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CHEMICAL SHIFT ASSIGNMENTS IN *N,N*-DISUBSTITUTED TRIFLUOROACETAMIDES

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Abstract—Due to hindered rotation about the central C—N bond in *N,N*-disubstituted trifluoroacetamides, $CF_3CONR_1R_2$, two resonance peaks are usually observed for each proton in R_1 and R_2. Chemical shift assignments are made for the following amides: **1**, $R_1 = R_2 =$ Me; **2**, $R_1 = R_2 =$ Et; **3**, $R_1 =$ Me, $R_2 =$ 2-Propyl; **4**, $R_1 =$ Me, $R_2 =$ 1-Butyl; **5**, $R_1 =$ Me, $R_2 =$ Cyclohexyl; **6**, $R_1 = R_2 =$ 2-Propyl; **7**, $R_1 =$ 2-Propyl, $R_2 =$ Cyclohexyl. Amides **6** and **7** show an inversion of the relative chemical shift for both the methine and methyl protons of the 2-propyl group as compared with **3**. For non-fluorinated amides, aromatic solvents shift the *trans* alkyl peaks to higher field faster than those *cis* (to the carbonyl oxygen atom); however, this generalization does not apply to all trifluoroacetamide proton peaks.

INTRODUCTION

THE USUAL methods of assigning NMR peaks to amide *N*-alkyl protons and thus determining the position *cis* or *trans* to the carbonyl oxygen atom are: (a) comparison of the long-range coupling constants, ^4J(HCNCH) or ^5J(CH_3CNCH) (assuming *trans* > *cis*[1]), (b) use of the Nuclear Overhauser Effect[1,2] and (c) benzene dilution shifts.[1,2] Methods (a) and (b) are not applicable to trifluoroacetamides, and method (c) is not reliable for all types of *N*-alkyl peaks, as will be discussed. The ^5J(CF_3CNCH) coupling constant is usually observed, however, and it is generally believed[3 to 7] that in amides J_{HF} (*cis*) > J_{HF} (*trans*).* This will be the primary method used for assigning peaks to protons from *N*-alkyl groups which are located *cis* or *trans* to the carbonyl oxygen atom. Then proton spin decoupling is used to associate resonances from the same R_1 or R_2 group. Because the *N*-methyl peak to lower magnetic field has the larger coupling to the CF_3 group in amide **1**, (1·60 Hz *vs.* 0·65 Hz), this peak is assigned to the *N*-methyl protons which are *cis* to the CF_3 group. Several other non-aromatic dimethylamides also have the lower field *N*-methyl peak most strongly coupled to fluorine:[4]† $CFCl_2CONMe_2$, $CF_2ClCONMe_2$, $CF_3(CF_2)_2CONMe_2$ and $(CF_3)_2CFCONMe_2$.

Only one NMR study has dealt with the assignment of the *N*-α-methine proton in trifluoroacetamides.[6] The general conclusion reached for a large number of amides (mostly non-fluorinated) was that protons in the plane of the amide bond are deshielded when they are located *cis* to the carbonyl oxygen atom and pointed toward it (thus shielded when *trans*): however, out-of-plane protons, such as methyl groups, are shielded when *cis* to the carbonyl oxygen atom.[6] Theoretical studies[8,9] yield the same general picture but are not yet able to describe the anisotropy of the amide bond in detail.

Experimental data are provided in this work which indicate that the shielding of a given proton in the *N*-alkyl substituent depends not only upon whether the group is

* Isomer ratio studies and comparisons of coupling constants with *N*-monosubstituted amides confirm that J_{HF} (*cis*) > J_{HF} (*trans*) for CF_3CNCH_3 amides. (To be submitted for publication.)

† P. C. Adlaf and B. L. Shapiro, unpublished results.

cis or *trans* to the carbonyl oxygen atom, but also upon preferred conformations of the *N*-alkyl group about the N—C—α bond. These conformations also determine the degree of shielding of the various protons of the amide in benzene solution, which is the ASIS [aromatic solvent-induced shift(s)].[10] In this work, ASIS = δ(5-mol % amide in CCl_4) − δ(5-mol % amide in benzene).

