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THE DIPOLE MOMENTS OF 1,3-DIMETHYLTHIOUREA, 1,3-DIMETHYL-2-CYANOGUANIDINE AND 1,1-BIS-METHYLAMINO-2-NITROETHENE IN AQUEOUS SOLUTION

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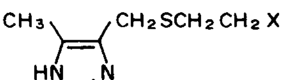
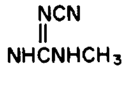
Abstract—The dipole moments, μ, of 1,3-dimethylthiourea, 1,3-dimethyl-2-cyanoguanidine and 1,1-bis-methylamino-2-nitroethene which are important partial structures of histamine H_2 receptor antagonist drugs have been determined in aqueous solution at 25° from static permittivities measured over a wide frequency range. The dipole moments were respectively 10.0, 13.1 and 15.1 Debyes, suggesting that each compound has a high degree of zwitterionic character in water.

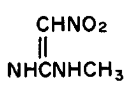
The recently described histamine H_2 receptor antagonists, metiamide (**1a**) and cimetidine (**1b**) incorporate thiourea and cyanoguanidine groups respectively, in their structures.[1,2] Based on structure-activity studies and a similarity in physico-chemical properties, these groups have been considered to be bioisosteric, and a point of interest is their relatively high dipole moments.[2,3] Another potentially isosteric group is 1,1-diamino-2-nitroethene, and the cimetidine analogue, viz. SK&F 92456 (**1c**) is also active as an antagonist.[4] This group is also present in the recently reported antagonist, ranitidine.[5]



(1a) X =

$X = \mathrm{NH}\overset{\overset{\displaystyle S}{\|}}{\mathrm{C}}\mathrm{NHCH_3}$

(1b) X =

$X = \mathrm{NH}\overset{\overset{\displaystyle NCN}{\|}}{\mathrm{C}}\mathrm{NHCH_3}$

(1c) X =

$X = \mathrm{NH}\overset{\overset{\displaystyle CHNO_2}{\|}}{\mathrm{C}}\mathrm{NHCH_3}$

Very little has been published on the physical chemistry of 1,1-diamino-2-nitroethenes, but recent work[6] suggests that this too is a very polar system.

In the present study we compare the dipolar nature of the group 'X' in compounds **1a–c** in greater detail. For this comparison, a new set of dipole moments has been measured using simple model compounds. We now report on the symmetrical dimethyl derivatives, **2a–4a** (Table 2), which, because of their much greater solubility in polar than in nonpolar solvents, have been examined in water.

EXPERIMENTAL

Calculation and measurement of dipole moments. The dielectric behaviour of an aqueous soln of polar molecules is typically as indicated in Fig. 1. Neglecting possible small effects arising from water of hydration, there are two dispersion regions with dielectric increments, Δ_1 and Δ_2 corresponding respectively to the solute and solvent molecules. The purpose of the present work is to determine the value of the dipole moment (μ_1) of the solute molecule from the measured value of Δ_1. Ideally, Δ_1 should be determined from dielectric measurements carried out over the entire course of both dispersions, but an acceptable alternative,[7] particularly useful when the dispersions overlap, as in the present case, is to measure the static permittivity of the solution ε_s, and to calculate Δ_1 from the expression, $\Delta_1 = \Delta_s + \Delta_\infty$ (Fig. 1). If the value of the static permittivity of water is ε_w then $\Delta_s = \varepsilon_s - \varepsilon_w$ is the elevation of the static permittivity of the solution over that of water. Δ_∞ is the depression of the solution permittivity below that of pure water at high frequencies. Therefore, if Δ_∞ can be obtained reliably by an independent method, the value of Δ_1 can be determined. Fortunately, there is a permissible assumption which can be made in the case of aqueous solutions because in the region 'Q' (Fig. 1) the relative permittivity of pure water is still near 80 but that of the solute has dropped to a value more than an order of magnitude lower, owing to the negligible contribution from orientation polarisation at these frequencies. Therefore it follows[7] that $\Delta_\infty \simeq V(\varepsilon_w - \varepsilon_{w\infty})$, where V is the volume fraction occupied by the solute, which is calculated from its partial molar volume,[8] and $\varepsilon_{w\infty}$ and ε_w are the infinite frequency and static permittivities of pure water.

