

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY OF THE UNIVERSITY OF CALIFORNIA]

The Dipole Moment and Structure of Urea and Thiourea<sup>1</sup>

BY W. D. KUMLER AND GEORGE M. FOHLEN

The only work in the literature on the dipole moment of urea is that of Bergmann and Weizmann,<sup>2</sup> who obtained a value of 8.6 in dioxane. A redetermination of the moment of this very important compound seems desirable for several reasons. First, the previous value is based on only one measurement at very high dilution; second, the value seems extraordinarily large compared with the dipole moments of other amides and substituted ureas; third, a recent study by Halverstadt and Kumler<sup>3</sup> shows that measurements in very dilute solutions are apt to give results that are too high due to solvent polarization (water) error unless rigid precautions are taken to exclude moisture; fourth, the previous authors filtered the solutions, thus giving ample opportunity for absorption of water.

The measurement of the dipole moment of urea in a non-polar solvent is complicated by the insolubility of the compound in all non-polar solvents. The only available solvent in which it is appreciably soluble is dioxane and here its solubility is only about 35 mg. per 100 cc. The low solubility of urea makes any solvent polarization error of great importance in the resultant value for the dipole moment. Errors in the dielectric constant will have a larger effect on the moment than usual, due to the small difference between the dielectric constant of the solvent and the various solutions.

The dipole moment of thiourea has also been redetermined. The value<sup>2</sup> 7.6 in the literature appears likewise to be high.

Thiourea has a somewhat greater solubility in dioxane than urea but it still is necessary to measure the compound in comparatively dilute solutions.

## Results

The results are given in Table I.

The symbols have the same significance as in the previous papers.<sup>3</sup> The moments have been calculated by a method described previously,<sup>3</sup>

(1) We are indebted to Professor John T. Edsall for suggesting this problem.

(2) Bergmann and Weizmann, *Trans. Faraday Soc.*, **34**, 783 (1938).

(3) Halverstadt and Kumler, "A Critical Study of Dielectric Polarization Concentration Curves," in publication.

TABLE I  
MEASUREMENTS IN DIOXANE AT 25°  
Urea

	$\omega_2$	$\epsilon_{12}$					
	0.0001225	2.2175					
	.0001655	2.2196					
	.0001847	2.2201					
	.0002751	2.2243					
	Thiourea						
	$\omega_2$	$\epsilon_{12}$	$v_{12}$				
	0.0002715	2.2239	0.97362				
	.0005179	2.2334	.97355				
	.0006755	2.2403	.97350				
	.0008978	2.2488	.97342				
	$\epsilon_1$	$v_1$	$\alpha$	$-\beta$	$P_{20}$	$P_{E_2}$	$\mu$
Urea	2.2120	0.97371	44.44	0.3	456	16	4.56
Thio- urea	2.2130	.97371	40.43	.322	521	24	4.89

employing the graphic modification, and using the equations

$$p_{20} = \frac{3v_1\alpha}{(\epsilon_1 + 2)^2} + (v_1 + \beta) \frac{(\epsilon_1 - 1)}{(\epsilon_1 + 2)}$$

$$P_{20} = p_{20}M_2$$

$$\mu = 0.0127\sqrt{(P_{20} - P_{E_2})T}$$

This method of calculating  $P_{20}$  is more accurate than the usual method and is particularly advantageous in dilute solutions where solvent polarization error may have a large effect on the moment.

In the case of urea the difference in density between the solutions and the pure solvent was within the experimental error, hence, the value of  $\beta$  could not be determined directly. We have taken a value of  $-0.3$ , which seems reasonable compared with the value of  $-0.322$  for thiourea. In any event  $\beta$  does not have a very large effect on the moment. If  $\beta$  is taken as zero the value of the moment is raised by only 0.04.

The  $\epsilon_{12}-\omega_2$  curves are linear in both cases showing that the molecules are not associated in these solutions.

## Discussion

The values for the dipole moments of urea, 4.56, and thiourea, 4.89, are much smaller than the values in the literature 8.6 and 7.6, respectively. This is the most striking example we have found to date of the large amount of error that can be

introduced in dipole moment values by solvent polarization errors.

The new values are in general consistent with the dipole moment values of substituted ureas that appear in the literature. The substituted ureas are sufficiently soluble so that a solvent polarization error would not have an enormous effect on their moment. It is perhaps also significant that none of the solutions of these substituted ureas were filtered, thus they did not have the same opportunity to pick up water as did the solutions of urea and thiourea. In some cases when determinations have been made by different workers they check reasonably well. Thus values of 4.85<sup>4</sup> and 4.9<sup>2</sup> are given for diphenylthiourea and values of 4.8<sup>4</sup> and 5.1<sup>5</sup> for *sym*-dimethylurea.

Let us examine the moment of urea and thiourea in the light of the published values for the substituted ureas which are listed in Table II.

