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Dipole Moments and Conformational Equilibrium in Some Substituted 1-Phenyl-1-fluoro-2-halogenoethanes

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Abstract □ Experimental dipole moments of substituted 1-phenyl-1-fluoro-2-halogenoethanes are compared with the vectorially and the theoretically calculated values using the CNDO/2 method. Results support the existence of a conformational mixture of these compounds as solutes; *gauche* structures are the prevailing conformations as in the related catecholamines.

Keyphrases □ Phenylfluorohalogenoethanes—substituted, dipole moments, conformations as solutes □ Dipole moments—substituted phenylfluorohalogenoethanes as solutes □ Conformations—phenylfluorohalogenoethanes as solutes

Potentially antiarrhythmic drugs can be prepared from substituted 1-phenyl-1-fluoro-2-halogenoethanes, because the latter are structurally related to catecholamines. However, conformations of these intermediates have to be portrayed. For this purpose, their experimental dipole moments and the vectorially as well as the theoretically calculated moments were compared in this report.

EXPERIMENTAL SECTION

Materials—The following compounds were studied: 1-phenyl-1-fluoro-2-chloroethane (I), 1-phenyl-(4′-bromo)-1-fluoro-2-chloroethane (II), 1-phenyl-(4′-chloro)-1-fluoro-2-chloroethane (III), 1-phenyl-(2′-bromo)-1-fluoro-2-bromoethane (IV), 1-phenyl-(2′-chloro)-1-fluoro-2-bromoethane (V), 1-phenyl-(2′,4′-dichloro)-1-fluoro-2-chloroethane (VI), 1-phenyl-(2′,-5′-dichloro)-1-fluoro-2-chloroethane (VII), and 1-phenyl-(2′,6′-dichloro)-1-fluoro-2-bromoethane (VIII). These compounds were prepared from the corresponding alcohols, in accordance with the process previously described (1).

Methods—The dipole moments of the compounds as solutes in anhydrous benzene were measured at 25.00 ± 0.05°C. The permittivity[1] and refractive index[2] of the solutions were extrapolated to infinite dilution according to Guggenheim (2) and Smith (3). The quantity $(\epsilon_{12} - n_{12}^2) - (\epsilon_1 - n_1^2)$ was plotted *versus* the molar concentration, C, of the solute. The slope of the curve at $C = 0$ was then used to calculate the dipole moment, μ, by:

$$\mu^2 = \frac{9kT}{4\pi N} \cdot \frac{3}{(\epsilon_1 + 2)(n_1^2 + 2)} \cdot \frac{(\epsilon_{12} - n_{12}^2) - (\epsilon_1 - n_1^2)}{C} \qquad \text{(Eq. 1)}$$

where k is the Boltzmann constant, N is Avogadro's number, T is the absolute temperature, and ϵ_i and n_i are the permittivities and refractive indexes, respectively, of the solutes (Index 1) and of the solutions (Index 12).

RESULTS AND DISCUSSION

The molecular geometry of the compounds studied is schematized in Fig. 1. Hence, six limit-conformers have to be considered, because of the presumable restricted rotation around the C_1—C_2 bond. These conformers, presented in Fig. 2, are noted (A) when bonds are staggered and (B) when bonds are opposed. The following bond increments were then used for vectorial calculations: H—$C_{sp}3$, 0.25 *D* (4); $C_{sp}3$—Br, 1.38 *D*; $C_{sp}3$—Cl, 1.46 *D*; $C_{sp}3$—F, 1.41 *D* (5); $C_{sp}3$—$C_{sp}2$, 0.4 *D*; $C_{sp}2$—Br, 1.54 *D*; and $C_{sp}2$—Cl, 1.58 *D* (6).

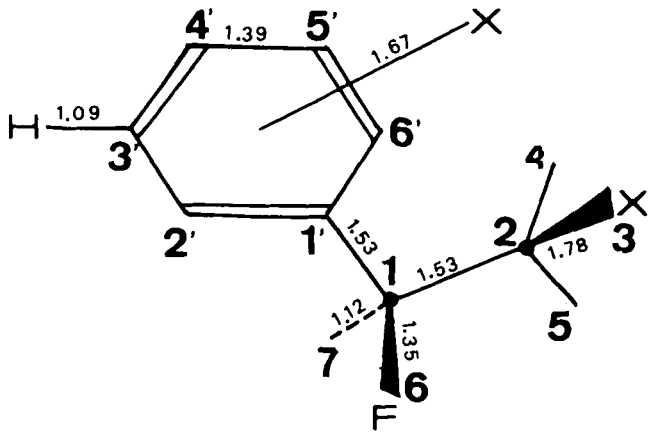

Figure 1—*Molecular geometry of the compounds studied.*

As regards the vectorial pattern of the molecules, it must be emphasized that spatial orientation of the phenyl ring *versus* the C_1—F bond is of no importance, except with the *ortho*-substituted derivatives. In the latter case, four possible orientations must be taken into account in accordance either with