Having obtained Δ_1, the dipole moment μ of the solute molecule in coulomb metres (1C.m = 3 × 10^{29}D) can be calculated[7] from the expression:

$$g\mu^2 = \frac{2kT\epsilon_0 M\Delta_1}{NC} \qquad (1)$$

Where k is the Boltzmann constant, T is the absolute temp, ε_0 is the permittivity of free space, M is the mol wt of the solute, N is the Avogadro constant, C is the concentration of the solute in aqueous soln in kg/m^3 and g is the Kirkwood correlation coefficient,[9] which is dependent upon short-range interactions and whose calculation is model sensitive. For macromolecules (e.g. proteins) in solution, g may be taken as unity,[10] while for pure water the value of g appropriate to correlation between the water molecules themselves is around 2.5.[11] For small solute molecules in aq soln (such as those considered in the present work) the value of g will lie between these limits. It is necessary to emphasise that in *any* experimental determination of dipole moment in aqueous soln the value obtained is $g^{\frac{1}{2}}\mu$ rather than μ

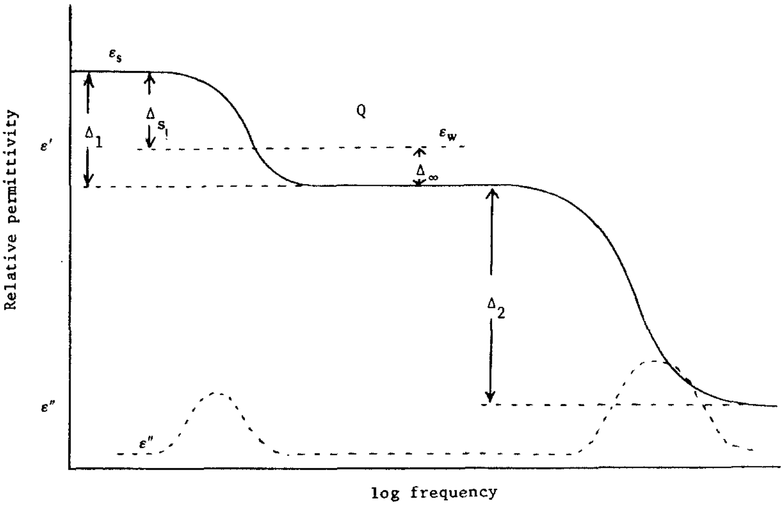


Fig. 1.

alone. Most of the previously published work on molecular dipole moments has implicitly assumed that $g = 1$ and this must be taken into account in any comparative study.

All three compounds investigated in the present work have mol wt of about 100, which, from previous experience with amino acids and urea,[12,13] suggests that their relaxation frequencies are likely to occur in the region of a few GHz. Therefore the value of ε_s was measured experimentally at several different frequencies by two independent techniques at 25°. Measurements below 100 MHz were made at three frequencies using a Boonton 33A bridge, as described previously.[14] In addition, values of complex permittivity were determined at twenty frequencies in the range 300–400 MHz by means of a coaxial line technique, which has been fully described elsewhere.[15,16] With the coaxial line technique, small corrections for the effect of solute dispersion were made, where necessary in order to obtain ε_s. The agreement between the values of ε_s obtained respectively by the bridge and coaxial line methods was well within experimental error, and the combined data gave a final error in the value of ε_s of ±0.5%, where this represents the 95% confidence interval.

For each of the three solns used, the density was determined using a 25 ml pyknometer at 25°, from which was calculated the partial molar volume[8] according to eqn (2).

$$\Phi = \frac{M}{d_0} - 1000\frac{d - d_0}{Cd_0}. \qquad (2)$$

Where Φ is the partial molar volume, M is the mol wt of the solute, C is the concentration of solute in water in moles per litre and d and d_0 are the densities of solution and pure water, respectively.

The value of Δ_1 was then calculated for the three compounds studied using the parameters shown in Table 1. The values of the effective dipole moment, $g^{\frac{1}{2}}\mu$, were calculated from eqn (1) and are listed in Table 1. To obtain absolute values of μ, it would be necessary to calculate g using an appropriate model for the solute molecule in its aqueous environment, but from previous experience the value of $g^{\frac{1}{2}}$ would be expected to lie in the range 1.0–1.4. However, for *comparing* values of dipole moment of molecules which are expected to have a similar local structure and co-ordination number, such as those considered here, one may assume that the value of g is likely to be similar in each case. For simplicity, the ensuing discussion is based on setting g equal to unity.

