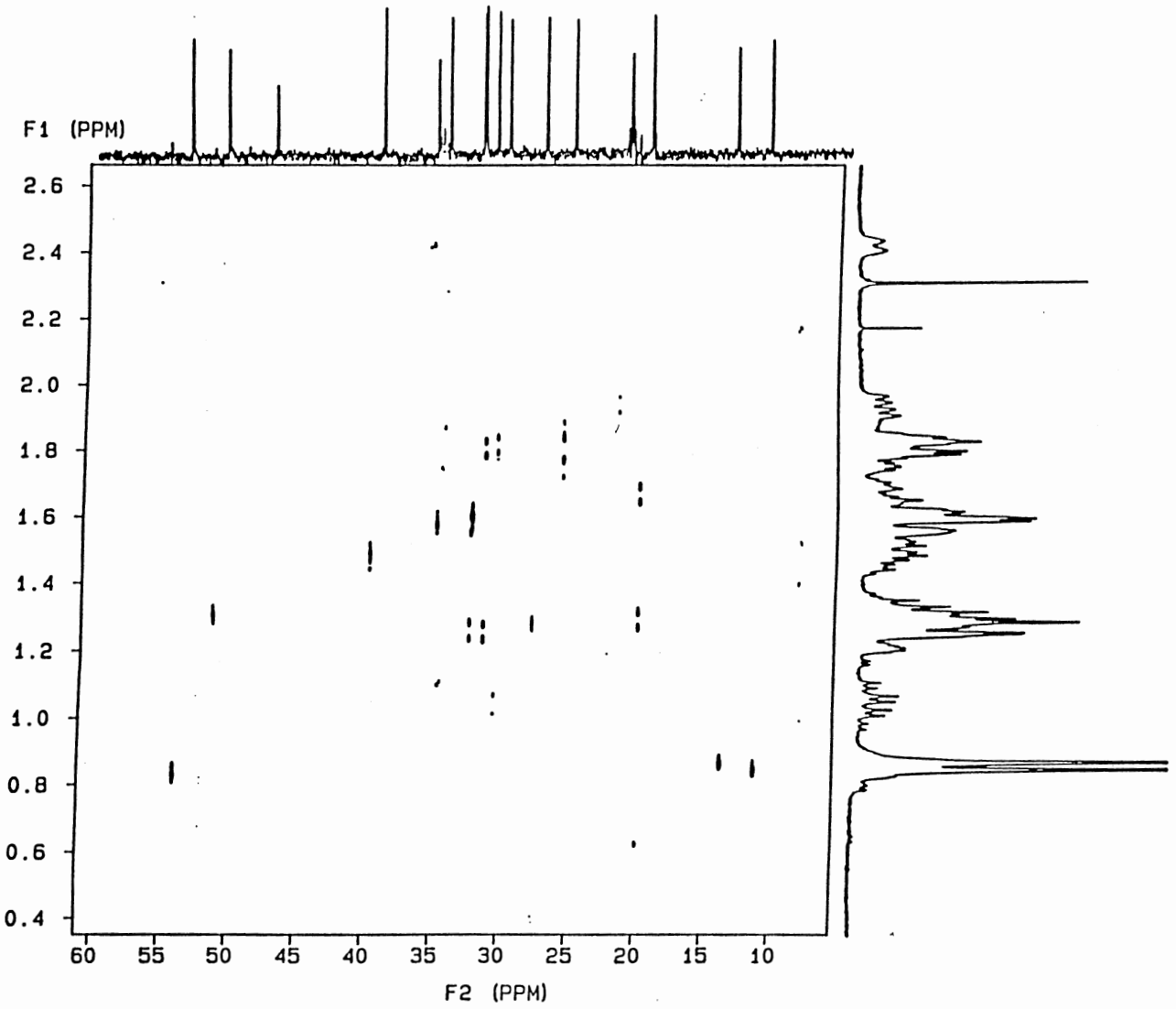
Spectrum 6. ^{1}H NMR (TFA-d) of Androsterone (49).



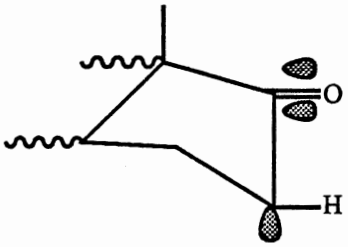
Spectrum 7. ^{1}H NMR (TFA-d) of Androsterone (49) After Exchange.



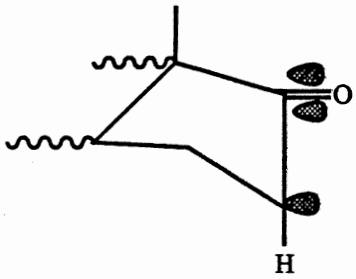
Spectrum 8. 2D NMR ($CDCl_3$) of Androsterone (49).



Spectrum 9. 2D NMR ($CDCl_3$) of Androsterone (49) After Exchange.



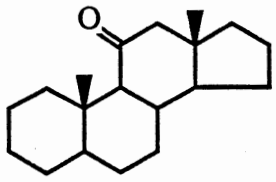
Bonding



Non-bonding

As discussed earlier on page 7, the rate determining step in acid-catalyzed enolization is the one involving α–proton abstraction. In addition, the α–proton removed must be perpendicular or trans coplanar (in the same plane) to the direction if the C=O bond in order to permit a stabilizing delocalization of the σ electrons of the C-α–H bond towards the π orbital of the carbonyl. In addition to the stereoelectronic factors discussed above, additional tortional effects as a result of unfavorable steric effects in the transition state to (or coming from) the enol might also contribute to such selectivity.

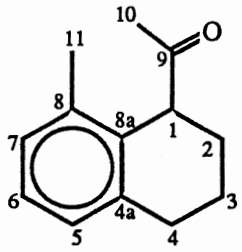
Such specific exchange has been observed in a few systems. It was found that 5-α–androstan-11-one (**50**) could be specifically deuterated in the axial positions with 91% incorporation using sodium in $MeOD/D_2O$.[41] Also, it has been reported that norbornyl 2-ketones, under basic conditions, exchanges primarily in the exo position.[22,23]



50

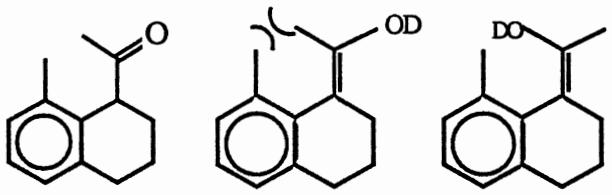
In the current study, it was found that d-camphor (**12**) did not undergo exchange when stirred in TFA-d for seven days at room temperature. However, exchange of both α-protons was achieved by refluxing (3x3 days) in TFA-d. The fact that more forcing conditions were needed, as compared to other ketones used in this study, is expected as additional energy would be required to induce enolization.

Ketone **38,** after four exchanges under conditions indicated in Table IV, gave a



38

product of 1.16% d_0, 11.82% d_1, 37.16% d_2, 39.62% d_3, 10.03% d_4 and 0.21% d_5. ^{1}H NMR indicated that only about 10% of the methine and 75% of the methyl protons had exchanged. After 10 exchanges, ^{1}H NMR indicated that only about 30% of the methine proton had exchanged although the acetyl methyl protons had completely exchanged by the seventh treatment. The disparity in the rate of the proton exchange at these two positions can be rationalized as follows. Examination of a Dreiding model indicates that a flattening of the tetralin ring takes place during enolization of the methine proton and formation of an exocyclic double bond. This would force either the methyl (**38E$_1$**) or the OD moiety (**38E$_2$**) into closer proximity of the methyl at C-8. Thus enolization leading to increased

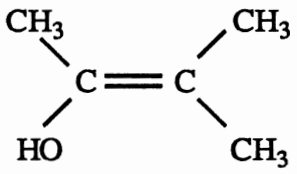


38 **38E$_1$** **38E$_2$**

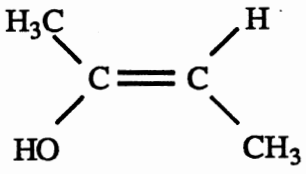
steric interaction would not be favored and the methine proton of ketone **38** is exchanged very slowly as compared to α–protons of other ketones, except d-camphor, used in this study.

Rappe and Sachs also observed steric inhibition to deuteration.[42] They found that the deuteration of the methine group of 3-methyl-2-butanone (**51**) is less than half as fast as the methylene group of 2-butanone (**52**). An examination of the intermediate enol of these

two compounds indicates greater steric interaction of the terminal methyl groups in **51E** as compared to **52E**.



51E

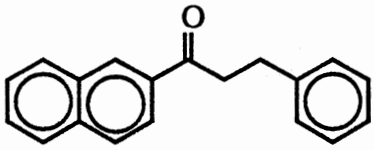


52E

Investigation of Possible Side Reactions of Ketones in TFA-d

Ketones **24, 40, 49** and **53** were studied with a view to investigating the possibility of dehydration, skeletal rearrangement and exchange of aromatic and benzylic protons in TFA-d. The experimental conditions and results obtained from these studies are summarized in Table V.

It was found that ketone **24**, exchanged only the α–carbonyl protons when stirred in TFA-d at room temperature but when heated in refluxing TFA-d until α–carbonyl protons completely exchanged there was exchange of some benzylic and aromatic protons.



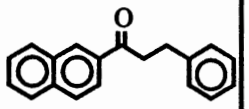
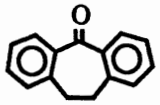
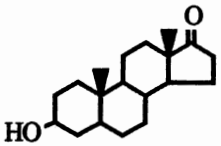
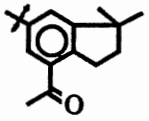
24

In order to estimate the relative percentage deuterium incorporation in the different parts of **24**, a comparative mass spectral analysis was done on each of the major fragments of this compound obtained from these two methods (room temperature and reflux) of labelling. The results are summarized in Table VI.

The data in Table VI indicate that when exchange was effected by refluxing there was about 10% deuterium incorporation in the napthyl ring and about the same amount at

Table V

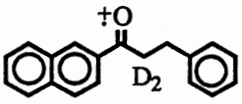
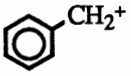
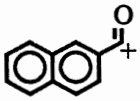
Side Reactions of Ketones in TFA-d

Ketone			TFA-d	Exchange(s)		Pot Residue	Product	%d					
Structure	No.	g (mmol)	mL (mmol)	condition[a]	# of	g (%)	g (%)	d_0	d_1	d_2	d_3	d_4	d_5
	**24**	2.60 (10)	6 (77)	RT 1 day (E)	4			1.25	5.81	92.34	0.61	0.00	0.00
	24	2.60 (10)	6 (77)	Reflux 1 day(F)	2			0.65	2.58	32.37	39.93	20.08	4.12
	**40**	2.083 (10)	6 (77)	RT 7 days (E)	1	0.049 (2.2)	2.030 (97)	99.59	0.41	0.00	0.00	0.00	0.00
	40	2.083 (10)	6 (77)	Reflux 7 days(F)	1	0.056 (2.7)	2.016 (97)	98.63	0.99	0.00	0.36	0.00	0.00
	**49**	0.145 (0.5)	3 (38.5)	RT 2 days (E)	3 4			4.81 6.37	93.68 93.63	0.00 0.00	0.00 0.00	0.00 0.00	1.51 0.00
	**53**	4.88 (20)	6 (77)	RT 1 day (E)	5			0.32	0.80	6.78	92.09	0.00	0.00

[a]Described under E or F in Experimental.

