THE DIPOLE MOMENTS AND MOLECULAR STRUCTURE OF SUBSTITUTED ACETAMIDES

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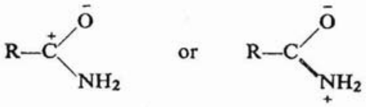
Thioacetamide has a dipole moment substantially higher than the vector sum of the normal characteristic moments of its constituent bonds. However, the effect can reasonably be accounted for on the scheme of alterations in charge distribution and hence of bond moments proposed by Smith, Ree, Magee and Eyring. The same is probably true for chloroacetamide even though the problem of rotation about the C—C single bond renders the conclusion less certain. For cyanoacetamide, the observed moment cannot be accounted for satisfactorily on this basis.

Although a knowledge of the detailed structure of the amide group is desirable because of the role of this group in many physiologically active compounds like peptides, the information that might be made available on this problem through dipole moment measurements is rather confusing.[1-6] On the other hand it is apparent that the structure of even the simple amides has to be established. In view of this, an investigation of the dipole moments of a few simple substituted derivatives of a true amide, viz., acetamide was undertaken so as to obtain information as to whether the contribution of polar resonance forms such as



is important in the structure of the amide group and how much their presence is affected by substituents in R or by replacement of oxygen by sulphur. The particular compounds studied were thioacetamide, chloroacetamide and cyanoacetamide in dioxan solutions.

EXPERIMENTAL

Materials.—*Dioxan*.—Commercial dioxan was purified by Eigenberger's method[7] by refluxing it for 12 h with 1 N hydrochloric acid, whilst a stream of nitrogen was passed through it to remove aldehydes. The product was dried with two successive portions of potassium hydroxide pellets and then refluxed with sodium until the latter remained bright. It was finally fractionally crystallized and distilled from sodium through a long fractionating column. The fraction of constant boiling point 101·3° C was used for the measurements. $d_{35^\circ\,\mathrm{C}} = 1{\cdot}01690$, $\epsilon_{35^\circ\,\mathrm{C}} = 2{\cdot}1890$.

Chloroacetamide.—This was prepared according to the method of Jacobs and Heidelberger[8] by allowing ice-cold ethyl chloroacetate to react with chilled aqueous ammonia. The recrystallized product from water melted at 119-120° C.

Cyanoacetamide.—This was prepared following Corson, Scott and Vose[9] by allowing ethyl cyanoacetate, prepared according to the method of Inglis,[10] to react with concentrated aqueous ammonia and allowing the reaction mixture to stand for 1 h in an ice + salt mixture. The slightly yellowish product when crystallized from hot alcohol was snow white in colour and melted at 119-120° C.

Thioacetamide.—This was prepared according to the method given by Barnett.[11] Five moles of acetamide and one mole of finely powdered phosphorus pentasulphide were boiled under a reflux condenser with a large excess of benzene (about 50 parts) for 20 min. The solution was then filtered and concentrated until thioacetamide crystallized out. Yellow prisms were obtained on recrystallization from ether; m.p. 107-108° C.

APPARATUS AND METHODS OF MEASUREMENT.—The dielectric constant measurements were made with an a.c. mains-operated heterodyne beat apparatus analogous to that of Hudson and Hobbs [12] with the following modifications. The crystal oscillator used a hermetically sealed quartz crystal with a frequency of 1000 kc/sec and a temperature coefficient of 0·0001 % per deg. and an R.C.A. 6V6 valve, operated with a plate voltage of 250 V. The electron coupled oscillator, the radio frequency mixer, the amplifier stage for the heterodyne signal, the mixer stage for combining the heterodyne signal with that from a 1000 cycle tuning fork (G.R. type 813A audio oscillator) and the final stage of amplification were all similar to that of Hudson and Hobbs. An efficient electronic stabilizer circuit following the power supply was used to achieve complete stabilization of plate potentials. To achieve frequency stability, the two units containing the crystal oscillator along with the mixer and the critical oscillator were maintained at a constant temperature of 35° ± 0·05° C by means of an air thermostat operated by an electronic relay of the Hawes type using a beam power 25L6 tube. The oscillators were constructed with great rigidity and shielded cables have been used in all r.f. current-carrying sections. The precision measuring condenser in parallel with the Sayce-Briscoe cell used for the dielectric constant determinations of the solutions in the critical oscillator circuit, was of the G.R. 722D type (1100 $\mu\mu$F). The attachment of a vernier to the rotating dial or scale disc enabled the precision condenser to be capable of finer adjustments and allowed small settings of the order of 0·01 $\mu\mu$F to be measured easily. The true capacity of the test cell was obtained after calibration of the precision condenser for its non-linearity [13] and applying corrections for leads [14, 15] and finally for the non-replaceable capacity by evaluation of zero capacity.[16]

