judged by the analysis. Such inclusion of solvent is not uncommon with phosphonium salts.[11]

*Anal.* Calcd for $C_{48}H_{39}O_3P \cdot C_2H_6O \cdot C_3H_8O$: C, 72.5; H, 6.0; P, 3.5. Found: C, 72.5; H, 5.7; P, 3.4.

**(−)-7-Hexahelicylmethyltrimethylphosphonium Bromide (5).**—A solution of 120 mg of (−)-6$^+$·D(−)-HDBT$^-$ ([α]$^{23}$D −1109°) and 3.5 g of tetraethylammonium bromide in 18 ml of methanol was refluxed for 48 hr and allowed to stir at room temperature for 72 hr. The methanol was removed under reduced pressure and the residue was stirred with 40 ml of water for 12 hr. The solid was collected by filtration, washed with water, and dried *in vacuo* over $P_2O_5$. Crystallization from methanol afforded 72.9 mg (95%) of (−)-**5**, mp *ca.* 354° dec. The infrared spectrum was identical with that of (±)-**5**. The following specific rotations were obtained at 23° from a solution of 0.400 mg in 2 ml of methanol: −1930° (589 mμ), −2070° (578), −2559° (546), −7563° (436), and 0° (365). Further recrystallization from methanol did not change the rotation significantly.

**(−)-7-Methylhexahelicene (3).**—A solution of 20 mg of (−)-**5** ([α]$^{23}$D −1881°) was stirred with 5 ml of 10% sodium hydroxide at ambient temperature for 24 hr. The yellow solid was collected by filtration and washed well with water. After drying *in vacuo* over $P_2O_5$, there was obtained 12.6 mg (92%) of (−)-**3**, mp 175–180°. One recrystallization from 2-propanol yielded 10.5 mg of (−)-**3**, mp 185–186°, with the following specific rotations (from 0.356 mg in 2 ml of chloroform): −3157° (589 mμ), −3399° (578), −4185° (546), −12,332° (436), and +219° (365). The structure of (−)-**3** was established by comparison with that of (±)-**3** with respect to ir and mass spectrum (M$^+$, 342).

**Registry No.**—(±)-**3**, 33835-50-6; (−)-**3**, 33835-51-7; (±)-**4**, 33872-33-2; (±)-**5**, 33835-52-8; (−)-**5**, 33835-53-9; (±)-6$^+$·D(−)-HDBT$^-$, 33835-54-0; (−)-6$^+$·D(−)-HDBT$^-$, 33835-55-1.

(11) M. Davis and F. G. Mann, *J. Chem. Soc.*, 3770 (1964); C. H. Chen and K. D. Berlin, *J. Org. Chem.*, **36**, 2791 (1971).

# The Conformations of Electronegatively Substituted Imines

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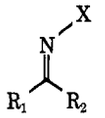
The preferred conformations of 1,1,1-trifluoroacetone hydrazone and azine have the substituent anti to the trifluoromethyl group. The assignments are based on the stereospecificity of six-bond, proton–fluorine coupling in selected *N,N*-dimethyl derivatives and correlations of the fluorine chemical shifts of syn and anti trifluoromethyl groups in hexafluoroacetone imine derivatives. Allylic proton–fluorine coupling is not a reliable indicator of stereochemistry.

The preferred conformations of unsymmetrical imines, hydrazones, oximes, azines, etc., are of continuing interest.[1] A related problem in symmetrical derivatives is the correct spectral identification of the syn and anti groups.[2] For those classes of compounds **1** where $R_1$ and $R_2$ are hydrocarbon, steric arguments suffice to predict conformation.[1,3,4]

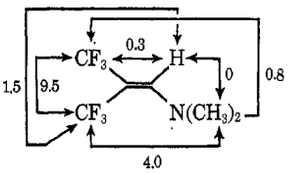


**1**, X = H, $CH_3$, $NH_2$, OH, F...
**1a**, $R_1 = CF_3$, $R_2 = CH_3$, X = $NH_2$

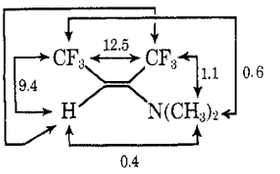
Trifluoroacetone hydrazone[5] (**1a**) and trifluoroacetone azine have single conformations in solution. Although steric arguments predict that the trifluoromethyl and the substituent should be anti,[6] dipole interactions between electronegative substituents may stabilize the syn form.[7] The purpose of this study is to determine the conformation of trifluoroacetone imine derivatives.