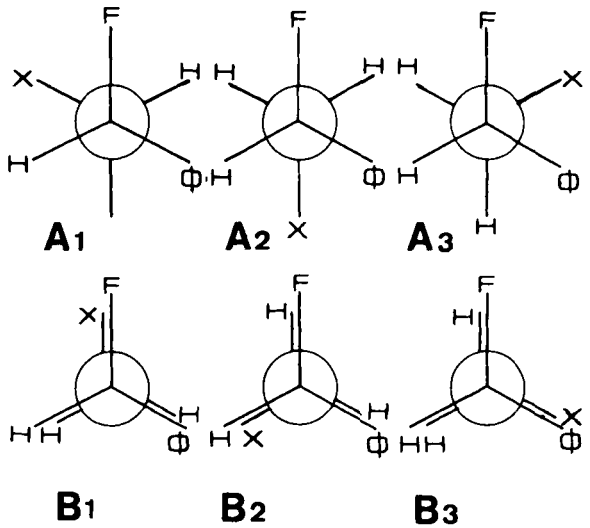

Figure 2—*Schemes of the staggered and the opposed limit-conformers used in the calculations.*

[1] W.T.W. DM 01 dipolmeter with a DFL 1 cell.
[2] O.P.L. Abbe type refractometer.

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Table I—Experimental and Calculated Dipole Moments [a]

Compound	μ_{exp}	Ring Orientation	Method	Calculated Moments: Conformers A-1	A-2	A-3	B-1	B-2	B-3	μ_{theor}	Conformer Population [b]: A-1	A-2	A-3
I	2.54	1-4	Vect	2.24	0.67	2.82	2.92	0.99	1.98	2.21			
		1	PCILO	2.80	0.64	2.96				2.57	0.54	0.20	0.26
		1	CNDO/2	3.30	1.14	3.12				2.94			
II	1.90	1-4	Vect	1.59	2.22	3.51	2.77	0.89	3.28	2.40	0.48	0.25	0.27
III	1.93	1-4	Vect	1.60	2.26	3.54	2.79	0.94	3.32	2.42	0.50	0.23	0.27
		2	CNDO/2	1.65	1.72	3.29				2.25			
IV	2.65	1a	Vect	3.63	1.35	3.99	4.34	2.16	2.73	3.65			
		1b	Vect	2.46	1.30	1.37	2.17	2.13	0.61	2.08			
		2a	Vect	2.71	1.33	2.99	3.20	1.76	2.16	2.74			
		2b	Vect	3.48	1.53	3.08	3.69	2.54	1.96	3.25			
		3a	Vect	3.50	1.42	4.05	4.29	2.01	2.86	3.60	0.58	0.07	0.35
		3b	Vect	2.75	1.36	1.77	2.55	2.29	0.91	2.38			
		4a	Vect	3.68	1.40	3.88	4.29	2.31	2.61	3.64			
		4b	Vect	2.21	1.37	1.35	1.97	1.98	0.92	1.91			
V	2.71	1a	Vect	3.67	1.38	4.03	4.37	2.20	2.76	3.64			
		1b	Vect	2.48	1.34	1.34	2.17	2.17	0.58	2.06			
		2a	Vect	2.73	1.36	3.00	3.22	1.79	2.18	2.72			
		2b	Vect	3.52	1.57	3.09	3.72	2.58	1.98	3.23			
		3a	Vect	3.54	1.45	4.08	4.33	2.05	2.89	3.59	0.56	0.10	0.34
		3b	Vect	2.77	1.40	1.76	2.56	2.33	0.90	2.35			
		4a	Vect	3.72	1.46	3.91	4.33	2.35	2.64	3.63			
		4b	Vect	2.23	1.41	1.33	1.95	2.01	0.91	1.89			
VI	1.65	1a	Vect	2.94	1.93	4.33	4.13	1.41	3.48	3.49			
		1b	Vect	1.17	1.99	1.99	1.50	1.49	2.20	1.63			
		1b	CNDO/2	1.72	2.19	1.26				1.61			
		2a	Vect	1.67	2.01	3.40	2.87	0.84	3.08	2.53			
		2b	Vect	2.68	1.98	3.38	3.33	1.89	2.80	2.92	0.50	0.10	0.40
		3a	Vect	2.87	2.11	4.45	4.14	1.37	3.66	3.53			
		3b	Vect	1.80	2.10	2.52	2.10	1.80	2.36	2.15			
		4a	Vect	3.07	2.05	4.25	4.11	1.75	3.42	3.52			
		4b	Vect	0.83	2.17	2.11	1.36	1.45	2.42	1.61			
VII	2.39	1-4	Vect	2.24	0.67	2.82	2.92	0.99	1.98	2.40	0.51	0.10	0.39
VIII	3.09	1-4	Vect	3.47	0.94	2.84	3.62	2.44	1.39	2.80	0.56	0.34	0.10

[a] In Debye units. [b] According to NMR data (17).