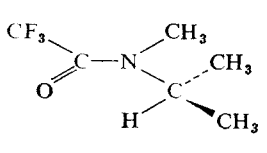
RESULTS AND DISCUSSION

The chemical shift assignments

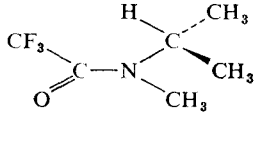
The amides studied in this work are listed in Table 1 together with the chemical shifts in CCl_4 and benzene solutions and the values of ASIS. The A protons are those protons which are attached to *N*-alkyl groups located *cis* to the carbonyl oxygen atom, the B protons are *trans*. Assignments were made by assuming that the *N*-alkyl protons having the larger coupling constant to the CF_3 group are B protons. Usually the long-range proton-fluorine coupling produces a resolved quartet only with *N*-methyl protons. For amides without *N*-methyl groups, the resonance of the B *N*-alkyl substituent is broadened relative to A. When the additional broadening could be removed by fluorine spin decoupling, this peak was assigned to the B position.

The assignment for **1** has been made previously.[3] The pattern of coupling for **1** (stronger fluorine coupling to the lower-field *N*-methyl peak) is also observed for the *N*-methyl protons of **3** to **5**. Upon dilution with benzene, the lower-field peak crosses over the higher-field peak in each case (Table 1). In **2**, the *N*-methylene peaks are almost coalesced at 31°C in CCl_4 solution, but separate in benzene (Table 1). The $NCCH_3$ peaks of **2** cross upon dilution with benzene. In 5-mol % benzene solutions, fluorine coupling is larger to the higher-field NCH_2 or $NCCH_3$ peak; therefore, these are B peaks.

In **3**, the lower-field *N*-methyl proton and the higher-field *N*-methine proton are coupled more strongly to CF_3. Therefore, these are B protons, and this determines the assignment for the other *N*-methyl and *N*-methine protons as A protons. (This inversion between *N*-methyl and *N*-methine protons is well-known for aliphatic amides.)[1] Assignments of the $NCCH_3$ doublets to **3a** and **3b** are done with proton spin decoupling. The higher-field methine septet is spin coupled to the lower-field methyl doublet. A check on the assignment is offered in the case of unsymmetrically



(3a)



(3b)

disubstituted amides. The preferred rotational isomer is **3a**. Therefore, the lower-field methine peak, the lower-field *N*-methyl peak and the higher-field $NCCH_3$ peak must have a larger integrated intensity than their **3b** counterparts. This assignment for the *N*-alkyl protons of **3** is the same as was found for the corresponding formamide and acetamide.[11]

The NCH_2 protons of **4** are the only ones in the butyl group which can be identified in the *cis* and *trans* configurations at 31°C and 60 MHz. Even so, they are almost

TABLE 1. CHEMICAL SHIFTS IN *N,N*-DISUBSTITUTED TRIFLUOROACETAMIDES AT 31°C

Amide	*N*-α-Methyl			*N*-α-Methylene			*N*-α-Methine			*N*-β-Methyl		
	CCl_4	C_6H_6	ASIS	CCl_4	C_6H_6	ASIS	CCl_4	C_6H_6	ASIS	CCl_4	C_6H_6	ASIS
(1) *N,N*-Dimethyl												
A	3·03	2·50	0·53									
B	3·15	2·43	0·72									
(2) *N,N*-Diethyl												
A				3·42	2·97	0·45				1·18	0·80	0·38
B				3·42	2·85	0·57				1·25	0·67	0·58
(3) *N*-Methyl-*N*-2-propyl												
A	2·85	2·37	0·48				4·69	4·48	0·21	1·18	0·65	0·53
B	2·94	2·32	0·62				4·24	3·83	0·41	1·26	0·68	0·58
(4) *N*-Methyl-*N*-1-butyl												
A	2·98	2·47	0·51	3·40	2·98	0·42						
B	3·10	2·40	0·70	3·40	2·87	0·53						
(5) *N*-Methyl-*N*-cyclohexyl												
A	2·87	2·50	0·37				4·18	4·23	−0·05			
B	2·95	2·47	0·48				3·67	3·57	0·10			
(6) *N,N*-Di-2-propyl												
A							3·52	3·02	0·50	1·42	1·25	0·17
B							4·17	3·90	0·27	1·27	0·77	0·50
(7) *N*-2-Propyl-*N*-cyclohexyl												
A							2-Pr 3·57	3·09	0·48	1·38	1·30	0·08
B							2-Pr 4·17	3·97	0·20	1·23	0·82	0·41
A							NCH_1 3·57	3·55	0·02			
B							NCH_1 3·57	3·55	0·02			

coalesced in CCl_4 solution, but separate in benzene solution. Application of the proton spin decoupler reduces both NCH_2 triplets to singlets, the higher-field peak, in benzene solution, being more strongly coupled to fluorine.