Table VI

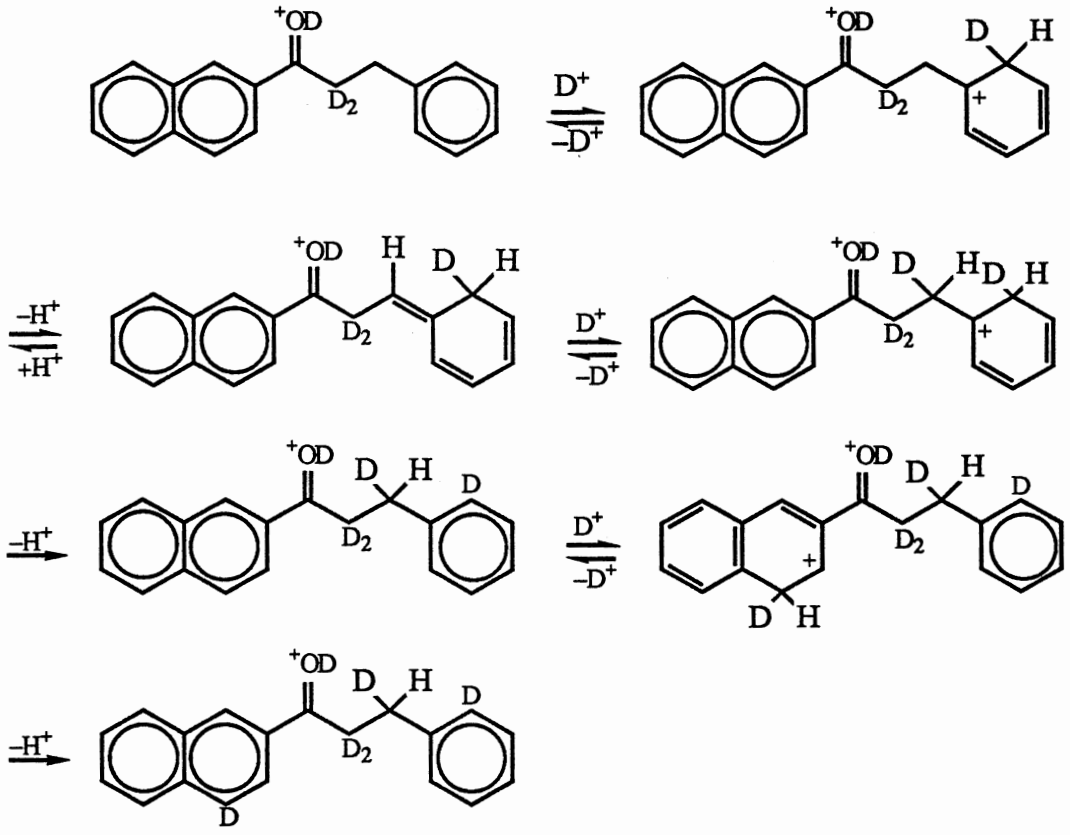
Comparison of Distribution of Deuterium in Product from Exchange of Ketone **24** with TFA-d at Room Temperature and at Reflux

M	Fragment Ion	Exchange Condition	% d					
			d_0	d_1	d_2	d_3	d_4	d_5
260		a	0.65	2.85	32.37	39.93	20.08	4.12
		b	0.64	4.31	94.31	0.52	0.00	0.23
77		a	54.49	15.95	8.31	10.33	8.31	2.60
		b	65.28	0.00	6.99	16.51	8.40	2.82
91		a	24.64	35.58	17.87	10.27	6.89	4.74
		b	73.98	12.51	0.00	3.01	5.16	5.33
127		a	85.30	10.26	0.87	1.05	0.60	1.91
		b	97.61	0.00	0.26	0.84	0.34	0.96
155		a	88.40	9.95	1.13	0.29	0.09	0.14
		b	98.92	0.30	0.64	0.14	0.00	0.00

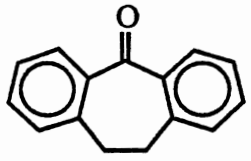
[a]Stirring at Reflux. [b]Stirring at Room Temperature.

the benzyl portion of the molecular. A significantly larger amount (~25%) of incorporation occurred at the benzylic position when α-exchange was carried out in refluxing TFA-d.

The following mechanism can be used to explain simultaneous exchange of the aromatic and benzylic protons of ketone **24**.



Dibenzosuberone (**40**) did not significantly exchange benzylic or aromatic protons when stirred for seven days in TFA-d nor did exchange exceed 1% d_1 (Table VI) when it was treated with TFA-d at reflux for 7 days.

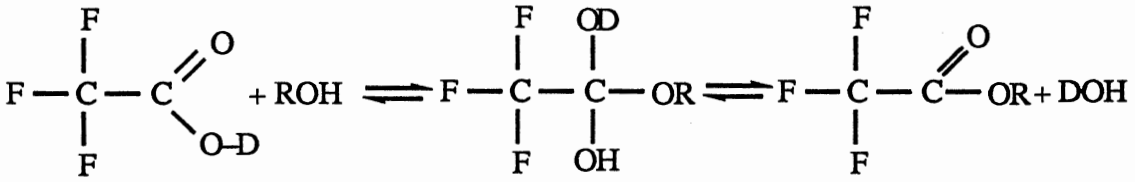


40

However, polycyclic aromatic hydrocarbons are generally more reactive than benzene towards both electrophilic and nucleophilic aromatic[44] substitution. Thus it is not surprising that the naphthyl portion of **24**, though deactivated by the carbonyl

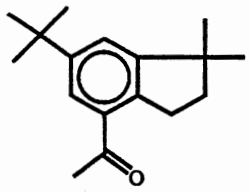
surprising that the naphthyl portion of **24**, though deactivated by the carbonyl group, still undergoes some exchange in refluxing TFA-d as shown for m/e 155 in Table VI.

The secondary alcohol, androsterone (**49**) does not dehydrate when stirred in TFA-d since esterification in excess TFA-d is more rapid than dehydration and consequently the trifluoro acetate results. The following mechanism can be written for this process:



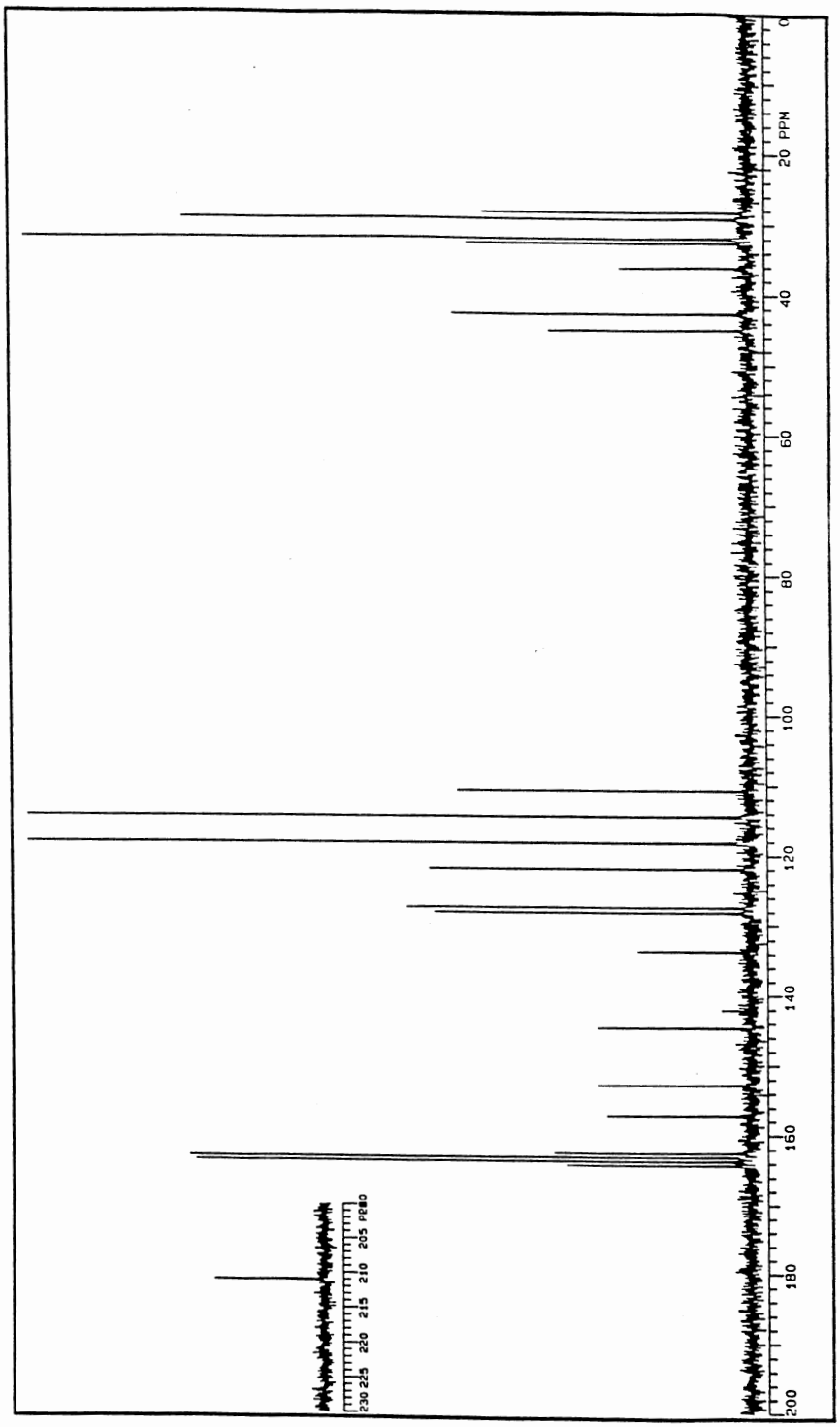
NMR evidence indicated that complete esterification of **49** resulted during the first two days of exchange.

Ketone, **53**, is known to lose the *tert.*butyl group on treatment with $AlCl_3$.[43] However, exchange with TFA-d at room temperature took place without side reactions as can be seen from a comparison of the ^{13}C NMR spectra at the beginning (Spectrum 10) and the end (Spectrum 11) of the reaction.

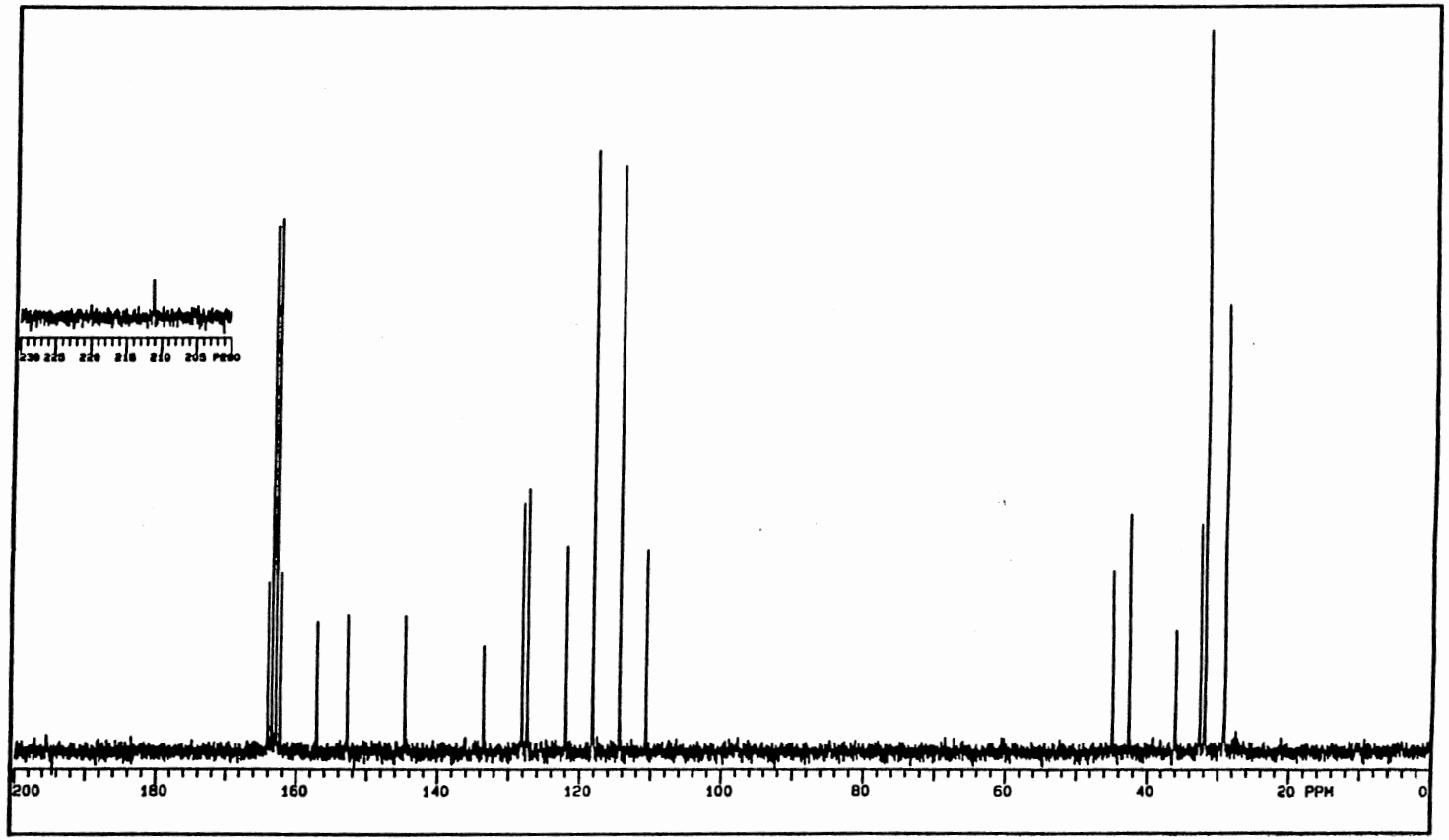


53

Nilsson and Olsson studied aliphatic and aromatic exchange in some polyalkylated hydrocarbons using TFA-d[45]. The hydrocarbon (0.23 mmol in 1 mL CCl_4) was added to 2 mL (26.6 mmol) of TFA-d; the mixture was kept at 40° for 60 h and the solvent and TFA-d were then distilled at reduced pressure. This procedure was repeated 3 times. They found that for compounds **54-63**, the aromatic protons were exchanged in all compounds except **56, 57** and **62** which are not sufficiently activated to undergo aromatic hydrogen

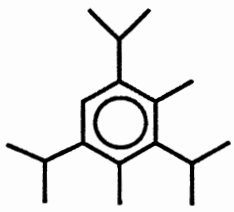


Spectrum 10. ^{13}C NMR (TFA-d) of Celestolide (53).

