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THE DIELECTRIC PROPERTIES OF SEVEN POLAR AMIDINE-CONTAINING COMPOUNDS OF BIOLOGICAL INTEREST

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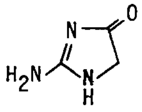
Summary: The static permittivities of seven polar molecules of biological interest have been determined in water and ethane diol, and estimates have been made of their effective dipole moments.

In a recent article[1] the experimental dipole moments were reported for model compounds corresponding to the thiourea, cyanoguanidine and 1,1-diamino-2-nitroethene moieties present in three H_2 receptor histamine antagonists, including cimetidine. The present communication reports dipole moment measurements made on a further seven polar compounds[2] of potential interest, for which no experimental dipole moments were hitherto available. These include the biologically-important bases cytosine (5) (4-aminopyrimidin-2-one), isocytosine (4) (2-aminopyrimidin-4-one) and glycocyamidine (1) (2-amino-2-imidazolin-4-one), two potentially zwitterionic compounds, 2-amino-3-hydroxypyridine (6) and p-hydroxybenzamidine (7) and two novel compounds, 2-methylamino-3-nitropyrrole (3) and 2-methylamino-3-nitro-4,5-dihydropyrrole (2).

In compounds 1-5, dipole moments arise mainly as the result of resonance contributions from zwitterionic species, whereas in compounds 6 and 7, analogous dipolar zwitterions are generated by tautomerism.



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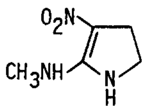

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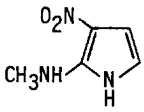

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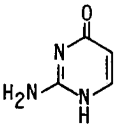

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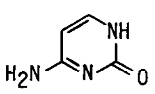

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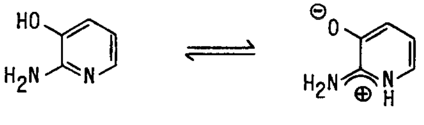

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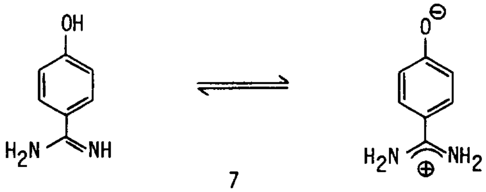

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Permittivity measurements were made at frequencies below 100 MHz using a Boonton 33A bridge as described elsewhere[3], employing water or ethane diol (E.D.) as solvent due to poor solubility in less polar solvents. The values obtained for the experimental parameters are given in table 1, together with the effective dipole moments, $g^{1/2}\mu$, calculated according to equation 1.[4]

$$g\mu^2 = \frac{2kT\varepsilon_0 M\Delta}{NC} \qquad (1)$$

Table 1 Dielectric parameters in water and ethane diol at 25°

Compound	Concn. (C) $kg.m^{-3}$ (solvent)	Static Permittivity (ε_s)	Dielectric Increment (Δ)	Effective dipole moment $g^{1/2}\mu$ debyes
1	34.1 (H_2O)	84.9	8.44	16.7 ± 0.5
2	92.6 (H_2O)	91.0	17.9	17.8 ± 0.3
	39.7 (E.D.)	47.7	7.24	17.3 ± 0.3
3	7.4 (H_2O)	79.05	1.21	*
	21.9 (E.D.)	43.63	2.73	14.2 ± 0.5
4	6.4 (H_2O)	79.1	1.2	*
	20.8 (E.D.)	43.75	2.82	13.1 ± 0.5
5	5.6 (H_2O)	78.94	0.99	*
6	29.2 (H_2O)	81.8	5.27	15.1 ± 0.6
7	21.5 (E.D.)	48.25	7.34	23.0 ± 0.4

* Mean value approximately 15 debyes with an upper limit of 25 debyes.

As some of the compounds in the present study were only sparingly soluble in water, it was convenient to use an alternative solvent. Dipole moment measurements in ethane diol have previously been noted[5] to be comparable with those measured in water, and this obtains in the present study for compound 2, where solubility in each solvent is sufficiently high to give reliable results.

For compounds 1 and 2, sufficient concentrations in water were attainable to allow dipole moments to be calculated to within 0.5D. The solubilities of compounds 3,4 and 5 in water were relatively low, and the values of $g^{1/2}\mu$ calculated for these solutions are therefore much less reliable, and hence only approximate values are given for these. Fortunately, compounds 3 and 4, and also compound 7 are reasonably soluble in ethane diol, and in each case, errors in $g^{1/2}\mu$ are estimated to be no greater than 0.5D.