TABLE 1.—DIELECTRIC CONSTANTS AND DENSITIES OF DIOXAN SOLUTIONS AT 35° ± 0·005° C

concentration in mole fraction	dielectric constant	density
THIOACETAMIDE		
0·008959	2·4631	1·02011
0·011354	2·5426	1·02039
0·014054	2·6233	1·02069
0·018940	2·7733	1·02124
CHLOROACETAMIDE		
0·007493	2·2848	1·02159
0·015546	2·3794	1·02404
0·020211	2·4330	1·02528
0·040972	2·6775	1·03187
CYANOACETAMIDE		
0·008213	2·4005	1·02088
0·010545	2·4389	1·02136
0·014203	2·5529	1·02215
0·019609	2·6992	1·02327

Densities of the dilute dioxan solutions were obtained using an Ostwald-Sprengel pyknometer with ground-in caps at both ends. The refractive indices of solutions of the various concentrations were made using a Pulfrich refractometer at 35° C. The molar refraction calculated by the additivity method of bond refractions [17] was compared with that obtained from measurements for the two compounds chloroacetamide and cyanoacetamide. The polarization of the solute at infinite dilution was obtained using the mean values of the Hedestrand constants α and β.[18]

The dipole moments for the three molecules together with the direct experimental data employed in their determination are presented in tables 1 and 2. The dipole moments are believed reliable to ± 0·01D on the basis of precisions of ± 0·1 % in solution concentrations, ± 10^{-4} g cm^{-3} in densities and ± 0·002 in dielectric constants. (Individual values of ϵ are reproducible to ± 0·00005, and this accuracy is attained with liquids such as benzene or carbon tetrachloride but not with dioxan solutions, presumably because of their hygroscopicity.)

TABLE 2

	thioacetamide	chloroacetamide	cyanoacetamide
Hedestrand α	14·06	5·299	11·630
Hedestrand β	0·111	0·297	0·202
molar refraction ^{a} (cm^3)	23·32	19·57	19·17
molar refraction ^{b} (cm^3)	—	18·26	17·55
total polarization (cm^3)	473·2	190·2	353·4
orientation polarization (cm^3)	449·9	170·7	334·2
dipole moment (D)	4·77	2·94	4·10

^{a} calculated from bond refraction.[17]
^{b} measured.

DISCUSSION

In order to calculate the dipole moments of these molecules, for comparison with the observed values it is necessary to know the geometrical structure of the basic acetamide molecule. Richards and Thompson [19] conclude on the basis of infra-red measurements that in dilute solution in dioxan the amides exist predominantly in the keto form (and as monomers only) which is in accord with the X-ray measurements on crystalline amides.[20-23] Already there have been assertions that the molecule is completely planar and accordingly Bates and Hobbs [5] have calculated the total moment of the molecule assuming that the two amino hydrogen atoms are in plane with the nitrogen and consequently with the rest of the molecule. This conclusion is also supported by the X-ray evidence of Corey and Pauling.[24] Therefore in spite of certain less conclusive infra-red studies suggesting the possibility of enolization,[25-28] a planar keto form for the amide group has been used with bond angles shown in fig. 1.

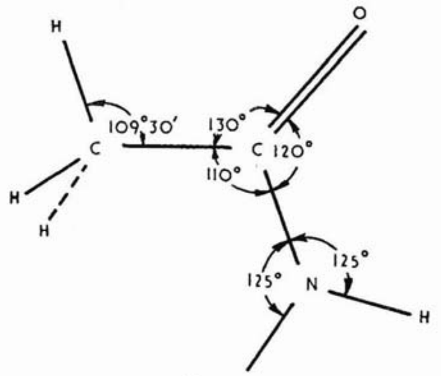


FIG. 1.