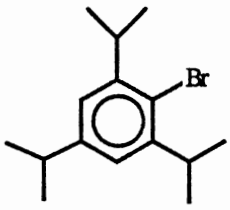


Spectrum 11. ^{13}C NMR (TFA-d) of Celestolide (53) After Exchange.

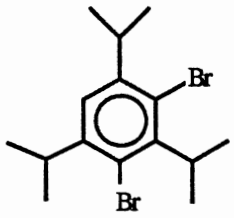
exchange under the experimental conditions.[45] Evidence for exchange of aliphatic protons in any of these compounds (**54-62**) was not found.[45] However, treatment of **63** under the



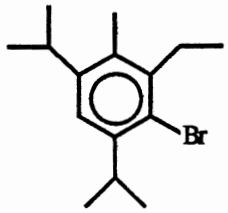
54



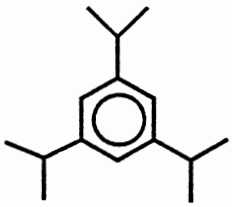
55



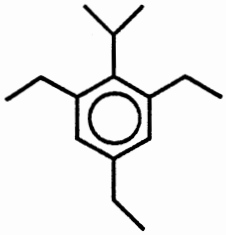
56



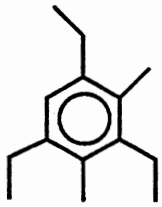
57



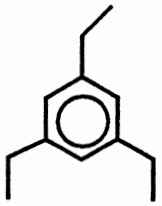
58



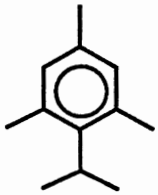
59



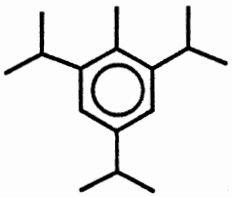
60



61



62



63

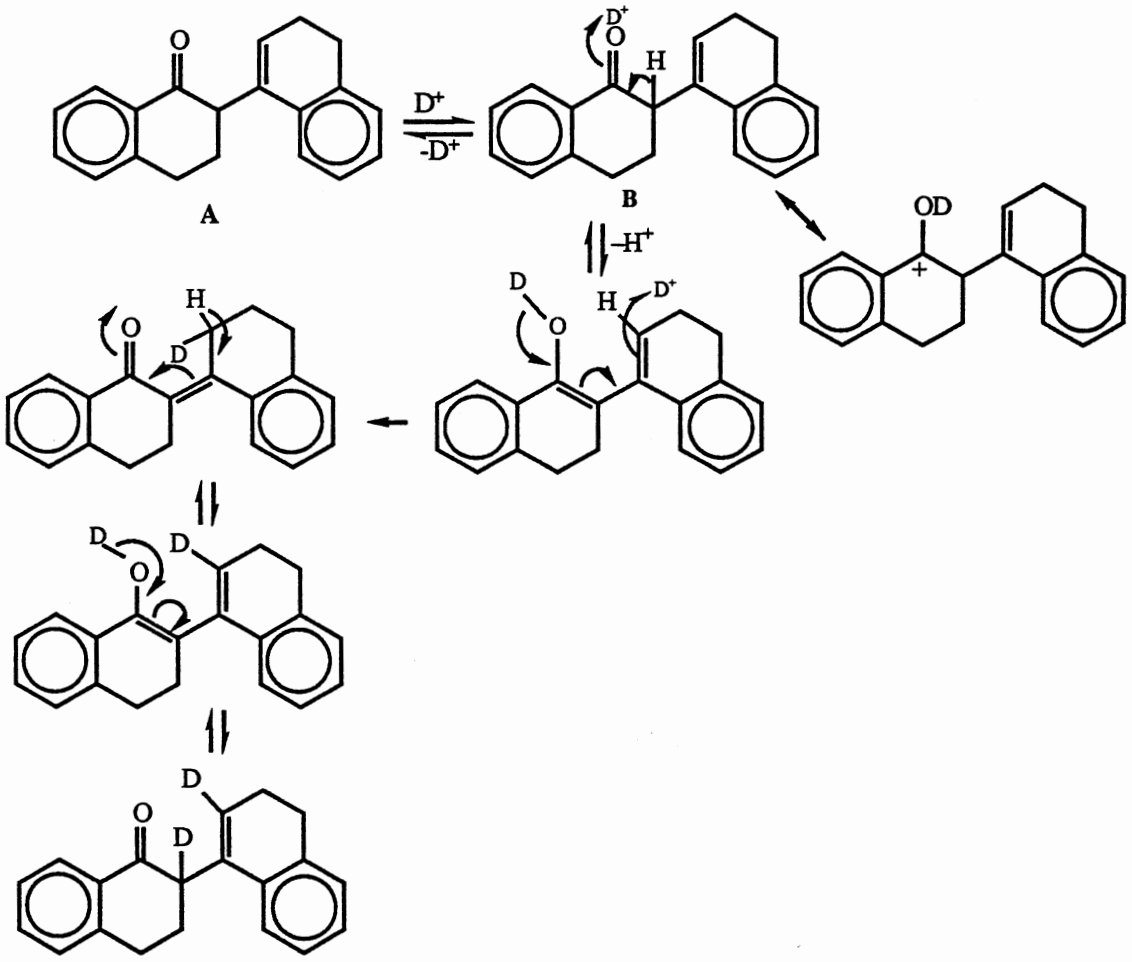
same conditions resulted in exchange of the aromatic protons and the methyl protons on the isopropyl group at C-4 resulting in a product with eight deuterium atoms.[45]

As indicated earlier, one of the limitations of TFA-d, as an exchange solvent, is that the process is slow. Much faster rates of exchange are obtained in refluxing TFA-d. However, this is not recommended as condensation products become significant and exchange of benzylic and aromatic protons is likely.

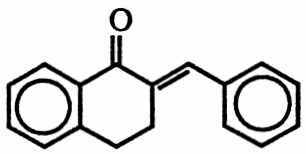
Exchange of Unsaturated Ketones in TFA-d

The use of TFA-d as an exchange solvent for the unsaturated ketones shown in Table VII was investigated.

Through careful control of the reaction conditions, it became possible to selectively label the dimer of α–tetralone, ketone **18**, in the α and 'γ positions. The labelling was adequate to permit mass fragmentation studies of this molecule. However, stirring for much longer periods or refluxing in TFA-d resulted in extensive bond migration. To explain this, the following mechanism is suggested.



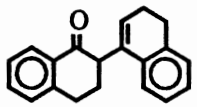
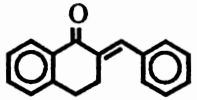
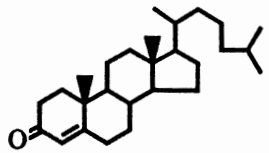
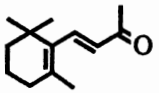
In ketone **42**, the exocyclic double bond is relatively stable as it is in conjugation



42

TABLE VII

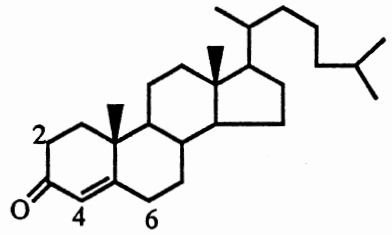
EXCHANGE OF UNSATURATED KETONES IN TFA-d

Ketone			TFA-d	Exchange(s)[a]		Pot Residue	Product	%d					
Structure	No.	g (mmol)	mL (mmol)	Time	# of	g (%)	g (%)	d_0	d_1	d_2	d_3	d_4	d_5
	**18**	0.274 (1)	4 (51)	3 h	1			9.93	0.00	89.10	0.00	0.00	0.97
	**42**	2.34 (10)	6 (77)	7 days	1			100.00	0.00	0.00	0.00	0.00	0.00
	**64**	3.84 (10)	10 (128)	1 day	4			0.00	0.00	20.66	42.23	33.79	3.32
	**65**	1.923 (10)	3 (39)	1 day	3	1.355 (70)	0.560 (29)						

[a]Stirring at room temperature. Described under E in Experimental.

with the carbonyl group and the phenyl ring and no exchange was seen, even after stirring in TFA-d for 7 days. However, refluxing for one day resulted in bond migration.

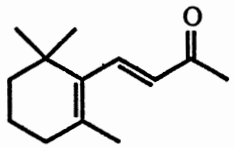
Cholestenone (**64**) was treated with TFA-d until the ^{13}C signal assigned to C-2 at δ 33.9 collapsed. Since, no additional ^{13}C signals were seen and mass spectral analysis



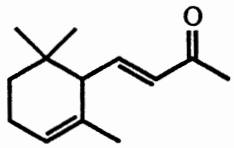
64

indicated a product with five deuterium atoms, the likely sites are C-2, C-4 and C-6. It appears that exchange could be continued to deuterate these sites completely without side reactions.

Attempts to effect exchange in β-ionone (**65**) resulted in mostly pot residue (70%) and a distillate which GC/MS indicated to be a complex mixture of products possibly arising from bond migration and cleavage. However, there are literature reports that both



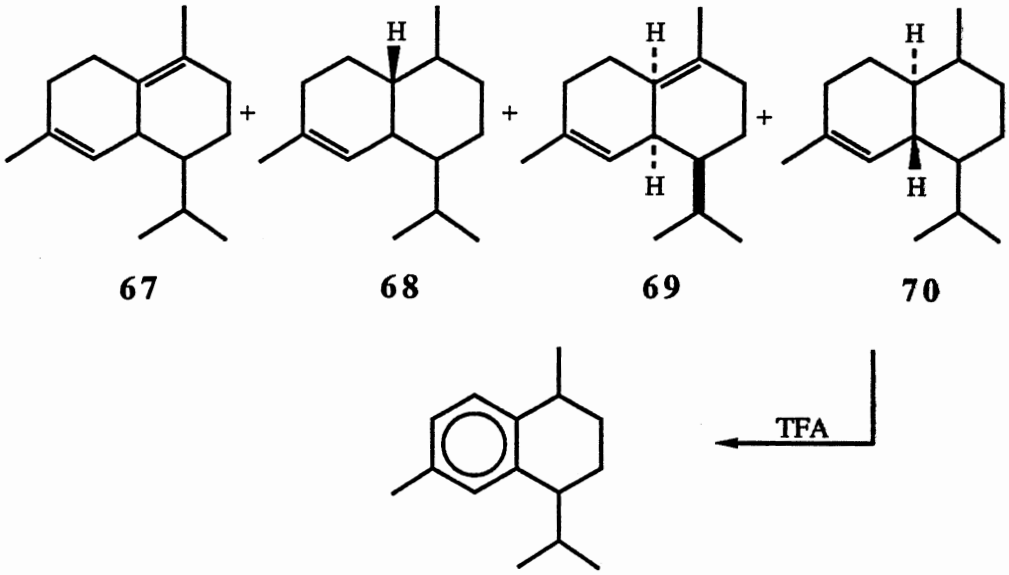
65



66

β-ionone (**65**) and α–ionone (**66**) were deuterated exclusively in the acetylmethyl group in D_2O/D_2SO_4[46] and in D_2O/base.[47]

It has been reported that the cadinane hydrocarbons (**67-70**) were each converted, in a few minutes, to calamenene (**71**) when a 1-5% n-decane solution of the olefin was



67 68 69 70

71

treated with excess trifluoroacetic acid at room temperature with stirring.[48]

The aromatization was explained by a mechanism that includes a step involving hydride abstraction either by intermediate cations from protonation of the hydrocarbons or by the high concentration of H^+ from the acid.[48]

In order to better understand this property of TFA and how it might limit TFA-d as an exchange solvent, the behavior of 9,10-dihydroanthracene (**72**) and anthracene (**73**) in TFA and TFA-d was investigated. The experimental conditions and results are summarized in Table VIII.