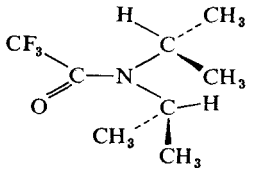
The methine proton, NCH_1, in the cyclohexyl ring of **5**, is in a similar position with respect to the amide bond as the methine protons of **3**, and in CCl_4 solution, it is also the upfield methine peak which is more strongly coupled to fluorine (Table 1). In **3** to **5** further checks on assignments come from isomer ratios. In each amide the isomer with the *N*-methyl group *cis* to the CF_3 group predominates.

In **6** and **7** there is an inversion of the relative chemical shifts of the 2-propyl substituent as compared with **3**. In **6**, the *lower*-field methine peak now has a larger coupling with fluorine. Proton spin decoupling shows that the lower-field methine peak is coupled to the higher-field $NCCH_3$ peak. Therefore, the A methine proton resonates to higher magnetic field than the B methine proton, while the A methyl protons resonate to a lower field than the B methyl protons, the opposite assignment from what was found for the 2-propyl group in **3** (Table 1).

Three of the four magnetically different methine protons in **7** resonate at approximately the same field in CCl_4. The fourth methine peak resonates to lower field and is a septet; therefore it is due to a 2-propyl methine proton. In benzene solution, the other 2-propyl methine peak separates from the broad coalesced NCH_1 peaks. The 2-propyl methine peak to lower field has a smaller integrated intensity and is more highly coupled to fluorine than is the corresponding peak to higher field. Proton spin decoupling then shows that the lower-field 2-propyl methine peak is coupled to the higher-field $NCCH_3$ peak.

The inversion of relative chemical shift in **6** and **7** is believed to be due to restricted rotation about the N—C—α bonds which results from steric interactions among the CF_3 group and the *N*-substituents. Restricted rotation may or may not lead to the observation of individual NMR peaks for the rotamers. Additional peaks have been observed at reduced temperatures for the methine protons of highly substituted *N*,*N*-di-*sec*-alkylamides.[12] Unequal broadening of the methine protons was observed for *N*,*N*-di-2-propylacetamide[12] and *N*-methyl-*N*-2-propylacetamide.[13] In more highly substituted amides, unequal broadening of the methine protons was shown to precede the appearance of subsets of peaks for the various rotamers as the temperature was lowered.[12] Our studies of **6** in $CDCl_3$ solution at 0°, −30° and −60°C did not reveal selective peak broadening. Unusual temperature dependence was obtained, however: the methine peak separation *decreased* as the temperature was lowered from 0°C to −60°C. This type of temperature dependence has been observed before for di-2-propylamides and diethylamides[14] and has been attributed to conformational changes within the *N*-alkyl substituents. If then, the rotation about the N—C—α bond is not slow enough to observe separate peaks for the allowed rotamers, the observed chemical shift will be a weighted mean of the chemical shifts of the protons in each rotamer. Because neither the chemical shifts of the rotamer protons nor the rotamer populations are known, 'most probable' rotamer structures are proposed on the basis of the amide chemical shifts in CCl_4, the ASIS (to be discussed in the next section) and with the goal of minimizing steric interactions.

The methine proton is placed in the amide plane and pointing toward the amide bond in **3** because this is a region of strong deshielding[6,8,9] and the A methine proton in **3** is deshielded by 1·1 ppm relative to the A methine protons of **6** or **7**. Judging



(6)

from the similarity of the chemical shifts, the preferred conformation of the B 2-propyl group is probably the same in **3b**, **6** and **7**. The inversion of relative chemical shift in the 2-propyl group between amide **3** and amides **6** and **7** comes about because of the conformation of the A isopropyl group in **6** and **7**. In order to reduce steric interactions the A methine proton now orients away from the amide bond, in a relatively shielded region[6] (Table 1).