The expected resultant dipole moments could be calculated from characteristic bond moments such as those tabulated by Smyth.[29] However, recently Smith, Ree, Magee and Eyring [30] have proposed a method of evaluating the modification of bond moments due to induction along the polarizable bonds. On this scheme each bond is uniquely characterized by two parameters, but the effective moment of each depends on the whole molecule. One of the parameters tabulated by the authors is derived from bond polarizabilities. The other must be obtained from dipole moment data, results from different molecules not being entirely consistent. Since it was desired to ascertain whether any reasonable choice of these parameters would lead to a calculated moment consistent with experiment, several combinations were employed as set forth in table 3.

TABLE 3.—PARAMETERS USED IN CALCULATING BOND MOMENTS BY THE SMITH, REE, MAGEE AND EYRING METHOD

bond	R_{ab}	β_{ab}	λ_{ab} (I)	γ_{ab} (II)	γ_{ab}(III)	γ_{ab} (IV)
H—C	1·071	0·13	*a*	*a*	+ 0·56	+ 0·56
Cl—C	1·761	0·71	− 1·49	− 1·49	− 2·57	− 2·57
O=C	1·215	0·45	− 2·32	− 2·04	− 1·43	− 1·59
N—C	1·471	*b*	*b*	*b*	*b*	*b*
H—N	1·000	0·14	+ 1·81	+ 1·81	+ 1·81	+ 1·81
S=C	1·605	1·30	− 3·30	− 2·81	− 1·77	− 2·05
N≡C	1·149	0·63	− 3·37	− 3·37	− 2·20	− 2·20
C—C	1·542	*c*	*c*	*c*	*c*	*c*

(*a*) In columns I and II the moment of the C—H bond in methane is taken as zero. The parameter $\gamma_{Cl—C}$ is derived from the observed dipole moment of methyl chloride, $\gamma_{O=C}$ from that of formaldehyde[31] (case I) or phosgene[32] (case II), $\gamma_{H—N}$ from that of ammonia,[33] $\gamma_{N—C}$ from that of methyl amine,[34] $\gamma_{S=C}$ from that of carbon oxysulphide[35] and $\gamma_{N\equiv C}$ from that of acetonitrile.[36] For cases III and IV the H—C bond in methane is taken as + 0·4D, the other sources of parameters remaining unchanged. Calculations have also been made using thiophosgene[37] as a source of the parameter $\gamma_{S=C}$ but these were unsatisfactory possibly due to the abnormally low moment of thiophosgene.

(*b*) The parameters needed here are $\beta^{C}_{N} = 0{\cdot}418$ and $\beta^{N}_{C} = 0{\cdot}344$ tabulated by Smith, Ree, Magee and Eyring and α_{NC}, which is calculated as − 1·13 for cases I and II and − 0·85 for cases III and IV from the dipole moment of methyl amine.

(*c*) The parameters used here are $\beta^{C}_{C} = 0{\cdot}718$ as given by Smith, Ree, Magee and Eyring and $\alpha_{CC} = 0$.

THIOACETAMIDE

Values of the dipole moment calculated according to the scheme of Smith, Ree, Magee and Eyring are 4·94D, 4·42D, 4·36D and 4·75D, for the four choices of parameters made. Ordinary vector addition of the usual bond moments gives 3·59D, the observed moment in dioxan solution being 4·77D. This value may be as much as 0·5D higher than the value that would be found for the vapour based on the behaviour of formamide.[5] The enhanced moment (over 3·59D) is explained in terms of resonance beteeen the covalent and dipolar ionic forms. It appears that these may be adequately described as due to induction, or at least that the empirical scheme devised by Smith *et al.* provides a satisfactory explanation. On this theory each atom is given a formal charge equal to the sum of quotient of bond moment by bond length for all its bonds. In accord with the idea that the procedure amounts to taking the existence of polar forms partially into account the result is that the formal charge on the NH_2 group less the formal charge on the C=S group increases from − 0·36 on the basis of usual bond moments, to + 0·84 to + 1·52 on the basis of the theory of Smith *et al.* depending on the choice of parameters used. Bates and Hobbs concluded that the observed moment for acetamide 3·90D is sufficiently close to the vector sum of the bond moments 3·30D to attribute the difference to the solvent effect in dioxan. Calculations with the parameters in table 3 lead to values of 4·02D, 3·67D, 3·78D and 3·91D suggesting that in this molecule also, significant alteration of the effective bond moments due to mutual interaction does occur.