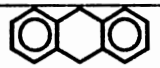
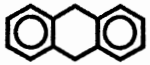
72 **73**

Stirring 0.72 mmol of compound **72** with 36 mL TFA-d and 5 mL THF for 7 days resulted in deuterated anthracene and undeuterated starting material in the ratio of 1.5:1 respectively. The use of TFA instead of TFA-d resulted in a mixture of anthracene (**73**) and starting material (**72**) in the ratio of 27:1.

Refluxing 0.72 g (4 mmol) of **72** in 12 mL of refluxing TFA-d resulted in the formation of deuterated anthracene (mainly d-10) and deuterated starting material (mainly d-

Table VIII

Effects of TFA/TFA-d on Anthracene and 9,10 Dihydroanthracene

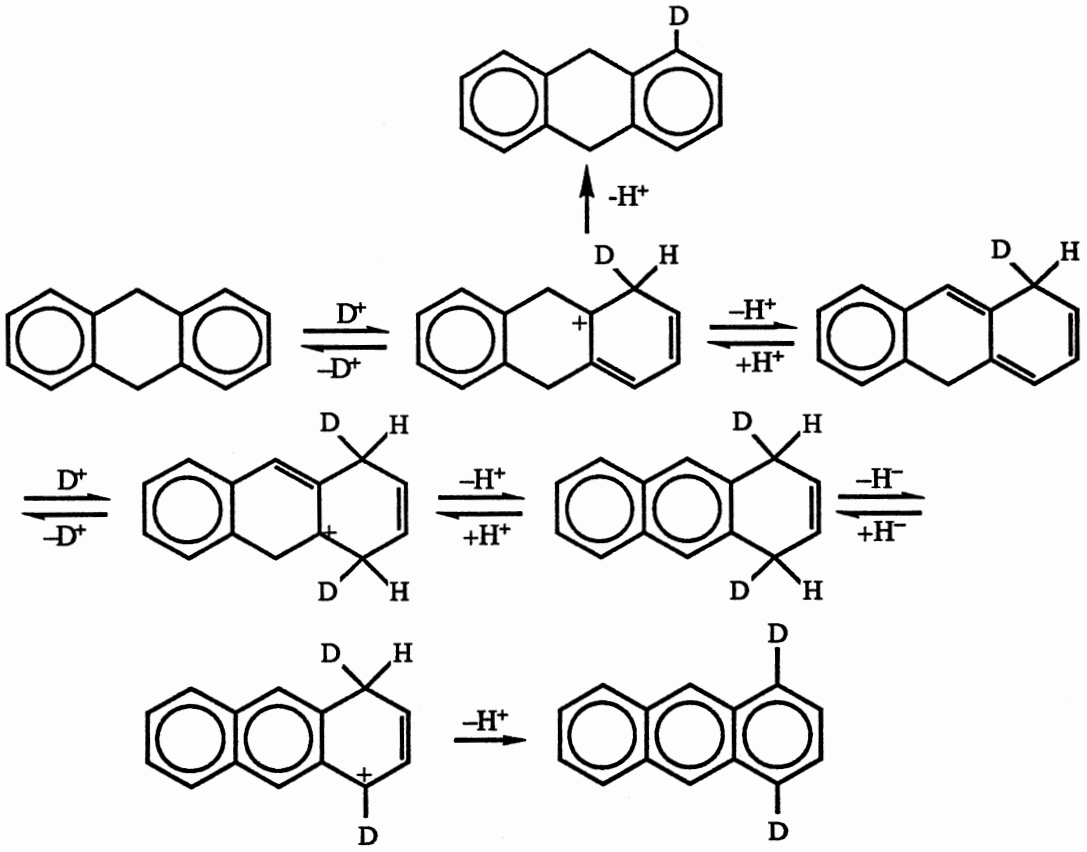
Hydrocarbon		g (mmol)	Amount of Reagent	Reaction Condition[a]	No. of Exchange	Products formed	
Structure	No.	Hydrocarbon					
	72	0.72 (4)	36 mol TFA-d in 5 mls THF	RT 7 days (G)	1	[b] 1 : 1.5 [c] D_0	[c] Mainly D_2
	72	0.72 (4)	36 mls TFA in 5 mls THF	RT 7 days (G)	1	[b] 1 : 30	
	72	0.72 (4)	12 mls TFA-d	Reflux 3 days (H)	2	[b] 6 : 1 [c] Mainly D_{14}	[c] Mainly D_{10}
	73	0.71 (4)	12 mls TFA-d	Reflux 3 days (H)	2		[c] Mainly D_{10}

[a]Described under G or H in Experimental. [b]Product ratios, [c]Deuterium incorporation.

14) in the ratio of 1:6. After two exchanges under these conditions, compound **72** was deuterated (mainly d-10).

These results indicate that exchange of aromatic protons can be achieved by refluxing in TFA-d. However, under such conditions benzylic protons (if present) will also exchange and where possible, as in compound **72**, this could lead to aromatization. In addition, aromatization is possible in systems such as 9,10-dihydroanthracene even at room temperature.

This aromatization can be rationalized by the following mechanism.



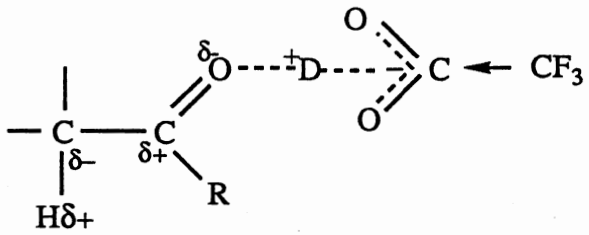
In light of the examples discussed, caution is indicated is the use of TFA-d to effect exchange in unsaturated ketones in which double bond migration and aromatization is likely.

TFA-d as an NMR Solvent for Ketones

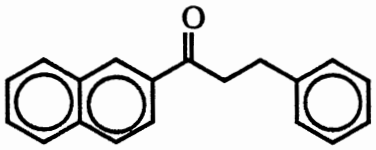
A major advantage of using TFA-d, as an exchange solvent for ketones, is that the progress of the reaction can be monitored by ^{1}H and ^{13}C NMR studies on the neat reaction mixture. Other methods do not afford this opportunity as separation of the exchange solvent/co-solvent and catalysts as well as purification of the product must be done before NMR spectra can be obtained.

In this study, it was noted that protons attached to the α–carbon atoms of ketones dissolved in TFA-d were deshielded by ~0.3 ppm relative to the resonance frequency of the same protons when the spectra was recorded for the ketone in $CDCl_3$. A similar shift was observed in the spectra obtained for ketones using trifluoroacetic acid.[49] The downfield shifts were attributed to hydrogen bonding of the ketone carbonyl with trifluoroacetic acid. It was felt that the acidity of the latter would not promote significant concentrations of the protonated species.[49] In addition, evidence for such hydrogen bonding, obtained from Raman and infrared spectral measurements were cited.[49]

Hydrogen bonding of the carbonyl (of ketones) results in enhanced charge distribution as illustrated below:

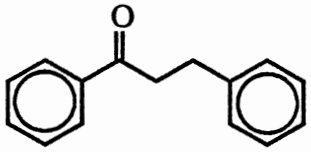


As such, the α–hydrogen(s) would be expected to be more positive with a resultant deshielding of its NMR signals. This deshielding of the α–carbonyl protons of ketones gives TFA-d an additional important advantage as an exchange solvent as it facilitates separation of signals due to α–carbonyl protons from overlapping signals in the ^{1}H NMR spectra. It also provides a simple and quick method for identifying α–carbonyl protons. For example, in the 60 MHz ^{1}H NMR spectrum of ketone **24**, in $CDCl_3$, the four aliphatic protons



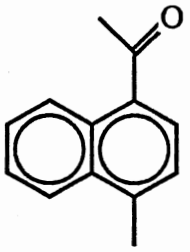
24

overlap at δ 3.0-3.5. However, in TFA-d, these protons appear at δ 3.1 (t, 2H) and 3.5 (t, 2H). Similarly, for ketone **23** in $CDCl_3$, δ 3.0-3.4 (m, 4H) separate to δ 3.2(t, 2H) and 3.7(t,2H) in TFA-d.



23

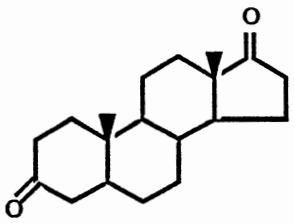
In the 300 MHz ^1H NMR spectrum of ketone **37**, in $CDCl_3$, the two methyl



37

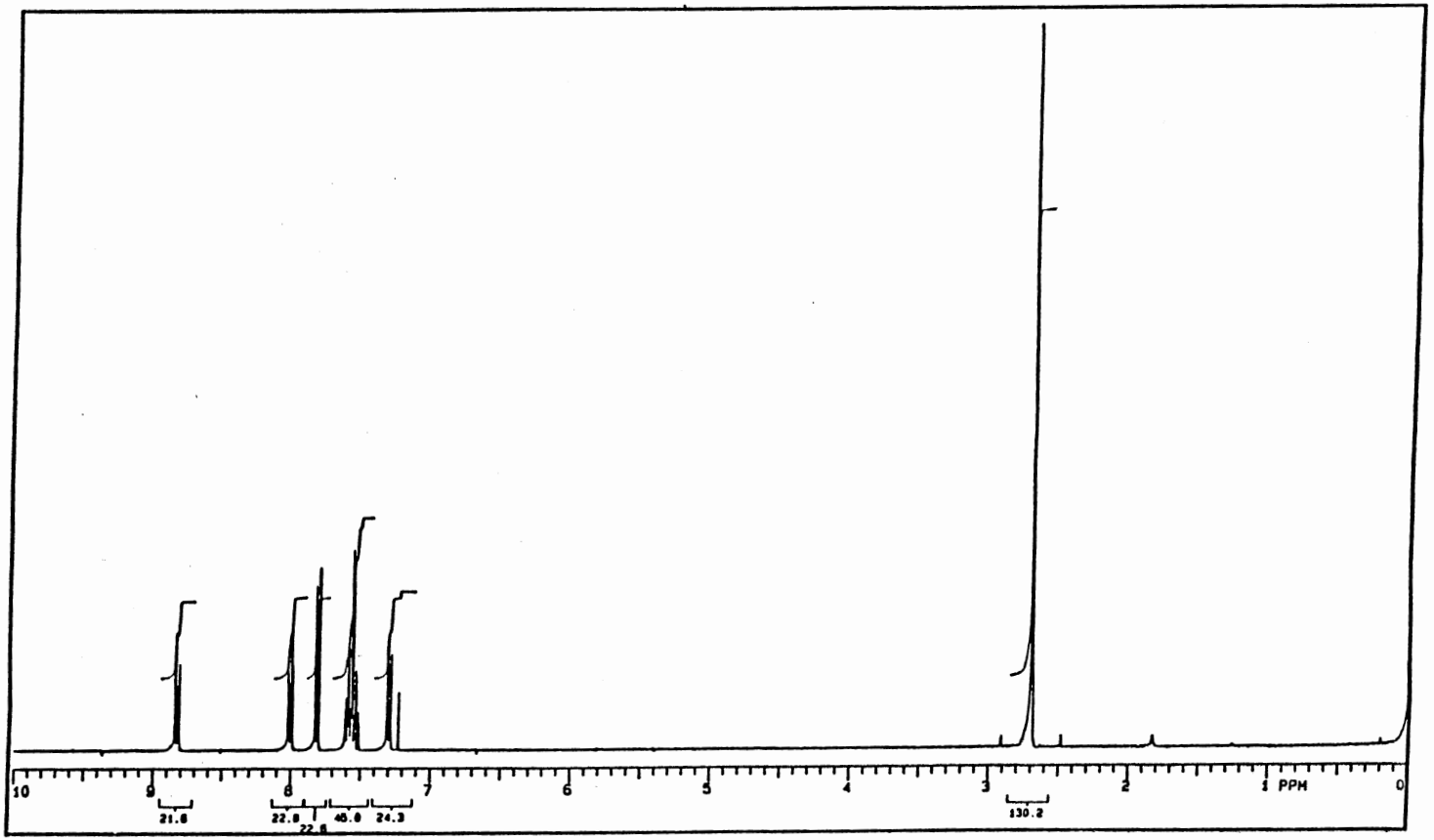
protons overlap and appear as a singlet at δ 2.62 (Spectrum 12). In TFA-d, these protons separate to δ 2.70 (s, 3H) and δ 2.85 (s, 3H) (Spectrum 13).