**Results.**—No single, simple, physical measurement unambiguously identifies the conformations of trifluoroacetone imines. Therefore a series of indirect studies was performed.

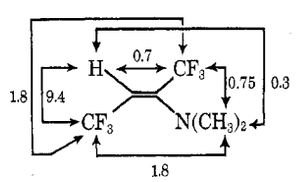
**Six-Bond, Proton–Fluorine Coupling.**—The methyl protons of enamine **2**[8] couple differently to the cis and trans trifluoromethyl groups. A 1.8-Hz, six-bond, proton–fluorine coupling was observed in the *trans*-hexafluorobutyne–dimethylamine adduct **3**, but the coupling in the cis isomer was not mentioned.[9] Couplings between all pairs of nuclei in both *cis*- and *trans*-**3** have now been observed and include the 0.6-Hz, six-bond, proton–fluorine coupling in *cis*-**3**. Hexa-



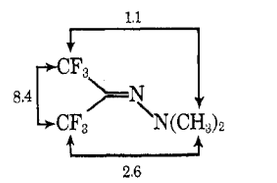
**2**



*cis*-**3**



*trans*-**3**



**4**

(1) G. J. Karabatsos, J. D. Graham, and F. M. Vane, *J. Amer. Chem. Soc.*, **84**, 753 (1962); G. J. Karabatsos, F. M. Vane, R. A. Taller, and N. Hsi, *ibid.*, **86**, 3351 (1964).

(2) For the use of the new Eu chelates to identify oxime conformations see Z. W. Wolkowski, *Tetrahedron Lett.*, 825 (1971); K. D. Berlin and S. Rengaraju, *J. Org. Chem.*, **36**, 2912 (1971).

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(6) R. Filler in "Advances in Fluorine Chemistry," Vol. 6, J. C. Tatlow, R. D. Peacock, and H. H. Hyman, Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1970.

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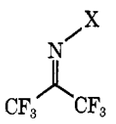
(9) W. R. Cullen, D. S. Dawson, and G. E. Styan, *Can. J. Chem.*, **43**, 3392 (1965).

fluoroacetone dimethylhydrazone (**4**) shows similar stereospecific, six-bond, proton–fluorine coupling. The two compounds **3** are distinguished by the well-established stereospecific, five-bond, fluorine–fluorine coupling.[10] The trifluoromethyl assignments for **2** and **4** follow from the six-bond, proton–fluorine coupling and the fluorine chemical shifts which are discussed below. No six-bond, proton–fluorine coupling is visible in trifluoroacetone dimethylhydrazone.

**Chemical Shifts of Hexafluoroacetone Derivatives.**— Syn and anti trifluoromethyl groups of some HFA derivatives have been assigned by long-range coupling considerations. The surest of these is the *N*-fluoroimine **5a**, for which the upfield, anti trifluoromethyl



**5a**, X = F **d**, X = $N(CH_3)_2$
**b**, X = H **e**, X = $NH_2$
**c**, X = $CH_3$

group has a fluorine–fluorine coupling half that of the downfield syn group.[11] Similar arguments based on proton–fluorine coupling led to identical assignments for the imine **5b**,[12] the *N*-methylimine **5c**,[12] and now for the *N*,*N*-dimethylhydrazone **5d**. Similar assignments can probably be made for other HFA imine derivatives and are summarized in Table I.