CHLOROACETAMIDE AND CYANOACETAMIDE

For these two molecules the calculated value of the dipole moment depends on what choice is made concerning rotation of the CH_2X group about the C—C single bond as well as on the parameters of table 3 or the usual bond moments.

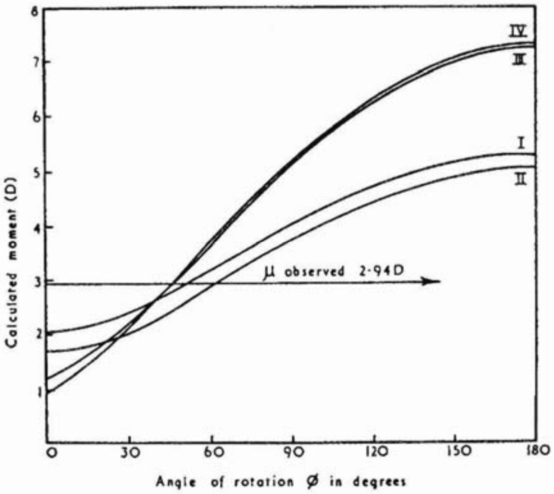


FIG. 2.—Chloroacetamide. Plot of calculated moment against angle of rotation of the CH_2X group with respect to a configuration with the CX bond in the plane of the $CONH_2$ group in a *trans*-configuration relative to the C=O bond. Curves I, II, III and IV correspond to the use of the respective γ_{ab} parameters of table 3.

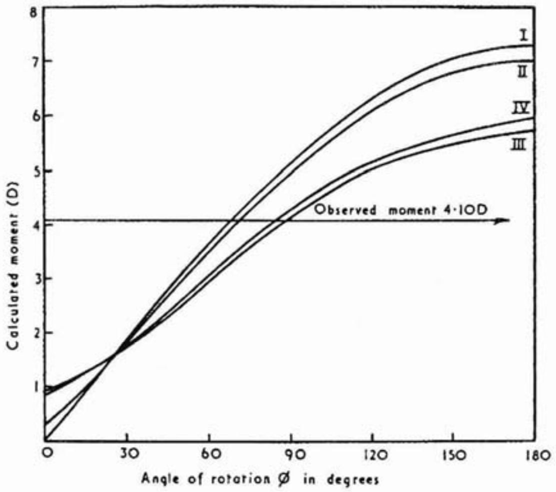


FIG. 3.—Cyanoacetamide. Plot of calculated moment against angle of rotation of the CH_2X group with respect to a configuration with the CX bond in the plane of the $CONH_2$ group in a *trans*-configuration relative to the C=O bond. Curves I, II III and IV correspond to the use of the respective γ_{ab} parameters of table 3.

In treatment of molecules of the type of CH_2X—CH_2Y all treatments show that the staggered configurations are more stable, in spite of the interaction of CX and CY dipoles which tend to favour a *cis* or *trans* configuration.

Calculations using the four sets of parameters γ_{ab} of table 3 have been made of the dipole moment as a function of the angle of rotation of the CH_2X group with respect to a configuration with the CX bond in the plane of the $CONH_2$ group in a *trans* configuration relative to the C=O bond. The results are shown in fig. 2 and 3.

It is apparent that the moment could be accounted for by assuming preponderance of a configuration of $\phi = 30°\text{-}70°$ for chloroacetamide and $60°\text{-}90°$ for cyanoacetamide, or by an unlimited variety of proportions of rotational isomers. For chloroacetamide, either a mixture of isomers of $\phi = 0°$ and $\phi = 60°$, or a continuous potential trough centred near $\phi = 30°$ is not unreasonable. Thus there is no compulsion on the basis of dipole moment data to assume that the chlorine substituent affects the charge distribution in the $CONH_2$ group other than by induction. For cyanoacetamide the dipole moment data are not so easily rationalized. The fact that the C—CN moment is larger than the C—Cl moment suggests that the *trans* configuration should be relatively more important, particularly since " overlapping " of electron shells is also less for CN than for Cl, whereas the observed moment seems to require the opposite.