Materials. Compound **2a** was obtained from Aldrich Chemical Co Inc., and recrystallised from benzene, m.p. 61–2°. Compound **3a** was prepared by the method of Birtwell *et al.*,[17] from 1 - methylthio - 3 - methylamino 2 - cyanoguanidine and methylamine, to give a colourless, crystalline solid, m.p. 177–8° (lit.[17] m.p. 174–5°). Compound **4a** was prepared by treating a soln of 1,1 - bis - methylthio - 2 - nitroethene[18] (4.95 g, 0.03 mole) in EtOH (100 ml) at 50° with an ethanolic soln of methylamine (9.0 g, 33%). After 3 hr stirring at this temp the mixture was allowed to cool, depositing the crude product which was recrystallised from EtOH to give colourless plates (2.65 g, 67% yield), m.p. 220–1° (dec). (Found: C, 36.65; H, 6.88; N, 31.91; Calc. for $C_4H_9N_3O_2$: C, 36.64; H, 6.92; N, 32.05%).

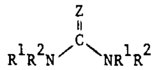
RESULTS AND DISCUSSION

The values derived for the dipole moments of the three compounds studied in the present work are shown in Table 2. In each case these were found to be high. 1,3-Dimethylthiourea (**2a**) was found to have a moment

Table 1. Dielectric parameters of **2a**, **3a** and **4a** in aqueous solution at 25°

	Concentration C (kg/m^3)	Partial Molar Volume Φ (ml)	Static permittivity ε_s	Dielectric increment Δ_1	Effective Dipole Moment $g^{\frac{1}{2}}\mu$ (D)
2a	110.6	91.0	80.2	9.7	10.0 ± 0.4
3a	33.7	97.6	80.9	4.8	13.1 ± 0.9
4a	115.3	111.5	90.3	18.5	15.1 ± 0.3

Table 2. Symmetrically substituted thioureas, cyanoguanidines and diamino-nitro ethenes



	Z	R^1	R^2	μ(D)	Solvent	temp.(°C)	Ref.
2a	S	Me	H	10.0*	water	25°	this work
7#				10.5	-	-	see text
2b	S	H	H	9.0*	water	20°	19
				4.93	dioxane	25°	21
2c	S	Et	H	4.9	dioxane	20°	20
2d	S	Ph	H	4.85	dioxane	20°	20
3a	NCN	Me	H	13.1*	water	25°	this work
8#				18.0	-	-	see text
10#				8.6	-	-	see text
3b	NCN	H	H	8.16	dioxane	35°	22
4a	$CHNO_2$	Me	H	15.1*	water	25°	this work
9#				16.5	-	-	see text
4b	$CHNO_2$	Me	Me	7.64	benzene	25°	6
4c	$CHNO_2$	$-(CH_2)-$	Me	7.39	benzene	25°	6

* these values correspond to $g^{\frac{1}{2}}\mu$ (see text)

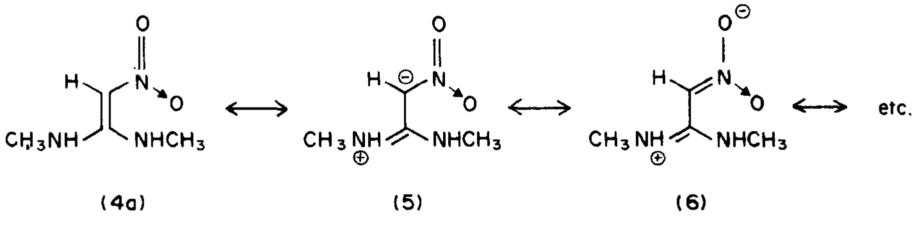
\# canonical structures

of 10.0D, which is in agreement to within experimental error with that of thiourea (9.0D, Experimental) reported by Keefe and Grant[19] measured in water at 20°, and much higher than that measured in dioxane.[20] Previously reported values determined in dioxane suggest that symmetrical disubstitution has little effect on the moment of thiourea; compare 1,3-diethylthiourea (**2c**) and 1,3-diphenylthiourea (**2d**)[21] with thiourea (**2b**),[20] (Table 2). Likewise, the measured dipole moment of 1,3 - dimethyl - 2 - cyanoguanidine (**3a**) in water (13.1D) is much higher than that reported for cyanoguanidine (**3b**) in dioxane,[22] which is the closest analogy reported. The 1,1 - bis - methylamino - 2 - nitroethene (**4a**) was found to have a dipole moment in water of 15.1D, which is much higher than the values reported for the analogous compounds, 1,1 - bis - dimethylamino - 2 - nitroethene (**4b**) and 1,3 - dimethyl - 2 - (nitromethylene) - imidazoline (**4c**) in benzene.[6]

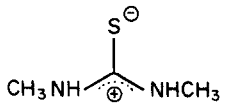
The dipole moments of compounds **2**–**4** arise mainly as a result of charge separation. This can be represented in terms of contributions from electron-delocalised canonical species, e.g. as indicated for 1,1 - bis - methylamino - 2 - nitroethene by the species **5** and **6**.