TABLE I
FLUORINE NMR PARAMETERS OF HEXAFLUOROACETONE IMINE DERIVATIVES

| X | Chemical shift (anti) (*J*, Hz) | Chemical shift (syn) (*J*, Hz) | Ref |
|---|---|---|---|
| H | −75.4 (0) | −73.6 (2.5) | *a* |
| $CH_3$ | −71.3 (1.8) | −65.2 (2.5) | |
| $NH_2$ | −66.7 | −64.9 | |
| OH | −67.7 | −65.6 | *a* |
| F | −66.8 (12) | −63.6 (24) | *b* |
| Cl | −69.1 | −67.5 | *b* |
| Br | −70.9 | −69.9 | *a* |
| $N(CH_3)_2$ | −63.8 (1.1) | −52.1 (2.6) | |
| $OCH_3$ | −67.3 | −65.1 | |
|  | −68.6 | −65.1 | *c* |
|  | −68.7 | −65.0 | *c* |
| HFA | −84.6 | | *d* |

[a] Reference 12. [b] Reference 11. [c] Reference 14. [d] C. H. Dungan and J. R. Van Wazer, "Compilation of Reported $F^{19}$ NMR Chemical Shifts," Wiley-Interscience, New York, N. Y., 1970.

While changes in the chemical shifts of the anti trifluoromethyl groups are small, the syn trifluoromethyl in dimethylhydrazone **5d** is shifted downfield 13 ppm from that in hydrazone **5e**. The cis trifluoromethyl group in enamine **2** is also shifted downfield. The chemical shifts of the trifluoromethyl groups of trifluoroacetone derivatives, including the *N*,*N*-dimethylhydrazone, are relatively insensitive to imine substitution. Thus trifluoroacetone hydrazone is assigned the conformation with the amino group anti to the trifluoromethyl group. See Table II.

TABLE II
FLUORINE CHEMICAL SHIFTS OF TRIFLUOROACETONE IMINE DERIVATIVES

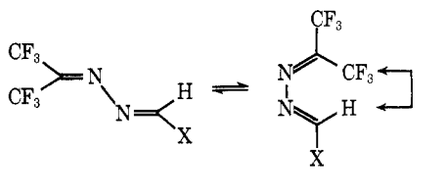
| X | Chemical shift, ppm |
|---|---|
| $NH_2$ | −71.4 |
| OH | −72.1 |
| $N(CH_3)_2$ | −72.1 |
|  | −73.5 |
| TFA[a] | −82.6 |

[a] C. H. Dungan and J. R. Van Wazer, "Compilation of Reported $F^{19}$ NMR Chemical Shifts," Wiley-Interscience, New York, N. Y., 1970.

## Discussion

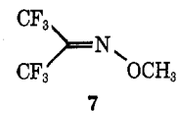
Burton[13] observed that cis four-bond, proton–fluorine coupling in the hydrogen chloride adducts of hexafluorobutyne was larger than trans coupling. This correlation has been used to assign the configuration of some HFA imines (correctly),[12] but in **2** and **3** the trans four-bond, proton–fluorine coupling is larger than the cis. Caution should be used in applying four-bond coupling as a criterion of stereochemistry. Signs of these couplings are unknown.

Both the benzaldehyde **6a** and isobutyraldehyde **6b**

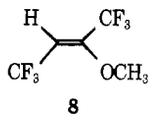


**6a**, X = $C_6H_5$
**b**, X = $CH(CH_3)_2$

azines of HFA show stereospecific, six-bond, proton–fluorine coupling between the aldehyde proton and the syn trifluoromethyl group.[14] What part through space interactions in cisoid conformations play in determining the stereospecificity of the couplings is unknown. Unless both cis and trans couplings are available, such as with **3** or HFA derivatives, the structure should not be based on six-bond coupling. Six-bond couplings in hexafluoroacetone oxime *O*-methyl ether (**7**)[12] and in the methanol adduct with hexafluorobutyne **8**[15] are not observable.



**7**



**8**

## Experimental Section

Proton nmr spectra were determined on a Varian A-60 and fluorine nmr spectra on a Varian A56/60. The preparation of **1a** has been described previously.[5] The mixture **3** was prepared by bubbling dimethylamine through a trichlorofluoromethane solution of hexafluorobutyne until no further exotherm was observed.[9] Examination of the crude product verified the presence of both isomers; distillation gave only the trans isomer.

