Dipole Moments and Conformational Structures of 2-Substituted Phenothiazines as Solutes

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Abstract □ Experimental dipole moments measured in anhydrous benzene and dioxane are compared to the calculated values of some 2-substituted phenothiazine derivatives. The dipole moments and the solvent effects support the existence of a conformational mixture of these compounds as solutes.

Keyphrases □ Phenothiazines—2-substituted, dipole moments and conformational structures as solutes □ Dipole moments—of 2-substituted phenothiazines as solutes □ Conformations—of 2-substituted phenothiazines as solutes

A previous report (1) on N-methylphenothiazine and its 2-chloro derivative suggested a mixture of conformers of these compounds in solution. This finding is important for a possible conformational explanation of phenothiazine polybiovalency. The conformational structures of some other 2-substituted molecules, which are the chemical forerunners of the clinically used phenothiazine drugs, were determined by comparing the theoretical dipole moments of peculiar conformations to experimental values. The experiment dipole moments were measured with the compounds as solutes due to the physical state of the biophase.

EXPERIMENTAL

Materials— The following compounds[1] were studied: phenothiazine (I), 2-chlorophenothiazine (II), 2-cyanophenothiazine (III), 2-methoxyphenothiazine (IV), 2-thiomethylphenothiazine (V), 2-acetylphenothiazine (VI), and 2-propionylphenothiazine (VII).

Method—The dipole moments of the compounds as solutes in anhydrous benzene and in anhydrous dioxane were measured at different temperatures. The permittivity[2] and refractive index[3] 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 $C = 0$ then was used to calculate the dipole moment, μ, by:

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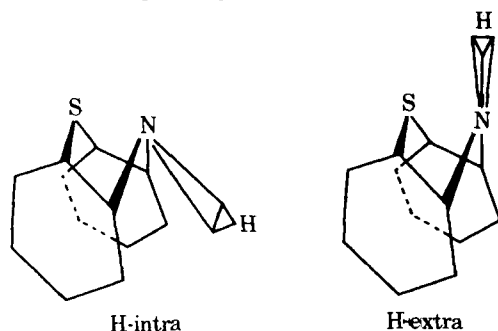
H-intra   H-extra

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).

Table I—Experimental Dipole Moments of 2-Substituted Phenothiazines

Compounds[a]	Dipole Moment, Debye units		
	10°	25°	37°
I (B)	2.20 ± 0.02	2.14 ± 0.02	2.12 ± 0.03
I (D)	2.49 ± 0.02	2.50 ± 0.02	2.51 ± 0.03
II (B)	2.02 ± 0.03	1.93 ± 0.02	1.89 ± 0.08
II (D)	2.19 ± 0.02	2.15 ± 0.02	2.16 ± 0.01
III (B)	3.72 ± 0.07	3.60 ± 0.04	3.55 ± 0.08
III (D)	3.63 ± 0.05	3.67 ± 0.03	3.69 ± 0.04
IV (B)	2.57 ± 0.07	2.49 ± 0.02	2.44 ± 0.03
IV (D)	2.80 ± 0.03	2.84 ± 0.03	—
V (B)	2.19 ± 0.02	2.16 ± 0.03	2.11 ± 0.04
V (D)	2.55 ± 0.04	2.54 ± 0.02	—
VI (B)	2.46 ± 0.05	2.38 ± 0.03	2.40 ± 0.05
VI (D)	2.40 ± 0.01	2.42 ± 0.01	2.41 ± 0.02
VII (B)	—	2.30 ± 0.03	2.29 ± 0.05
VII (D)	2.35 ± 0.05	2.35 ± 0.02	2.34 ± 0.02

[a] The solvent was benzene (B) or dioxane (D).

Table II—Dipole Moments of Molecular Increments Used in Calculations

Compound	Dipole Moment, Debye units
Dimethylsulfide	1.49
Diphenylamine	1.11
Chlorobenzene	1.59
Anisole	1.25
Methylphenylsulfide	1.27
Benzonitrile	3.90
Acetophenone	2.89
Propiophenone	2.88

Table III—Experimental and Calculated Dipole Moments of Amines

Compound	Dipole Moment, Debye units	
	Exp. (4, 5)	Calc.[a]
Trimethylamine	0.86	0.83 (U)
N-Methyldiphenylamine	1.56	1.54 (C)
		1.12 (U)
Diphenylamine	1.11	1.08 (C)
		1.29 (U)
Triphenylamine	0.51	1.12 (C)
		0.49 (U)
Aniline	1.53	1.50 (C)
		1.65 (U)
N-Methylaniline	1.68	1.62 (C)
		1.08 (U)
N,N-Dimethylaniline	1.61	1.65 (C)
		0.76 (U)

[a] Conjugated (C) and unconjugated (U) structures generally were considered.