In some systems, ^{13}C NMR is more helpful than ^1H NMR in monitoring exchange. For example, the α–carbonyl protons of ketone **48** are not easily distinguished in the ^1H

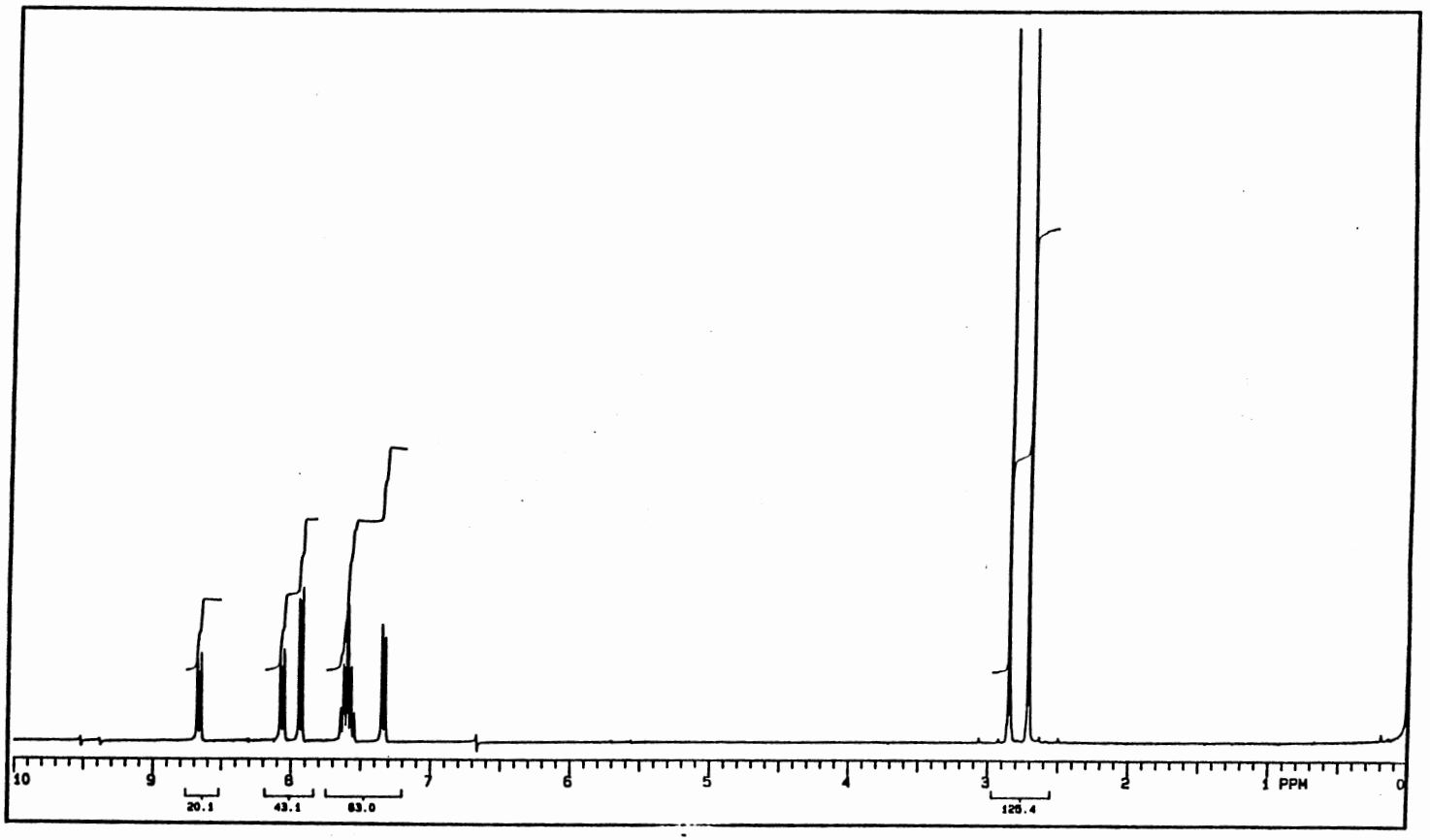


48

NMR spectrum. However, the ^{13}C NMR spectrum shows that two of the carbons (six-membered ring) had exchanged completely with some exchange on a third carbon (five-



Spectrum 12. ^{1}H NMR ($CDCl_3$) of of 2-Acetyl-5-methylnapthalene (**37**).

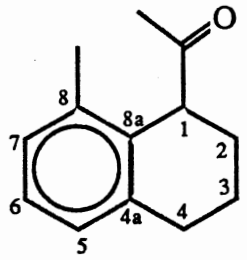


Spectrum 13. ^{1}H NMR (TFA-d) of 2-Acetyl-5-methylnapthalene (37).

membered ring) after 7 exchanges. This indicates a disparity in rate of exchange of the α-carbonyl protons. ^{13}C NMR spectra can be obtained for most ketones in TFA-d as the solvent signals are two characteristic quartets at δ 110.61, 114.37, 118.13, 121.89 and 162.04, 162.61, 163.19, 163.76; regions in which aliphatic and most aromatic protons do not overlap. The ketones used in this study did not have overlapping carbon signals with those of the solvent (TFA-d).

In cases where the strong solute-solvent interaction such as local association due to H-bonding or dipole-dipole complex is expected, the ^{13}C chemical shifts may be strongly affected by the magnetic anisotropy of the solvent molecule.[50] It has been demonstrated that there is 1:1 and 1:2 adduct formation between benzophenone and trifluoroacetic acid in diphenylmethane solvent.[51] NMR evidence from the present study indicates that TFA-d is associated with ketones resulting in additional shielding and deshielding (as compared to $CDCl_3$) of carbons and protons remote from the carbonyl group.

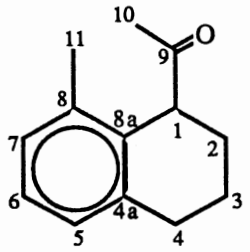
Some peculiarities were observed in the ^1H NMR spectrum of ketone **38**. The spectral data are summarized in Table IX. At room temperature in $CDCl_3$, the protons at C-3 have a single multiplet at δ 1.65-1.78. However, in TFA-d, at the same temperature, these signals separate to δ 1.62-1.75 (m, 1) and 1.80-192 (m, 1). At higher temperature (60°C) in TFA-d, these signals merge to, δ 1.65-1.78 (m, 2). At low temperatures (-60°C; in $CDCl_3$) two separate multiplets, δ 1.55-1.70 (m, 1) and 1.72-1.85 (m, 1), are seen. As pointed out above, this separation is seen at room temperature in TFA-d. These data



38

Table IX

^{1}H NMR Data of Ketone **38**



Proton(s) on Carbon No	δ ($CDCl_3$, 20°)	δ (TFA-d, 20°)	δ ($CDCl_3$, -60°)	δ (TFA-d, 60°)
3	1.67-1.78(m,2)		1.55-1.70	1.65-1.78(m,2)
3		1.62-1.75(m,1)	1.55-1.70(m,1)	
3		1.80-1.92(m,1)	1.72-1.85(m,1)	
10, 11	1.95-2.15(m,8)		1.92-2.22(m,5)	
11		2.05(s,3)		2.05(s,3)
2		2.20-(m,2)		2.10-2.20(m,2)
10		2.45(s,3)	2.30(s,3)	2.38(s,3)
4	2.74-2.82(m,2)	2.75-2.85(m,2)	2.70-2.80(m,2)	2.75-2.85(m,2)
1	3.90(t,1)	4.20(t,1)	3.95(t,1)	4.15(t,1)
5, 7	6.95(d,2)	7.00(d,2)	7.00(d,1)	6.95-7.05(m,2)
6	7.10(t,1)	7.15(t,1)	7.15(t,1)	7.10(t,1)

indicate that in TFA-d, conformational changes in ketone **38** are slower than in $CDCl_3$ at the same temperature.

A Dreiding model of ketone **38**, shows a skewed conformation of the tetralin ring with the acetyl group in close proximity of C-3 when it is placed in an axial arrangement. When the conformation of the ring is such that the acetyl group at C-1 is equatorial, the acetyl group is brought into the vicinity of C-8 and thus into close proximity with the methyl group attached to C-8.

It is possible that at lower temperature (-60°) in $CDCl_3$ and at room temperature in TFA-d, the acetyl group spends more time (on the NMR scale) in close proximity to C-3 and thus the hydrogen on the same face of the ring (as the acetyl) is deshielded. This results in a separate multiplet further downfield. The slower conformational changes in TFA-d as compared to $CDCl_3$ at room temperature can be ascribed to hydrogen bonding of the ketone in the former solvent.

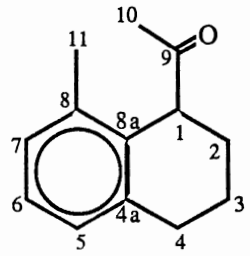
The ^{13}C data, presented in Table X, support this argument. The CH_3-Ar and C-3 signals have chemical shifts of 19.68 and 19.70 ppm ($CDCl_3$, 20°) and overlap in the printed spectrum. In TFA-d at 20°C these signals separate to 20.04 and 20.87 and in $CDCl_3$ at low temperature (-60°) they shift to 18.86 and 19.89 ppm.

It is significant that changing from $CDCl_3$ to TFA-d (at room temperature), besides the expected increased deshielding of the carbonyl carbon of ketone **38**, shown in Table X, the α-carbons, C-1 and CH_3-CO are further deshielded by dissimilar amounts, δ 2.22 and 0.69 respectively. In addition, the β-carbons, C-2 and C-8a are deshielded by an additional 2.26 and 2.41 ppm respectively. Additional systems, described below, were studied with a view to understanding this effect.

Table XI lists the chemical shifts observed for cyclohexanone (**5**) in $CDCl_3$ and in TFA-d. Much greater additional deshielding is observed at C-3 than at other carbons. It can be envisioned that TFA-d associates with the ketone in such a way that there is

Table X

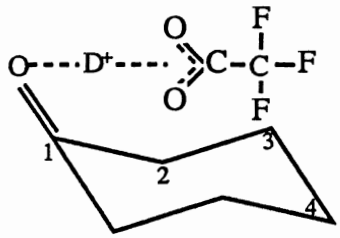
^{13}C NMR Data of Ketone **38**



Assignment[a]	δ in $CDCl_3$(20°C)	δ in TFA-d(20°C)	Δδ (TFA-d-$CDCl_3$, 20°C)	δ in TFA-d(60°C)	δ in $CDCl_3$(-60°C)
C-1	19.68	20.04	0.36	19.98	18.86
C-3	19.70	20.87	1.17	21.11	19.89
C-2	26.60	28.26	2.26	28.46	25.82
C-10	28.16	28.85	0.69	28.78	28.76
C-4	29.76	30.85	1.09	30.96	29.45
C-1	50.55	52.77	2.22	52.79	49.81
C-6	126.60	129.90	2.49	129.12	126.69
C-5	127.18	129.17	1.99	129.87	127.09
C-7	127.80	129.81	2.01		127.46
C-8	133.04	132.60	-0.44	133.06	132.61
C-4	136.63	138.60	1.95	138.71	136.50
C-8a	137.55	139.96	2.41	140.11	137.35
C-9	210.40	224.40	14.00	223.58	211.63

[a]cf. Reference 52.