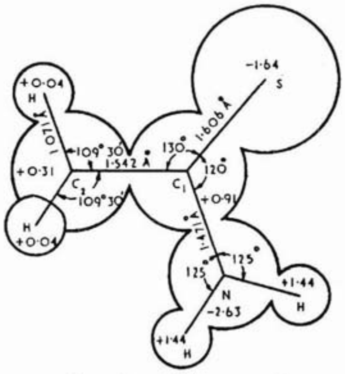


FIG. 4A.—Thioacetamide.

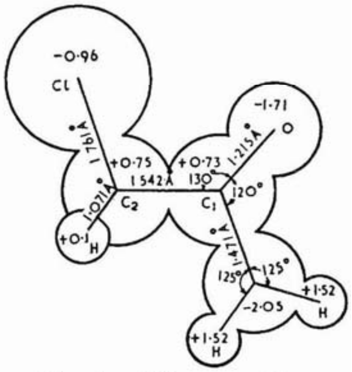


FIG. 4B.—Chloroacetamide.

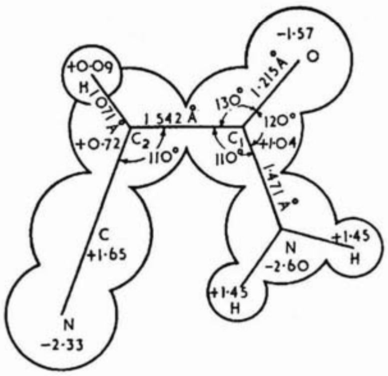


FIG. 4C.—Cyanoacetamide.

Further insight into the plausibility of assuming that the amide group is composed of essentially covalent bonds somewhat polarized by inductive effects can be had by considering the charge distribution which, unlike the dipole moment, does not depend on geometrical parameters (except bond lengths). Table 4 contains values for the formal charges for each atom and group of the three molecules, calculated according to the Smith, Ree, Magee and Eyring scheme using the parameters (II) of table 3 (calculations using any of the other sets do not change the conclusions). Relation of the tabulated numbers to the various parts of the molecule is facilitated by reference to fig. 4.

The calculation results in assigning a number to the well-known tendency of the electron-attracting groups, chloride and cyanide to withdraw electrons from the amide group whose net charge increases from − 0·39 to + 0·01 going from acetamide to chloroacetamide.

TABLE 4.—FORMAL CHARGE DISTRIBUTION IN AMIDES

atom or group	formal charges			
	acetamide	thioacetamide	chloroacetamide	cyanoacetamide
H (on carbon)	+ 0·03	+ 0·04	+ 0·10	+ 0·09
C (methyl)	+ 0·35	+ 0·31	+ 0·75	+ 0·72
C (amide)	+ 0·92	+ 0·91	+ 0·73	+ 1·04
O (or S)	− 1·61	− 1·64	− 1·71	− 1·57
N	− 2·61	− 2·63	− 2·05	− 2·60
H (on nitrogen)	+ 1·45	+ 1·44	+ 1·52	+ 1·45
X	—	—	− 0·96	− 0·68[a]
amide group	− 0·39	− 0·48	+ 0·01	− 0·23

[a] composed of + 1·65 for C and − 2·33 for N.

For cyanoacetamide, the charge increase in the amide group is only from − 0·39 to − 0·23. Since cyanoacetic acid is stronger than chloroacetic acid (pK 2·5 instead of 2·8) so small a charge increment is contrary to expectation. Moreover, Ives and Sames[38] point out that β-chloropropionic acid and β-cyanopropionic acid are of virtually equal strength, in contrast to the substituted acetic acids. These considerations support the conclusion from the dipole moment itself that polar structures such as $N^- = C^+$ and $N^+ = C^-$ not automatically included in the present scheme and presumably resulting from proximity of the $C\equiv N$ and —$CONH_2$ groups, contribute importantly to the structure of the molecule.

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