(10) G. V. D. Tiers, *J. Chem. Phys.*, **35**, 2263 (1961).
(11) J. K. Ruff, *J. Org. Chem.*, **32**, 1675 (1967).
(12) W. J. Middleton and C. G. Krespan, *J. Org. Chem.*, **30**, 1398 (1965).
(13) D. J. Burton, R. L. Johnson, and R. T. Bogan, *Can. J. Chem.*, **44**, 635 (1966).
(14) F. J. Weigert, submitted for publication in *J. Fluorine Chem.*
(15) E. K. Raunio and T. G. Frey, *J. Org. Chem.*, **36**, 345 (1971).

Several weeks at room temperature were required for the re-equilibration.

**Hexafluoroacetone Dimethylhydrazone** (4).—2,2,2-Trifluoro-1-(trifluoromethyl)ethylidenimine (11 ml) was bubbled into a chilled solution of 6.0 g of *N*,*N*-dimethylhydrazine in 25 ml of ether. After the addition was complete, the solution was warmed to room temperature and poured onto 30 g of phosphorus pentoxide.

Distillation gave only a trace of the desired hydrazone. The product was purified by gas chromatography on a 6 ft × 0.25 in. column of 20% silicone #200 on 60/80 Chromo "W." At 50° and 10 cc/min the retention time was 50 min; pmr ($CCl_4$) $\delta$ 3.24 (q, $J$ = 1.2, q, $J$ = 2.4 Hz).

*Anal.* Calcd for $C_5H_6F_6N_2$: mol wt, 208.0434. Found: mol wt, 208.0429 (high-resolution mass spectrum).

**1-[1-(Trifluoromethyl)ethylidenehydrazono]-1-(trifluoromethyl)ethane.**—To a stirred solution of 25 g of trifluoroacetone in 200 ml of ether at −30° was added dropwise 25 g of anhydrous hydrazine. An extremely exothermic reaction occurred. The solution was allowed to warm to room temperature and phosphorus pentoxide was added until further addition produced no change. The solution was distilled through a spinning-band column, giving 10 g of product as a pale yellow liquid: bp 58–62° (180 mm); $^{19}F$ nmr ($CCl_4$) $\delta$ −73.48 (s); pmr $\delta$ 1.5 (s); ir ($CCl_4$) 7.5, 8.3, 8.7, and 9.0 $\mu$.

*Anal.* Calcd for $C_6H_6F_6N_2$: C, 32.8; H, 2.8. Found: C, 32.8; H, 3.0.

**Trifluoroacetone Dimethylhydrazone.**—To a solution of 11.2 g of trifluoroacetone in 25 ml of ether at −20° was added dropwise with stirring under nitrogen 6 g of *N*,*N*-dimethylhydrazine. The solution was stirred for 1 hr at room temperature after the addition was complete. Phosphorus pentoxide was added until no further exotherm was observed. The liquid was distilled through a small spinning-band column, giving 2.5 g of product as a colorless liquid: bp 100–103°; ir ($CCl_4$) 3.3, 3.45, 6.8, 6.9, 7.4, 8.3, 9.0, 9.8, 10.4, and 14.4 $\mu$; pmr $\delta$ 2.00 (s, $CCH_3$), 2.67 (s, $NCH_3$).

*Anal.* Calcd for $C_5H_9F_3N_2$: mol wt, 154.0718. Found: mol wt, 154.0717 (high-resolution mass spectrum).

**Registry No.**—**1a** (X = $NH_2$), 34226-09-0; **1a** (X = OH), 34226-10-3; **1a** [X = $N(CH_3)_2$], 34226-11-4; **1a** [X = $N{=}C(CH_3)CF_3$], 34226-12-5; *cis*-**3**, 4639-94-5; *trans*-**3**, 4592-87-4; **4**, 34224-15-2.