Table IV—Calculated Dipole Moments of 2-Substituted Phenothiazines [a] for Selected α Values

α	I_i	I_e	II_i	II_e	III_i	III_e	IV_i	IV_e	V_i	V_e	VI or VII$_i$	VI or VII$_e$
180°	1.80	1.80	1.81	1.81	3.52	3.52	2.49	2.49	2.00	2.00	3.96	3.96
170°	2.12	1.45	1.97	1.65	3.48	3.56	2.77	0.94	2.14	1.68	4.07	2.02
160°	2.32	1.18	2.05	1.56	3.39	3.69	2.90	0.89	2.29	1.51	4.14	2.17
150°	2.51	0.87	2.12	1.46	3.31	3.64	3.04	0.93	2.41	1.35	4.22	2.40
140°	2.64	0.61	2.15	1.40	3.19	3.65	3.12	1.03	2.50	1.24	4.25	2.59
130°	2.73	0.39	2.15	1.25	3.09	3.67	3.14	1.23	2.54	1.18	4.21	2.84

[a] When necessary, H-intra structures (i) are distinguished from H-extra structures (e).

RESULTS AND DISCUSSION

The experimental dipole moments are given in Table I. The theoretical values were calculated using a vectorial incremental addition. The molecular increments and their dipole moments (4, 5) are listed in Table II.

Because folding along an NS axis is well known in phenothiazine derivatives (6–8), calculations were performed for different values of the angle, α, between each aromatic moiety of the heterocycle. Both H-intra (quasiequatorial) and H-extra (quasiaxial) limit conformations (9) were considered. Consequently, the following assumptions were used (10): $\mu_{CN \text{ conjugated}}$ (e.g., H-intra structure) = 1.7 D, and $\mu_{CN \text{ unconjugated}}$ (e.g., H-extra structure) = 0.8 D. Such values followed from a study of dipole moment geometrical structural relationships (Table III).

Theoretical dipole moments of the studied compounds are presented in Table IV.

The comparison between experimental and theoretical dipole moments agreed with a folded structure for these molecules. However, there were different α values with each. Compounds I–V sometimes had a quasiaxial structure and sometimes a quasiequatorial one, demonstrated by the dielectric behavior of the compounds in dioxane. Dioxane interacts with conformable solutes by hydrogen bonds (11). Such an interaction is included in the dipole moment value of the solute. Here, there were solute–solvent interactions only with an H-intra conformation because of the electronic hindrances of the H-extra conformer, as can be shown by a molecular framework. Dipole moments measured in benzene and dioxane must agree with one another only for an H-extra structure. The experimental values agreed. Unfortunately, the structures of VI and VII could not be elucidated by correlating experimental and calculated dipole moments except when the following classical relation was used:

$$\mu^2_{\text{experimental}} = \mu^2_{\text{H-intra structure}} x_1 + \mu^2_{\text{H-extra structure}} x_2 \qquad \text{(Eq. 2)}$$

Table V—Molar Fractions of the H-Intra Structure Calculated for Several α Values

α	I	II	III	IV	V	VI or VII
142°	0.65	0.67	0.21	0.60	0.67	0.46
146°	0.66	0.67	0.22	0.62	0.69	0.49
150°	0.69	0.68	0.23	0.64	0.71	0.52
154°	0.72	0.70	0.23	0.66	0.74	0.55
158°	0.77	0.73	0.19	0.69	0.78	0.58

where x_1 and x_2 are the molar fractions of the selected conformers. Thus, a conformational mixture was admitted. Results obtained by applying this conclusion to all of the compounds are listed in Table V.

These results were in agreement with those of the previous study of N-methylphenothiazine derivatives (1). Moreover, contradictory results about NH phenothiazine compounds from theoretical calculations (9), NMR studies (12, 13), and crystallographic data (14) could be explained if the prevalence of this or that conformer was considered for each molecule. Thus, a mixture of conformations is suggested for dibenzoparathiazine and its substituted derivatives in solution. This result supports the action pattern proposed (15, 16) for phenothiazine drugs.

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