The importance of such contributions depends on their energy relative to the uncharged form and is determined *inter alia* by the ability of groups like nitro to accommodate negative charge, and on the polarity of the solvent.

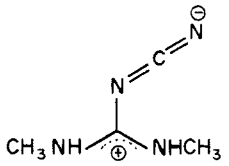
In the present work, all three compounds have very high dipole moments, indicating that in water, there is a high degree of charge separation for each. This is supported by the theoretical dipole moments for the zwitterionic forms **7**, **8** and **9** (obtained in Debye units by multiplying the electronic charge, 1.60×10^{-19}C, by the charge separation in metres and then dividing by 3.33×10^{-30}).



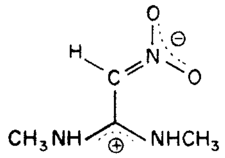
(4a) (5) (6)



(7)

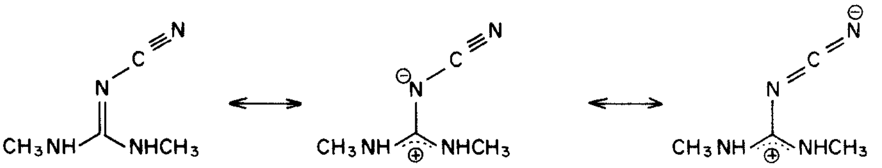


(8)



(9)

For this purpose, the amidinium nitrogens have been assumed to be equivalent, and the positive charge has been positioned at the geometric centre of the triangle formed by the carbon and two nitrogen atoms of this group. The negative charge in **9** is assumed to be centred midway between the two O atoms. Simple MO calculations have indicated that all three atoms in the amidinium system share the positive charge, with the greatest amount of charge residing on the C atom,[23] while in alkane nitronate anions, the O atoms alone carry the negative charge.[24] Using crystallographic molecular dimensions,[25–27] moments of 10.5D, 18.0D and 16.5D are obtained for **7**, **8** and **9** respectively. For both the thiourea and the diaminonitroethene compounds, the calculated moments are close to those measured in water (Table 2), suggesting that structures **7** and **9** may be reasonable descriptions of compounds **2a** and **4a** in this solvent. The moment calculated for **8**, however, is higher than the value measured for **3a** in water, indicating an over-estimate in the degree of charge-separation for this compound. In this case it is likely that there is a significant contribution from the alternative charge-separated form, **10**, whose dipole moment, calculated in the same way, would be 8.6D.



(3a) (10) (8)

This conclusion is in qualitative agreement with that of Hirshfeld and Hope[28] from an X-ray crystallographic study of cyanoguanidine, although in previous discussions on the dipole moment and structure of cyanoguanidine,[22,29] only the terminal cyano N atom was considered as a negatively-charged centre in contributing canonical forms.

As can be seen from Table 2, the dipole moments determined in this work for aqueous solutions are much higher than those reported for related compounds in nonpolar solvents. This is in accord with an enhancement of charge delocalisation caused by dielectric stabilisation of the charge-separated canonical forms relative to the neutral form. In dioxane solution, Kumler and Fohlen[20] concluded that thiourea was "not chiefly in the zwitterion form", but rather that its dipole moment could be explained by a 20–30% contribution from its charge-separated form.

In summary, the high dipole moments found in the present study for aqueous solutions of 1,3-dimethylthiourea (**2a**), 1,3 - dimethyl - 2 - cyanoguanidine (**3a**) and 1,1 - bis - methylamino - 2 - nitroethene (**4a**) are consistent with a high degree of zwitterionic character for each compound. The relative magnitude of these moments, which increases in the series **2a** < **3a** < **4a** is in agreement with the trend expected for progressively increasing the separation of the centre of electronegativity from the amidine system.

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