# 7,8,9-Trimethoxy-4a,10b-*trans*- and -4a,10b-*cis*-1,2,3,4,4a,5,6,10b-octahydrophenanthridines. Configurational and Conformational Changes in Epimerization of N-Substituted Derivatives[1]

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*Received October 6, 1971*

Proton exchange and epimerization of salts of N-substituted 7,8,9-trimethoxy-4a,10b-*trans*- and -4a,10b-*cis*-1,2,3,4,4a,5,6,10b-octahydrophenanthridines were studied by nmr. The hydrochloride salts of the *N*-methyl derivatives of the trans and cis isomers each crystallize to give only one epimeric form, **5a** and **6a**, respectively. In formic acid proton exchange and equilibration of epimers are relatively slow processes and the equilibration is catalyzed by sodium formate. Crystalline **5a** dissolved in formic acid is shown to have the cyclohexane and hetero rings in chair and half-chair conformations, respectively, with the *N*-methyl group in equatorial orientation and cis to H-4a. Epimerization of **5a** involves an inversion of the nitrogen without any change in conformations of the six-membered rings. The nmr data for the crystalline cis isomer **6a**, in formic acid, indicates chair and half-chair conformations of the two rings, with H-4a having an equatorial orientation relative to the cyclohexane ring and being axial relative to the hetero ring, with the *N*-methyl group equatorial and cis to H-4a. Epimerization to **6b** is associated with an inversion of conformation of the hetero and cyclohexane rings; thus the *N*-methyl group has an equatorial orientation in both epimers. Exchange processes were also investigated to a limited extent in other solvents, including chloroform-*d*, trifluoroacetic acid, and $D_2O$. The conformations of the free bases are also discussed.

7,8,9-Trimethoxy-4a,10b-*trans*- and -4a,10b-*cis*-1,2,3,4,4a,5,6,10b-octahydrophenanthridines and a number of N-substituted derivatives have been prepared by known methods from *trans*- and *cis*-2-(3,4,5-trimethoxyphenyl)cyclohexylamines[2] (**1** and **2**) for pharmacological evaluation.

Under conditions of slow proton exchange on the nmr time scale, the nmr spectra of the salts of the tertiary amines showed an equilibration between two geometrical isomers. This epimerization was studied more extensively in the hydrochloride salts of the *N*-methyl isomers **5** and **6**. The hydrochloride salts of **5** and **6** each crystallize in a single epimeric form, the form that is thermodynamically most stable in solution in each case. The nmr spectra of freshly prepared solutions of the crystalline salts of **5** or **6** dissolved in formic acid show the presence of only one epimer in each case (**5a** or **6a**), followed by a slow appearance of a second minor isomer (**5b** or **6b**). The rate of equilibration is enhanced by sodium formate. Melts of the salts give the spectra of the equilibrated systems.

Spectrum A, Figure 1, shows part of the nmr spectrum of a solution of the crystalline hydrochloride salt of **5** in 99% formic acid, and spectrum B is that of the equilibrated system after addition of sodium formate. Spectrum A indicates the presence of a single epimer. The most relevant signals are the *N*-methyl doublet at $\tau$ 6.83 ($J_{NH-CH_3}$ = 5 Hz) and the signals of the diastereotopic hydrogens on C-6 which appear as sets of doublets of doublet with chemical shifts of $\tau$ 5.29 and 5.68. The C-6 hydrogen giving the lower field signal will be referred to as H-6 and the one giving the upper field signal as H-6′. The signals of H-6 and H-6′ yield the following coupling constants: $J_{6,6'}$ = 16 Hz, $J_{NH,6}$ = 4 Hz, and $J_{NH,6'}$ = 8.6 Hz. The difference of coupling constants between the ammonium proton and the two diastereotopic C-6 hydrogens is of importance in the assignment of configuration to epimer **5a** (*vide infra*). The spectrum of **5a** in trifluoroacetic acid has the same pattern as in formic acid (Table I)

(1) This investigation was supported by Grant MH 12204 from the National Institute of Mental Health, U. S. Public Health Service. The compounds were submitted to Eli Lilly and Co. for pharmacological evaluation.

(2) W. F. Trager and A. C. Huitric, *J. Pharm. Sci.*, **54**, 1552 (1965).