References and Notes

1. R.C. Young, C.R. Ganellin, M.J. Graham and E.H. Grant, Tetrahedron, 38 (10), 1493 (1982)
2. Commercial samples of 4,5 and 6 were used without further purification. Compound 1 was prepared as the hydrochloride by the method of Bengelsdorf[6] and basified by King's method[7], and 7 was prepared by the method of Partridge and Short[8].
   Compounds 2 and 3 were prepared as follows:
   A solution of 2-methylthio-3-nitropyrrole[9] (2.5g, 0.016mol) in glacial AcOH (70ml) and H_2O_2 (30%, 2ml, 0.017mol) was heated at 60° for 4.5hr. The solvent was removed in vacuo (after first checking that no peroxide remained), and the residue was recrystallised from iPrOH to give 2-methylsulphinyl-3-nitropyrrole (2.3g, 85%) mp. 162-164°. Anal. ($C_5H_6N_2O_3S$) C,H,N,S. A solution of 2-methylsulphinyl-3-nitropyrrole (0.6g, 0.0034mol) in EtOH was treated with a solution of $MeNH_2$ in EtOH (33%, 40ml) and heated under reflux for 6 days. The solvent was removed in vacuo and the residue chromatographed (SiO_2-EtOAc) to give a crude product which was recrystallised from EtOAc/$CHCl_3$, affording 2-methylamino-3-nitropyrrole (3) (0.2g, 42%) mp. 206-208°. Anal. ($C_5H_7N_3O_2$) C,H,N.
   A solution of 1-nitro-2-methylthio-2-methylsulphinylethene[10] (2.0g, 0.011mol) and aziridine (0.5g, 0.012mol) in MeOH (20ml) was stirred at room temperature for 1hr. The solid which crystallised out was filtered off to afford 1-nitro-2-methylthio-2-aziridinoethene (1.3g, 74%) mp. 107.5°-110°. NMR δ ($CDCl_3$) 2.4 (s, CH_2CH_2, 2.56 (s, CH_3), 7.15 (s, CH =). Nitrogen was passed through a solution of 1-nitro-2-methylthio-2-aziridinoethene (0.5g, 0.003mol) in dry MeAc (15ml) for 15 min and the temperature was raised to 35°. Addition of KI (2.5g, 0.015mol) to the

solution yielded a yellow precipitate which was washed with H_2O then MeAc to give 2-methylthio-3-nitro-4,5-dihydropyrrole (0.17g, 34%) mp. 207-209°. Anal. ($C_5H_8N_2O_2S$) C,H,N,S. A mixture of 2-methylthio-3-nitro-4,5-dihydropyrrole (1.8g, 0.011mol) and a solution of $MeNH_2$ in EtOH (33%, 20ml) was heated under reflux for 1hr. The solution was cooled, and the product filtered off. Recrystallisation from MeOH/iPrOH then MeOH/EtOAc gave 2-methylamino-3-nitro-4,5-dihydropyrrole (1.0g, 63%) dec. > 180°. Anal. ($C_5H_9N_3O_2$) C,H,N.

3. C.G. Essex, G.P. South, R.J. Sheppard and E.H. Grant, J. Phys. E., <u>8</u>, 385 (1975)
4. Δ = dielectric increment = $\varepsilon_S - \varepsilon + V(\varepsilon - \varepsilon_\infty)$; ε_0 = permittivity of free space; ε_S = static permittivity of solution; ε = static permittivity of pure solvent (78.3 and 41.6 for water and E.D. respectively) at 25°C; ε_∞ = infinite frequency of pure solvent (5 and 4 for water and E.D. respectively); k = Boltzmann constant; N = Avogadro constant; T = absolute temperature; M = molecular weight of solute; C = concentration of solution ($kg.m^{-3}$); g = Kirkwood correlation parameter; V = volume fraction = $(w/\rho)v$; w = weight of solute dissolved in solvent of total volume v; ρ = density of solute
5. S.E. Keefe and E.H. Grant in "Protides of the biological fluids" (ed. H. Peeters), 355, Pergamon Press, Oxford (1972)
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7. H. King, J. Chem. Soc., 2374 (1930)
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9. A. Kumar, H. Ila and H. Junjappa, J. Chem. Soc. Chem. Commun., 593 (1976)
10. G.R. White (Smith Kline & French Labs Ltd.) U.S. Pat. 4,028,379

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