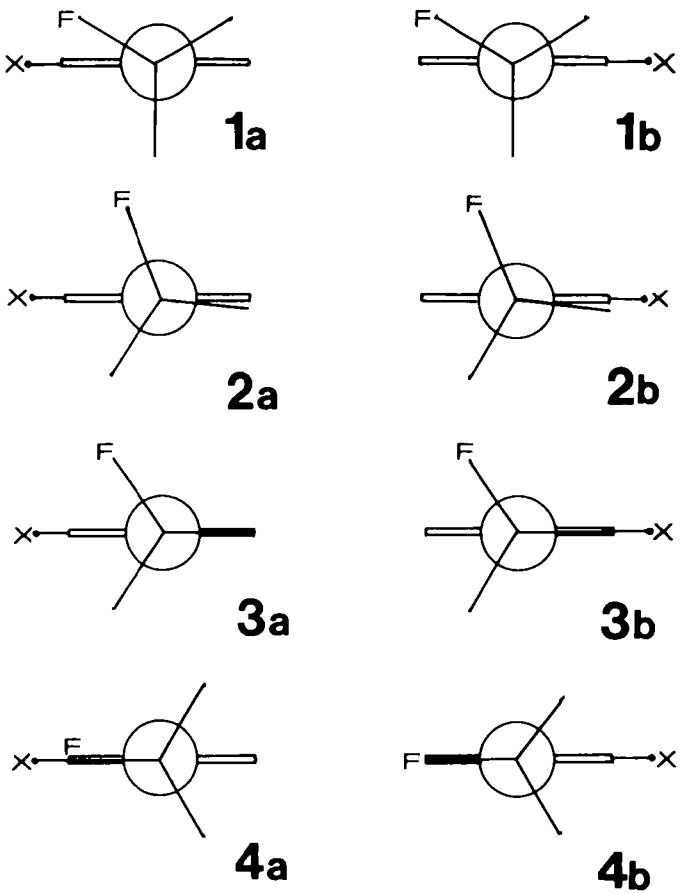

Figure 3—*Ring orientations* versus *the fluorine-carbon bond, in case of orthohalogeno(X)-substituted derivatives.*

experimental results concerning benzyl fluorides [Fig. 3, part 1 (7); Fig. 3, part 3 (8); Fig. 3, part 4 (9)] or crystallographic data about homologues of the compounds studied (Fig. 3, part 2)[3].

Experimental dipole moments and the vectorially calculated moments as well as some values theoretically calculated by means of the CNDO/2 (10) or PCILO (11) methods are given in Table I. On the one hand, all the calculated values are in satisfactory agreement, whatever are methods of calculation. The slight deviations noted are due to the bond increments herein used in the vectorial calculations instead of molecular increments. Under these conditions, atomic interactions through either bonds (12) or space (13) are neglected, although they lead to an inductive moment to be added or subtracted to the bond moments (14).

On the other hand, every vectorially calculated value can be alternately compared with the measured value of the dipole moments. In so doing, structures labeled "B" can be left out. This latter hypothesis directly proceeds from the conformational energy mapping (15), where energy minima only correspond to the "A" conformers. Under these conditions, it follows from the comparison that *gauche* structures (quoted as A-1 or A-3) prevail. However, existence of a conformational mixture cannot be ignored, because of the difference between experimental and calculated values. This is in agreement with the IR results (16). Nevertheless, relative populations cannot be then readily calculated using dielectric data, contrary to NMR data. Indeed, the coupling constants J^{t}_{HH}, J^{g}_{HF}, and J^{t}_{HF} calculated from the latter lead to values of conformational populations (17). Therefore, by using these values, theoretical dipole moments of each compound can be calculated according to the following:

$$\mu_{theor} = \sqrt{\mu^2_{A\text{-}1} \cdot P_1 + \mu^2_{A\text{-}2} \cdot P_2 + \mu^2_{A\text{-}3} \cdot P_3} \qquad \text{(Eq. 2)}$$

These results are also presented in Table I.