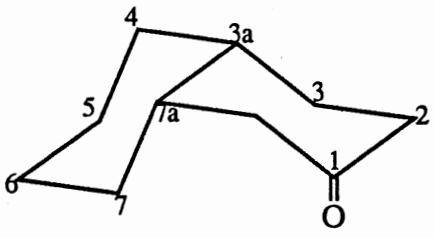
maximum interaction with C-3 resulting in greater deshielding of this carbon as shown below:



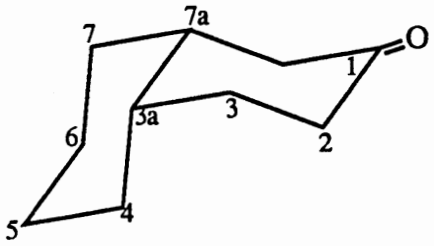
In addition, in TFA-d, two signals are observed for C-1 and C-3. This is likely the result of slower conformational changes of the ketone in TFA-d as compared to $CDCl_3$.

The spectral data observed for 3,3,5,5-tetramethylcyclohexanone (**74**) are listed in Table XII. Again much greater additional deshielding is observed for C-3. Also, multiple signals are seen in TFA-d for C-3 and C-5.

In *cis*-2-decalone (**75**), 2-confomers are possible as shown below:



Conformer A



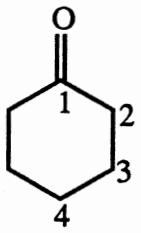
Conformer B

The chemical shifts observed for **75** are listed in Table XIII. It is significant that in addition to the greater deshielding observed at the β-carbons (C-7a and C-3), there also is a comparable additional deshielding at C-7 (3 carbons away). This is understandable because in confomer A, C-7 has a close spacial relationship with the carbonyl. Finally, a doubling of ^{13}C signals was observed for most of the carbons of *cis*-2-decalone in TFA-d.

In norcamphor (**76**) a rigid ketone, only a single ^{13}C signal was seen for each carbon as listed in Table XIV. In addition, much greater additional deshielding was observed for C-4, 6 and 7 (β-carbons) as compared to C-5 (γ-carbon). In the other rigid

Table XI

^{13}C NMR Data for Cyclohexanone (**5**)

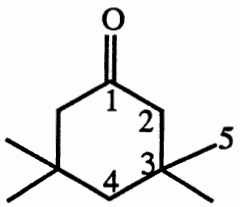


δ TFA-d	δ $CDCl_3$	Δδ (TFA-d-$CDCl_3$)	Assignment[a]
227.32(18)	212.24(19)	15.08	C-1
227.25(16)			C-1
43.02(204)	41.99(212)	1.03	C-2
28.72(180)	27.05(201)	1.67	C-3
28.67(107)			C-3
25.83(158)	25.00(103)	0.83	C-4

[a]cf. Reference 53.

Table XII

^{13}C NMR Data for 3,3,5,5-Tetramethylcyclohexanone (**74**)

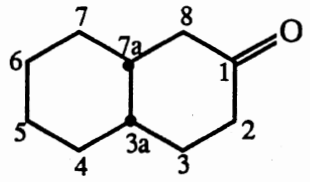


δ in TFA-d	δ in $CDCl_3$	Δδ (TFA-d-$CDCl_3$)	Assignment[a]
227.83(17)	212.52(13)	15.31	C-1
55.20(151)	53.95(178)	1.25	C-2
52.60(86)	51.59(90)	1.01	C-4
39.35(24)			
39.31(65)	36.19(51)	3.12	C-3
39.26(19)			
31.97(50)			
31.91(205)	31.37(335)	0.54	C-5
31.83(37)			
31.78(30)			

[a]By anaology with assignment for cyclohexanone.

Table XIII

^{13}C NMR Data for *Cis*-2-Decalone (**75**)

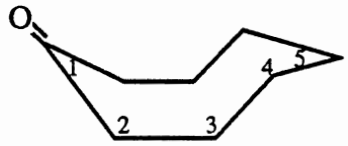


TFA-d		CDCl3		Δδ
δ	Assignment	δ	Assignment[a]	(TFA-d-$CDCl_3$)
227.66(13)	C-1			
227.60(15)	C-1	212.78(35)	C-1	14.88
46.54(52)	C-8	45.43(88)	C-8	1.11
46.44(25)	C-8			
41.32(139)	C-2	39.35(131)	C-2	1.97
41.26(70)	C-2			
40.39(80)	C-7a	38.55(181)	C-7a	1.84
40.34(53)	C-7a			
36.41(225)	C-3a	34.82(201)	C-3a	1.59
30.85(36)	C-3			
30.70(56)	C-3	28.79(175)	C-3	1.91
30.32(110)	C-7	28.29(193)	C-7,C-4	2.03
29.31(60)	C-4			1.02
29.21(48)	C-4			
24.81(47)	C-5	23.69(71)	C-5	1.12
24.70(36)	C-5			
24.41(21)				
24.30(43)	C-6			
24.20(48)	C-6	22.92(84)	C-6	1.28

[a]cf. Reference 54.

ketones studied using TFA, androsterone (**49**), androstanedione (**48**), cholest-4-en-3-one (**64**) and d-camphor (**12**), a single signal was seen for each carbon in TFA-d.

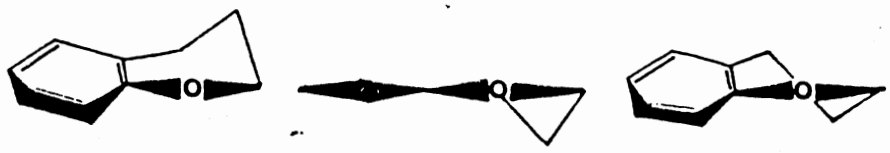
For cycloctanone (**77**) the boat-chair conformation was calculated to be the most stable.[55] It is likely that **77** will have this conformer as the most stable one. Table XV lists the observed chemical shifts. There is no greater deshielding of C-3. In the more stable conformer of cyclooctanone, shown below



77

C-3 is away from the plane of the carbonyl unlike cyclohexanone and 3,3,5,5-tetremethyl cyclohexanone. Also, multiple signals were recorded, in TFA-d for each of the carbons.

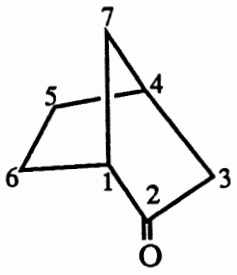
The spectral data for α–tetralone (**45**) are listed in Table XVI. Additional deshielding (β-carbon) is not observed at C-3. Examination of the more stable conformers of α–tetralone[56], shown below, indicate that C-3 is away from the plane of the carbonyl unlike cyclohexanone and 3,3,5,5-tetramethylcyclohexanone.



In addition, much greater deshielding was observed for C-6 and C-4a than for the other carbons. However, additional factors might be operative as shown by drawing canonical structures representing π electron delocalization from the mesometric effect of C=0: TFA-d, shown.

Table XIV

^{13}C NMR Data for Norcamphor (**76**)

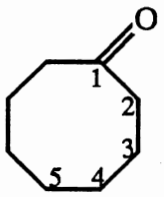


δ(TFA-d)	δ($CDCl_3$)	Δδ(TFA-d-$CDCl_3$)	Assignment*
234.01	218.28	15.73	C-2
52.47	49.86	2.61	C-1
46.97	45.26	1.71	C-3
39.46	37.70	1.76	C-7
37.31	35.32	1.99	C-4
27.72	27.19	0.53	C-5
25.86	24.19	1.67	C-6

[a]cf. Reference 54.

Table XV

^{13}C NMR Data for Cyclooctanone (77)

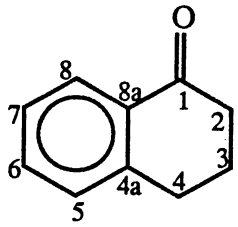


δ in TFA-d	δ in $CDCl_3$	$\Delta\delta$(TFA-d-$CDCl_3$)	Assignment[a]
234.42(16)			
234.36(25)	218.35(16)	16.01	C-1
43.52(48)			
43.44(137)	41.95(225)	1.49	C-2
28.49(52)			
28.41(137)	27.18(221)	1.23	C-3
28.32(43)			
27.67(45)			
27.60(132)	25.67(208)	1.93	C-4
27.51(22)			
27.45(43)			
26.55(104)	24.72(112)	1.83	C-5

[a]cf. Reference 53.

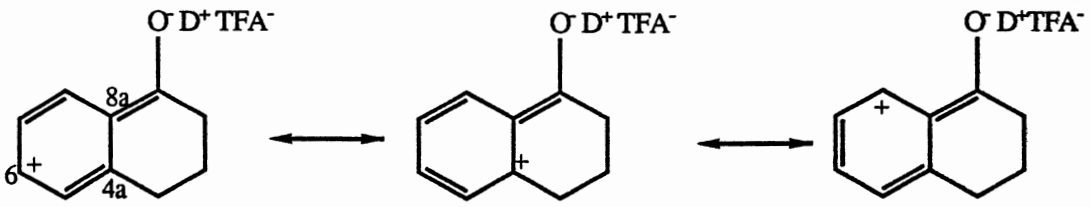
Table XVI

^{13}C NMR Data for α-Tetralone (**45**)



δ(TFA-d)	δ($CDCl_3$)	Δδ(TFA-d-$CDCl_3$)	Assignment[a]
208.94	198.34	10.60	C-1
39.79	39.14	0.65	C-2
30.67	29.67	1.00	C-4
24.37	23.26	1.11	C-3
128.65	126.58	2.07	C-7
129.34	127.09	2.25	C-8
130.83	128.77	2.06	C-5
137.74	133.37	4.27	C-6
132.63	132.56	0.00	C-8a
148.97	144.47	4.50	C-4a

[a]cf. Reference 57.



As such, hydrogen bonding of α–tetralone in TFA-d should decrease the electron density at C-4a, C-6, and C-8 resulting in increased deshielding at these centers.

Only one signal was observed for each carbon of α–tetralone in TFA-d in contrast to the double signal described for the other flexible ketone. This could result from rapid conformational changes in α-tetralone.

In summary, TFA-d offers several advantages as an NMR solvent for ketones. Alpha carbonyl protons can be readily identified by recording the spectra in $CDCl_3$ and then observing the additional deshielding in TFA-d, flexible ketones may be differentiated from rigid ketones by observing the number of signals obtained in TFA-d and conformation effects, observed at low temperature in $CDCl_3$, may be observed in TFA-d at room temperature. Thus, an indication of the spatial relationship of carbons in relationship to the carbonyl is possible.

Discussion of Experimental Techniques

The efficient synthesis of compounds of high isotopic content often requires much care and elaborate techniques. The use of neat TFA-d as an α–exchange solvent necessitated the development and use of special techniques. These will be described next.

TFA-d is very corrosive, quite volatile (bp 75°C) and moderately toxic.[25,26,27] This necessitated handling in a well-ventilated fume hood and wearing eye-protection as well as acid-resistant gloves.

TFA-d was prepared by dropwise addition of a molar equivalent of D_2O to trifluoroacetic acid anhydride. As the hydrolysis is exothermic and TFA-d is hygroscopic and volatile, small batches (0.1 mol) were made as needed. This is best done by dropwise

addition of a weighed amount of D_2O to a measured amount of anhydride in a dry flask attached to a condenser protected with a drying tube containing molecular sieves.

The glassware was baked (see experimental) and assembled while hot. Sample vials and Kugelrohr receiving flasks were, in addition, conditioned by rinsing with D_2O and baking once more.

The exchange apparatus, shown in Figure 2, consisted of a long-necked flask with a magnetic stir bar and a condenser to which was attached a drying tube containing 4Å molecular sieves. The condenser provides headspace for TFA-d and stirring facilitates dissolution of the ketone in the solvent initially and also aids removal of the solvent during aspiration.

The reaction flask was connected via a Kugelrohr receiving vessel, two Dry ice traps and two indicating soda-lime traps, in series, to a vacuum pump as shown in Figure 2. Exposure of the soda lime (Matheson Coleman and Bell, 4-8 mesh, CB 1060) to TFA-d results in a pink coloration. On first indication of color change in the first soda-lime trap it was emptied and recharged. The recharged trap was connected as the number 2 (next to the pump) trap.