The possible orientations of two amide 2-propyl groups have been discussed in detail[12] and conformer **6** corresponds to rotamer C_3T_6 of Ref. 12. The inversion of relative chemical shift also occurs when the formyl proton in $HCON(2\text{-}Pr)_2$ is replaced by a methyl, ethyl or 1-propyl group.[13] The similarity of inversion behavior in *N,N*-dialkylamides[13] and *N,N*-dialkyl trifluoroacetamides when both alkyl groups are branched at the carbon atom, together with the small change in chemical shift when an amide acetyl group is replaced by a trifluoroacetyl group, ($\delta_A = 2{\cdot}85$, $\delta_B = 3{\cdot}01$ ppm for a 5-mol % solution of dimethylacetamide in CCl_4), suggests that the CF_3 group does not greatly change either steric interactions within the amide, or the total magnetic anisotropy.

It is of interest to note that the assignment which was made for the methine proton in **6**, was also made for $CCl_3CON(2\text{-}Pr)_2$ by Siddall and Stewart[15] on the basis of a very low-field chemical shift for one of the methine protons (4·70). This was attributed to attractive forces between the C—Cl dipole(s) and the C—H dipole, thus the assignment of the B methine proton to the low-field chemical shift. In a later paper,[12] however, the same authors 'believe that the low-field methine signals should always be assigned to the 2-propyl group that is *cis* to oxygen'. The evidence for the latter view, comes from studies of acetanilides and other amides in which it is known that the methine proton lies in the amide plane and toward the amide bond, and in these cases (for example amides **3** and probably **5**), this seems to be the correct assignment. When steric interactions force the methine protons to the positions shown in **6**, however, then inversion of the relative chemical shifts does occur, as the same authors[16] have shown for $CH_3CSN(2\text{-}Pr)_2$. In this thionamide, the barriers about the N—C—α bond and the C—N bond are larger than for $CH_3CON(2\text{-}Pr)_2$ and two conformers (four sets of resonance peaks) have been observed by NMR.[16]

The benzene dilution shifts

The details of the interaction between aromatic solvents and polar solutes are not understood. The formation of a 1:1 collision complex has been widely assumed[1] and the disadvantages of this concept have been considered in detail.[17] The recent concept of a time-averaged cluster of aromatic solvent molecules around the polar solute[17] (the polar solute in a continuum of solvent molecules) seems a more realistic picture of the association. The ASIS value is proportional to a site factor, which is

given by $(3\cos^2\theta - 1)/r^3$, where r is the distance between the proton and a point dipole within the solvated polar site, and θ is the angle which r makes with the polar solute bond axis. The constant of proportionality has been shown to be a function of solvent properties.[17] For camphor, a solute with a single polar site and protons in fixed location, the calculation of the site factors is quantitative.[17] When the molecule has two polar sites, the site factors and ASIS values are additive.[17] The approximation for the site factor is the McConnell equation,[18] used here for the trifluoroacetamides to express the net shielding at an *N*-alkyl proton when the polar sites of the molecule are solvated.

Applying the cluster model to a series of ten *N,N*-disubstituted alkylamides,[13] qualitative agreement with the experimental ASIS values was found when the axis of the shielding cone ($\theta = 0°$) was placed along the straight line between the carbonyl oxygen atom and the B *N*—α-carbon atom with the point dipole located at the oxygen atom. This line is almost parallel to the electric dipole moment vector of formamide.[19]

For the trifluoroacetamides, the choice of location for the $\theta = 0°$ axis is also arbitrary, as is the choice of location for the point dipole. Four choices were reduced to two by taking a vector sum of the CF_3 bond moment (2·32*D* in benzene solution[20]) and a typical *N,N*-dialkylamide dipole moment (3·7*D* in benzene solution[21]). Since the electric dipole moments of *N,N*-disubstituted amides change little upon varying the *N*-alkyl group[21] the resultant (3·8*D* at an angle of 4° to the central C—N bond axis) should be valid for amides **1** to **7** as the $\theta = 0°$ axis. [The site factor predicts a conical node (ASIS = 0) at $\theta = 54°$.] The choice of site for the point dipole is arbitrary. The CF_3 carbon atom and the carbonyl oxygen atom were regarded as the centers of maximum negative charge of this system. A straight line was drawn between these atoms and the intersection of this line with the (extended) central C—N bond axis was taken as the location of the point dipole. This model may be used to qualitatively discuss the ASIS values (Table 1).