The conformational multiplicity is then confirmed by the good relationships noted between the theoretical and the experimental moments. Added to this, the spatial orientation of the phenyl ring can now be figured for IV, V, and VI. Indeed, experimental dipole moments of these molecules are pointed out in Fig. 4, referring to the theoretical moments calculated for the various orientations previously quoted. In the cases of IV and V, the geometrical structure intermediate between 2b and 3b is certainly favored because of the

[3] B. Chion, C. Charlon, and C. Luu Duc, unpublished results.

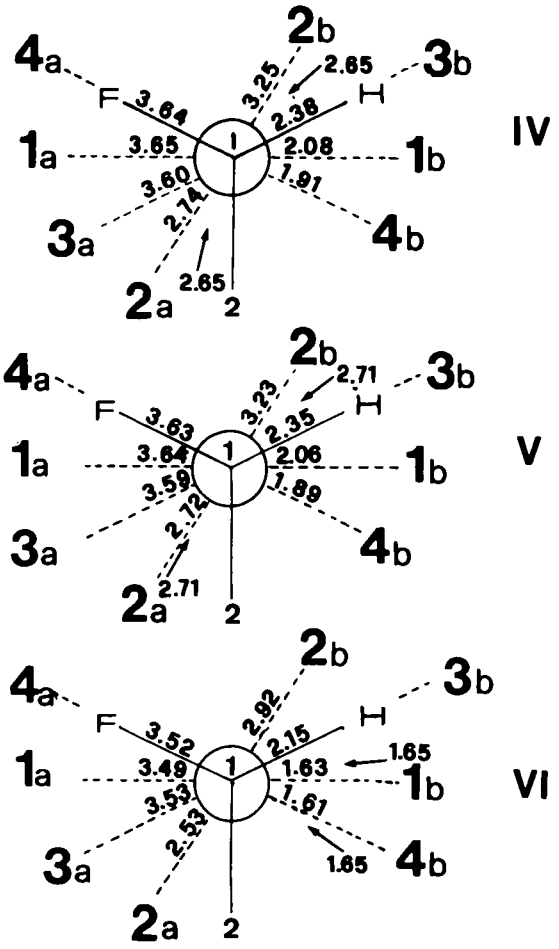

Figure 4—*Experimental dipole moments (values with arrows) and theoretical moments calculated for each ring orientation for IV, V, and VI.*

steric hindrances between halogens in the 2a structure. Conversely, structures 1b and 4b would have to be equally possible for VI, because the C_1—F and the C_2—X bonds are practically *anti* in each case. However, as steric hindrances between the halogen bonded to C-2 and the phenyl ring are minimized in position 1b, the latter will be more stable. These results are in close agreement with ^{13}C-NMR data (18).

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Synthesis and Biological Evaluation of New 2,3-Dihydrothiazole Derivatives for Antimicrobial, Antihypertensive, and Anticonvulsant Activities

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Received December 2, 1982, from the *Pharmaceutical Chemistry Department, Faculty of Pharmacy, University of Alexandria, Egypt.* Accepted for publication August 2, 1983.

Abstract □ A novel series of 2-arylimino-2,3-dihydrothiazole derivatives, substituted in the 3-position with a β-phenethyl moiety and the 4-position with substituted aryl functions, was synthesized as potential antimicrobial, antihypertensive and anticonvulsive agents. While no antimicrobial or significant antihypertensive activity was observed for the products, XII, XIII, and XXI displayed potent anticonvulsant activity.

Keyphrases □ 2,3-Dihydrothiazole derivatives—synthesis antimicrobial, antihypertensive, and anticonvulsant properties □ Antimicrobial activity—2,3-dihydrothiazole derivatives, antihypertensive and anticonvulsant properties

The synthesis and pharmacological properties of a variety of thioureas (1-3), thiosemicarbazones (4-6), thiosemicarbazides (1, 7, 8), thiazoles (2, 6, 7), and thiadiazines (9) derived from various biologically active nuclei (1-5, 8), aromatic (6), and heterocyclic compounds (7, 9) have been recently described in connection with our studies on the structure-activity relationships of certain thio compounds. The high bactericidal activity displayed by some 3,4-diarylthiazolin-2-oxo-(3-substituted 4-oxoquinazolin-2-yl)hydrazones (7) prompted the investigation of a novel series of 2-arylimino-2,3-dihydrothiazoles (VIII-XXXIII) which bear a structural similarity to such active thiazolines with respect to the substituents in the 4-position. This paper reports the synthesis and evaluation of these materials for antimicrobial, antihypertensive, and anticonvulsant activities.

RESULTS AND DISCUSSION

Chemistry—The *N*-substituted *N'*-(2-phenethyl)thiourea derivatives (II-VII), Scheme I, were synthesized (Table I) by treating 2-phenethylamine (I) with the appropriate aryl- or aralkylisothiocyanate in refluxing ethanol

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