Joints with 0-ring (silicone rubber and Viton) are not recommended as they are not stable to TFA-d and require frequent replacement. But if teflon coated 0-rings are unavailable, these would serve.

Aspiration of TFA/TFA-d results in cooling of the reaction flask and thus decreases the rate of aspiration of spent TFA-d. Immersion of the reaction flask, in a beaker of warm water, was found to considerably increase the aspiration rate. Our initial experiment showed that four hours of aspiration removed at least 95% of the spent TFA-d and as such this aspiration time was adopted for succeeding exchanges.

Residual traces of TFA-d were removed by addition of a few drops of dry pentane and further aspiration (48 h). The effectiveness of pentane was evident from the fact that its addition and aspiration induced crystallization in the solid ketones.

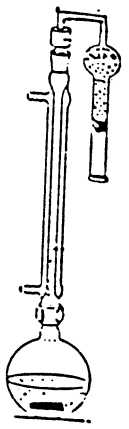


Figure 3. Exchange Apparatus.

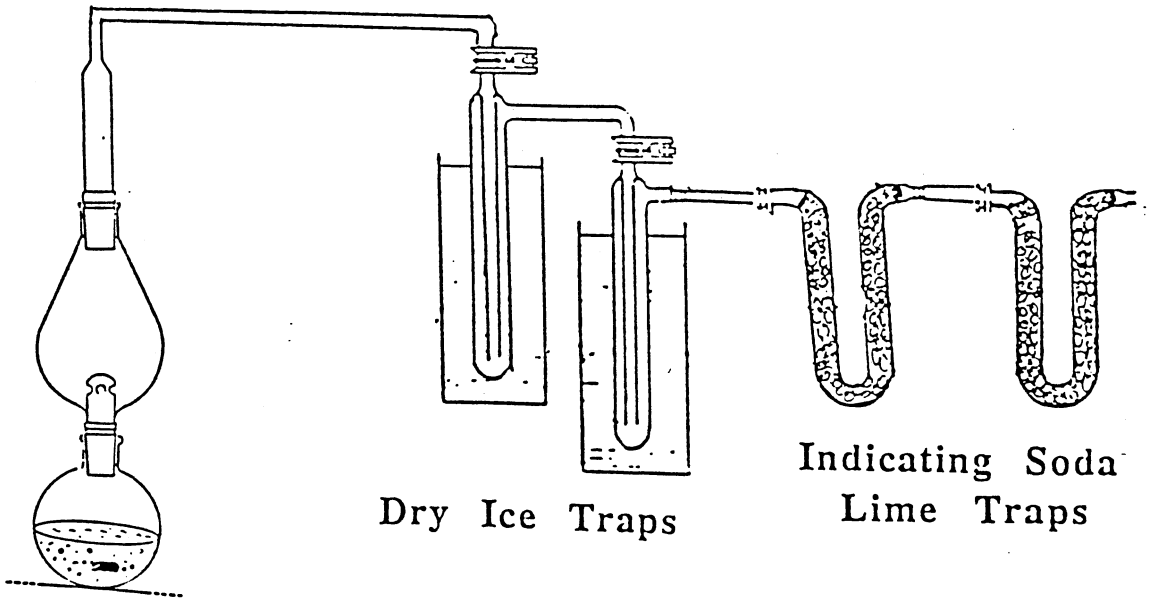


Figure 4. Aspiration Apparatus.

The complete removal of TFA-d must be ascertained as residual traces accelerate coloration and back exchange of the product on storage. That complete removal of TFA/TFA-d had been accomplished was determined by ^{13}C NMR analysis of the aspirated residue. For some of the liquid ketones, pentane addition and aspiration was repeated to ensure complete removal of TFA-d.

Anhydrous diethyl ether was found to be more effective in rapid removal of traces of TFA-d in some trial runs. However, it was not used due to concern about storage problems associated with ether.

During aspiration, the reaction flask was attached, via a Kugelrohr receiving flask, to the traps and pump. There often was foaming (in the reaction flask) during aspiration; use of a larger flask (150 mL) contained this problem in most cases. In the few instances where residue was splashed to the receiving flask, it was washed back to the reaction vessel with TFA-d.

On complete aspiration of the solvent, the product was directly distilled from the reaction flask to the Kugelrohr collection flask (used during aspiration). After Kugelrohr distillation, the ice bath was removed, and the collection flask and laboratory bench top were dried thoroughly and allowed to reach room temperature before the vacuum was broken. The sample was transferred, for storage, to dry sample bottles with Teflon lined caps.

In the higher molecular weight ketones (**18, 24, 42, 48, 49** and **64**), the deuterated product was not distilled since ^{13}C and ^{1}H NMR indicated no additional signals in the deuterated products. These generally were off-white crystals, with melting points corresponding to the undeuterated ketones. Mass spectral data were obtained on the product without any further clean up. However, if very pure samples were required, these ketones were crystallized by aspirating some of the TFA-d (from the reaction mixture) and dropwise addition of D_2O. The crystals then were washed with anhydrous pentane and aspirated.

As with any deuterium labelling operation, much care was taken to exclude moisture at all stages.

CHAPTER III

EXPERIMENTAL

Proton NMR spectra were determined at 300 MHz using a Varian XL-300 and a 60 MHz (Hitachi R-24B) with tetramethyl silane (TMS) as internal standard in $CDCl_3$ or in TFA-d. ^{13}C NMR spectra were determined at 75 MHz (Varian XL-300) with TMS as internal standard in $CDCl_3$ or in TFA-d. Mass spectra were obtained on a VG Tritech TS 250 with a VGII-250 data system and the % deuterium incorporated was calculated by comparison of mass spectra of starting material and deuterated product using a program from Finnigan-MAT.

All glassware was baked at 165° for at least 3 days and assembled while hot. Sample vials, distillation flasks and NMR tubes were, in addition, rinsed with D_2O and re-dried.

TFA-d was made up as 0.2 mol batches by adding D_2O (2.0 g, 0.1 mol of 99.8% D) dropwise to trifluoroacetic anhydride (2.10 g, 0.10 mol).

Deuterium Exchange Reactions

A. Exchange in an NMR Tube on Addition of TFA-d

About 0.5 mmol of the ketone was dissolved in 0.3 mL of $CDCl_3$ and the ^1H NMR spectrum was obtained; approximately 0.3 mL of TFA-d was then added to the tube which was vigorously shaken and the ^1H NMR spectra was re-recorded.

B. Exchange by Stirring in TFA-d for 18-20 Hours

A dry 5-mL, round-bottomed flask was equipped with a Teflon-coated magnetic stirring bar, reflux condenser and a drying tube was assembled while hot. Deuterium oxide (0.5 mL) was added to the flask which was then heated to reflux for 6 h. The D_2O was discarded and the flask was then baked in an oven at 165° (5 minutes).

To the conditioned flask was added 0.5 mmol of ketone (0.25 mmol for compounds **18**, **24** and **39**) and 0.3 mL TFA-d. For ketones, **5**, **30** and **31**, 0.70 mmol and 0.5 mL TFA-d were used. The mixture was stirred for 18 h and the solvent was then pumped off (~4 h). A fresh charge of TFA-d was added and the procedure was repeated until complete exchange was indicated by ^1H and ^{13}C NMR studies on the neat reaction mixture and mass spectrometry studies on the distillation residue.

C. Exchange in Refluxing TFA-d

To the conditioned flask was added 0.5 mmol of the ketone and 1 mL of TFA-d. The mixture was heated at reflux with magnetic stirring for 68 h and the solvent was then pumped off. Fresh TFA-d was added and the procedure was repeated twice. ^1H and ^{13}C NMR and mass spectra were obtained on the residue.

D. Relative Rates of Exchange of Benzylic and Terminal Methyl Protons of Ketone 21

The apparatus as per condition B was assembled and 1.072 g (8 mmol) of ketone **21** and 6.2 mL of TFA-d were added. The mixture was stirred for 12 h at which time a ^{1}H NMR spectrum of the reaction mixture was recorded. The TFA-d was then pumped (24 h) off and the residue was distilled. A mass spectrum of the distilled product was obtained. The experiment was repeated using the same amounts of ketone and TFA-d but stirring time of 1 (24 hours), 2, 3, 4, 7, and 9 days were used.

E. Preparation of α–Labelled Ketones with TFA-d at Room Temperature

A previously baked 100 mL, long-neck, round-bottom flask, Teflon-coated magnetic stir bar and reflux condenser with drying tube were assembled hot. To the (cooled) flask, was added the ketone and TFA-d and the mixture was stirred for 20 h except for ketones **18, 40** and **42**. In the former, a stirring time of 3 h and in the latter two, seven days of exchange were used. The solvent was then aspirated (4 h) and a fresh charge of TFA-d was added. The procedure was repeated until exchange was completed (as indicated by ^{1}H and/or ^{13}C NMR studies of the neat reaction mixture). The residue was then pumped until foaming had ceased (4-6 hours). A few drops (1-2 mL) of dry pentane were then added and the mixture was further aspirated until foaming had ceased (1-2 h). The ^{13}C NMR (in $CDCl_3$) spectrum of the residue was obtained to verify complete removal of TFA-d. In those cases which retained traces of TFA-d, the procedure was repeated until there was complete removal of TFA-d as shown by absence of signals at 110-122 and 162-164 ppm. The residue was then aspirated for 48 h and the product was distilled (except for ketones **24, 39, 42, 48, 49, 53** and **64**), ^{1}H and ^{13}C NMR and GC/MS data were obtained on the deuterated product.

F. Preparation of α–Labelled Ketones by Refluxing in TFA-d

The procedure was the same as procedure E except that the mixture was heated at reflux for 20 h, 68 h and 168 h (7 days) for ketones **12, 24,** and **40,** respectively.

G. Effect of TFA-d and TFA on 9,10-Dihydroanthracene (72)

The apparatus was assembled as for procedure E. The hydrocarbon (0.7 g) was added to 36 mL of the acid and 5 mL of THF. The mixture was stirred for 7 days after which the solvent was pumped off (48 h), the residue was distilled and the product was analyzed by GC/MS.

H. Effect of Refluxing 9,10-Dihydroanthracene (72) and Anthracene (73) in TFA-d

The Apparatus was set up as in procedure E. The hydrocarbon (0.72 g) and 12 mL TFA-d were heated at reflux for 36 h. The TFA-d was pumped off (4 h). The procedure was repeated with a fresh charge of TFA-d added. After 48 h, the solvent was aspirated. The residue was distilled and the product was analyzed by GC/MS.