The similarity of the ASIS values for both A and B protons of amides **1** to **5** results from the $\theta = 0°$ axis lying almost parallel to the C—N bond axis. The similar $\langle\theta\rangle_{av}$ and $\langle r\rangle_{av}$ values for these protons lead to similar site factors and thus $(ASIS)_B - (ASIS)_A$ has a maximum value of 0·2 ppm. This contrasts dramatically with the $(ASIS)_B - (ASIS)_A$ value for similar protonated amides such as dimethylacetamide (0·7 ppm).[13] The reason, according to the cluster model, can be found in the different site factors for fluorinated *vs.* protonated amides, due primarily to the $\theta = 0°$ axis being at an angle of approximately 38° to the C—N bond axis in the latter amides.[13]

The ASIS values for the *N*-methyls of **5** are considerably smaller than those for **1**, **3** or **4**. This may be due to: (a) a smaller degree of interaction between **5** and the benzene cluster, (b) the increased molar volume[17] of **5**, or (c) an opening up of the C—α—N—C—α angle, due to the increased steric interaction between the *N*-substituents, to a value greater than 114°, the value used for the peptide bond.[22] Because of the good agreement among the ASIS values of **1** to **4**, it is felt that (a) and (b) contribute in a minor way to the decreased ASIS in **5**. A larger C—α—N—C—α angle would move both the *N*-methyl protons and the NCH_1 proton toward the nodal region. It appears, at least in the most probable conformation of **5**, that the A NCH_1 proton is located in a region where $\theta > 54°$, since ASIS is negative (Table 1). Assuming an equal increase in the C—N—C bond angle for each configurational isomer, the B NCH_1 proton is also in the amide plane and pointed toward the amide bond,

but remains just within the conical shielding region (on a time-averaged basis) with ASIS = +0·1 ppm.

Amides **6** and **7** are the only amides in this study which are: (a) solids at room temperature (b) branched at both N—C—α carbon atoms and (c) inverted in their relative chemical shift assignments compared with the 2-propyl groups of **3**. The similarity in chemical shifts in CCl_4 solution as well as ASIS values (Table 1) for **6** and **7** suggests similar preferred conformations for these amides. The conformation proposed for **6** places the A methine proton and the B $NCCH_3$ protons well within the shielding cone, while the B methine proton and the A $NCCH_3$ protons are nearer the node. (Actually the methine protons are rotated 30° out of the amide plane[12].)

The general observation[1,2,11,13] that benzene shifts protons which are *trans* to the carbonyl oxygen atom more than those *cis* is therefore not true for the methine protons of **6** (or of **7**), (Table 1). Since the higher-field 2-propyl methine peak and the lower-field 2-propyl methyl peak have the larger integrated intensities, the configuration having CF_3 *trans* to the 2-propyl group is preferred.

CONCLUSION

Evidence is obtained, both by studying long-range proton–fluorine coupling constants, and by measuring benzene-induced chemical shifts, that relative chemical shift assignments in the 2-propyl group of **6** and **7** are reversed from those in amide **3**. This is attributed to steric interactions between the *N*-substituents in **6** and **7** which lead to restricted rotation about the N—C—α bond. Thus peak assignments in amide *N*-alkyl groups depend upon preferred conformations as well as upon whether the alkyl group is *cis* or *trans* to the carbonyl oxygen atom.

The benzene-induced shifts show that the generalization that aromatic solvents shift the *trans N*-alkyl amide peaks to higher field faster than those *cis* (to the carbonyl oxygen atom) does not apply to the isopropyl methine protons of **6** or **7**. This is the first known exception to this generalization. The time-averaged solvent cluster model proposed by Engler and Laszlo[17] qualitatively explains the observed benzene-induced shifts.

EXPERIMENTAL

All amides were prepared by adding trifluoroacetic anhydride dropwise to the dried amine in ether solution at −5°C. Amides **1** to **5** were purified by vacuum distillation. Amides **6** and **7** were sublimed as white crystals. All amides were pure by NMR.

Solutions were 5-mol % in CCl_4 or in benzene, with a small amount of added tetramethylsilane as internal reference.

A Varian A-60A NMR spectrometer, operating at 31°C, was used for all NMR measurements. Spin decoupling was performed with a Varian V-6058A proton spin decoupler or an NMR Specialities Inc. HD-60B fluorine spin decoupler.

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