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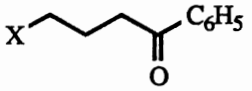
GLOSSARY OF STRUCTURES



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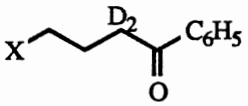

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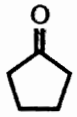

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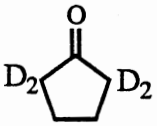

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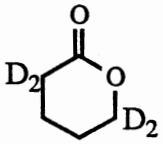

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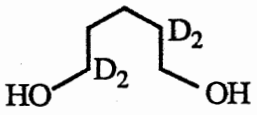

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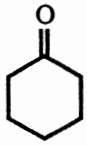

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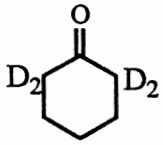

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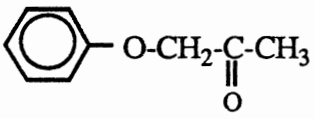

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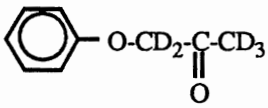

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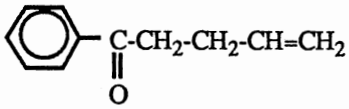

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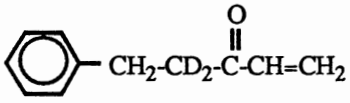

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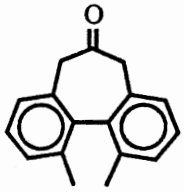

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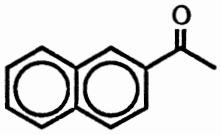

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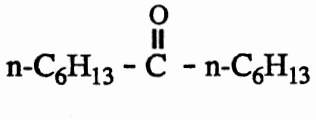

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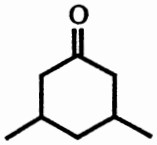

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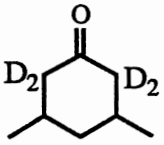

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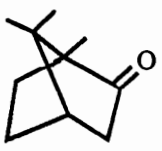

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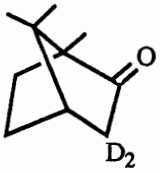

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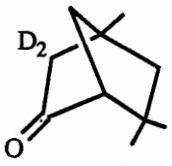

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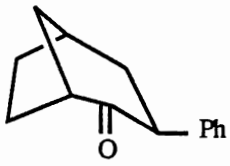

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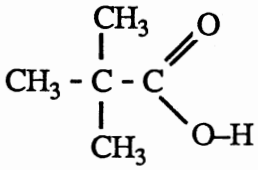

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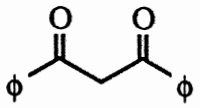

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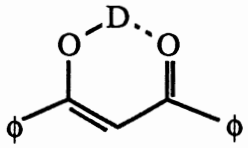

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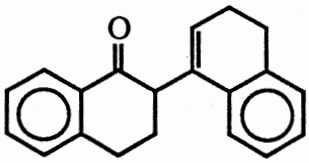

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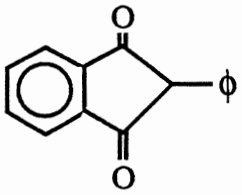

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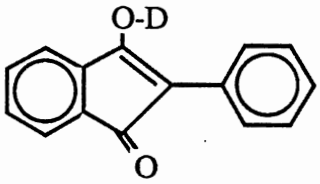

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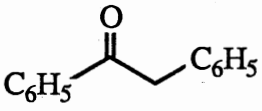

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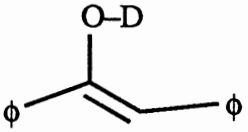

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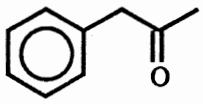

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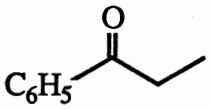

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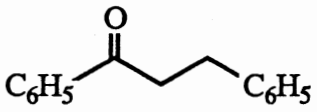

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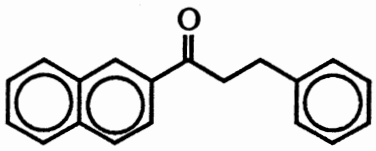

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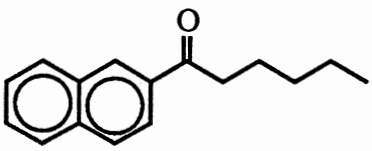

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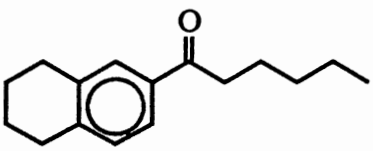

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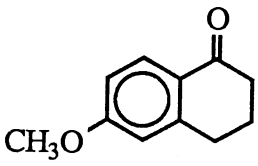

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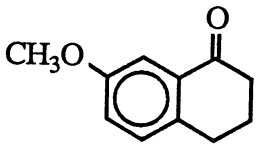

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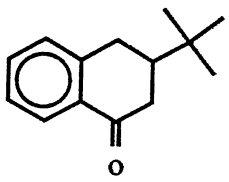

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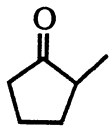

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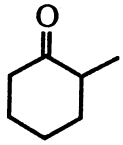

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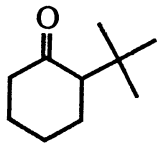

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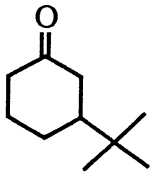

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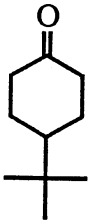

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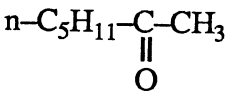

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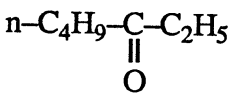

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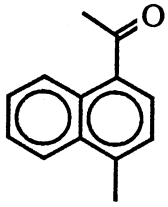

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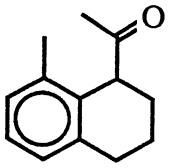

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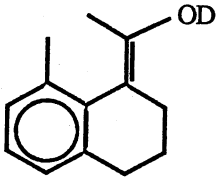

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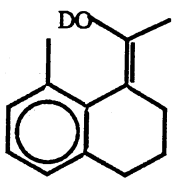

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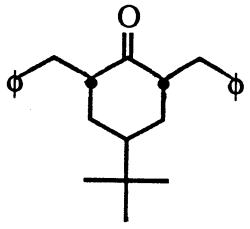

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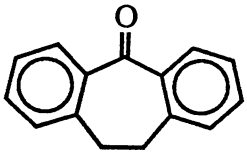

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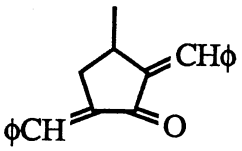

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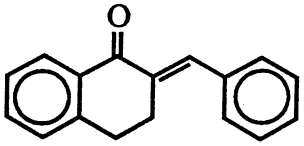

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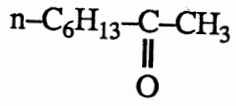

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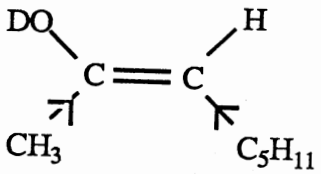

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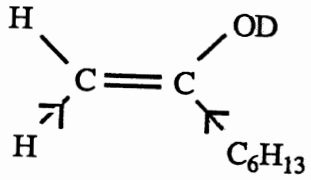

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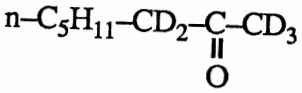

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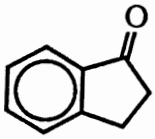

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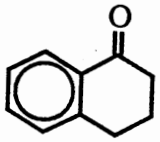

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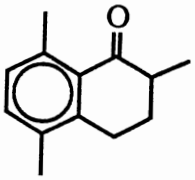

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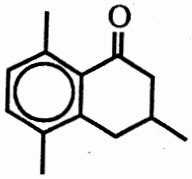

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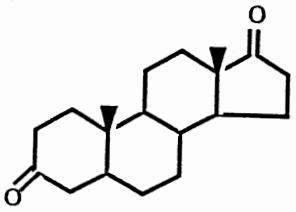

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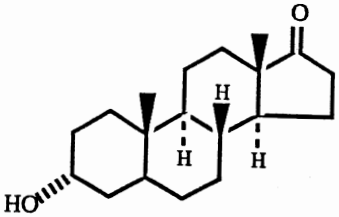

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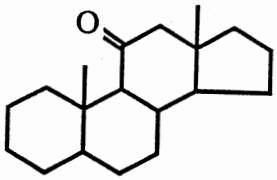

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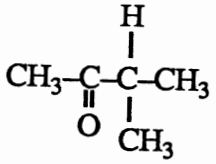

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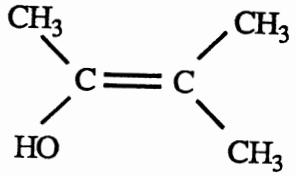

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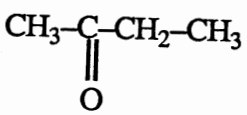

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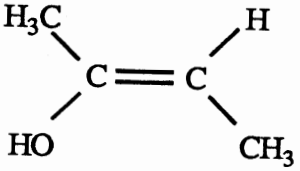

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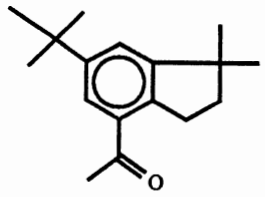

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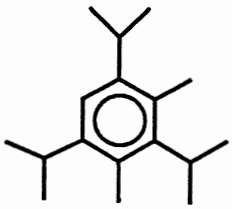

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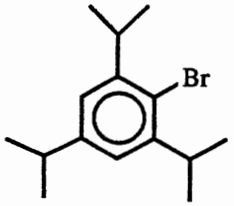

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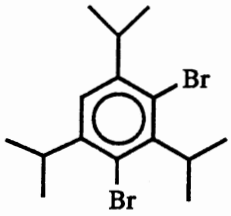

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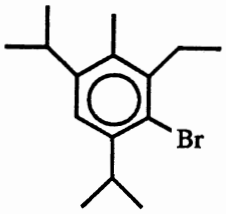

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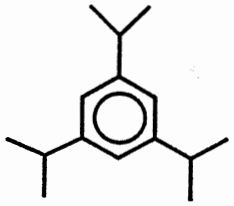

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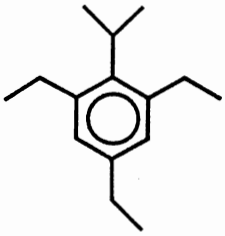

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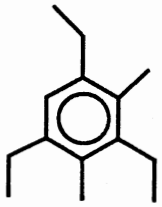

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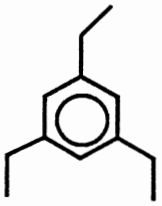

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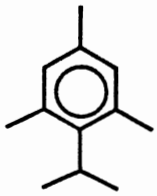

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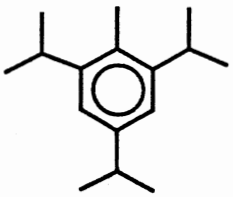

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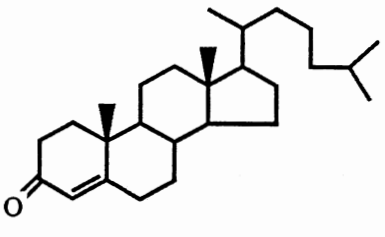

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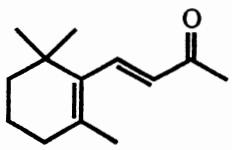

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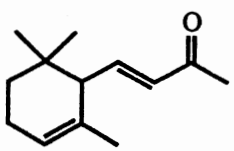

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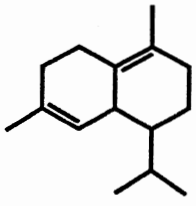

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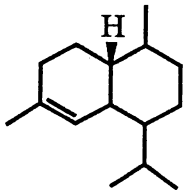

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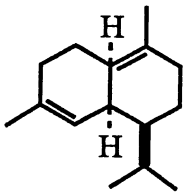

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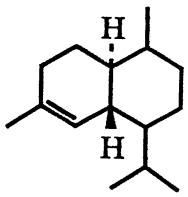

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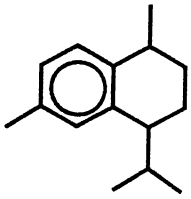

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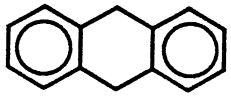

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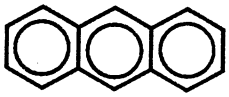

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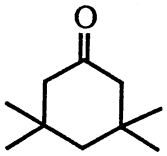

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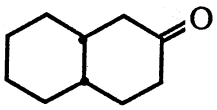

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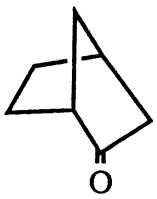

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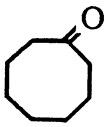

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VITA

Brahmadeo Dewprashad

Candidate for the Degree of

Doctor of Philosophy

Thesis: TRIFLUOROACETIC ACID-D AS A DEUTERIUM EXCHANGE SOLVENT FOR KETONES

Major Field: Chemistry

Biographical:

Personal Data: Born in Palmyra, Guyana, February 25, 1955, the son of Dewprashad and Bishundai Tewari.

Education: Graduated from Berbice High School, Guyana, 1973; received the Bachelor of Science degree in Chemistry from the University of Guyana, 1977. Received the Master of Science degree in Medicinal Chemistry from Loughborough University of Technology, 1979; completed requirements for Doctor of Philosophy degree at Oklahoma State University in July 1989.

Professional Experience: Teaching Assistant, Department of Chemistry, Oklahoma State University, 1984-1989; Sr. R&D officer, Guyana Pharmaceuticals, 1982-1984; Chemist, Guyana Pharmaceuticals, 1979-1981; Associate Lecturer, University of Guyana, 1979-1984.