TABLE II

Urea	4.56
Propylurea <sup>5</sup>	4.1
Phenylurea <sup>2</sup>	3.6
<i>sym</i> -Dimethylurea <sup>4</sup>	4.8
<i>sym</i> -Diethylurea <sup>4</sup>	4.9
<i>sym</i> -Diphenylurea <sup>4</sup>	4.6
<i>unsym</i> -Diphenylurea <sup>2</sup>	2.7
N,N-Diethyl-N'-phenylurea <sup>2</sup>	3.2
<i>sym</i> -Dimethyl-diphenylurea <sup>2</sup>	3.6
Tetraethylurea <sup>5</sup>	3.3
Thiourea	4.89
Methylthiourea <sup>2</sup>	4.2
<i>sym</i> -Diethylthiourea <sup>4</sup>	4.9
<i>sym</i> -Diphenylthiourea <sup>4</sup>	4.85
Allyl-piperylthiourea <sup>6</sup>	4.61

Urea and thiourea have moments about 1 unit higher than those of the simple amides whose moments are in the range 3.7-3.9.<sup>7</sup> A calculation similar to that made previously with acetamide<sup>7</sup> where the contribution of the excited form was of the order of 6-15%, gives a contribution of 20-30% for the excited form in urea and thiourea. This is in qualitative agreement with the greater resonance energy<sup>8</sup> of these compounds and the fact that they have two equivalent forms with a separation of charge that can contribute to their structure.

Thiourea and the substituted thioureas have

(4) Hunter and Partington, *J. Chem. Soc.*, 87 (1933).

(5) Devoto and Di Nola, *Gazz. chim. ital.*, 63, 495 (1933).

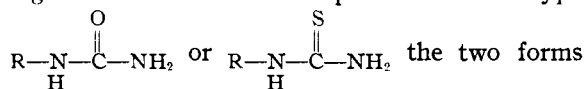
(6) Kremann and Fruhwirth, *Monatsh.*, 69, 319 (1936).

(7) Kumler and Porter, *THIS JOURNAL*, 56, 2549 (1934).

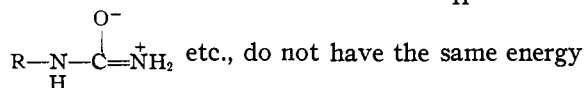
(8) Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, New York, 1939.

slightly higher moments (0.1-0.3) than the corresponding ureas. The introduction of an alkyl group into urea or thiourea lowers the moment by 0.5-0.7. The introduction of one phenyl group reduces the moment by 1.0. Two phenyl groups, if placed on the same nitrogen, reduces the moment by 1.9. In contrast with these reductions in moments is the fact that when two alkyl or two phenyl groups are placed symmetrically in the molecule the moment remains virtually the same. Thus urea, *sym*-dimethylurea, *sym*-diethylurea and *sym*-diphenylurea have moments differing by 0.3, while thiourea, *sym*-diethylthiourea and *sym*-diphenylthiourea have moments that differ by only 0.05.

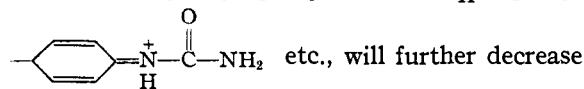
These moments can be interpreted on the basis of the number and contribution of the resonating forms.<sup>8</sup> Thus in compounds of the type



with a separation of charge,  $\text{R}-\overset{\ominus}{\text{N}}=\overset{\oplus}{\text{C}}(\text{H})-\text{NH}_2$ ,



and consequently do not contribute much to the structure, hence the moments of these compounds are less than those of the unsubstituted molecules. If R is a phenyl group the resonance between the phenyl group and the  $\overset{\ominus}{\text{N}}(\text{H})$  group,

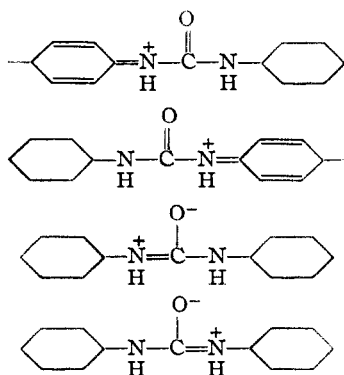


the contribution of the form  $\text{Ph}-\overset{\oplus}{\text{N}}(\text{H})=\overset{\ominus}{\text{C}}(\text{H})-\text{NH}_2$  due to cross conjugation. Furthermore, this resonance between the ring and the  $\overset{\ominus}{\text{N}}(\text{H})$  group introduces forms with a separation of charge which can oppose the resultant moment in the molecule and hence reduce the moment. When two phenyl groups are substituted on the same nitrogen these combined effects are sufficient to bring the moment down to 2.7 which is one unit less than the moment of simple amides.

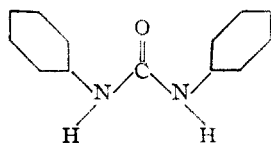
When two like groups are substituted on different nitrogen atoms so the molecules are symmetrical the forms with a separation of charge are again equivalent and these forms, as in the case of the unsubstituted compounds, make a comparatively larger contribution to the structure.

Hence, the moments of the symmetrical disubstituted compounds are approximately the same as those of the parent compounds, urea and thiourea.

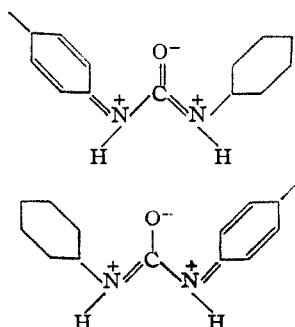
The cases of *sym*-diphenylurea and *sym*-diphenylthiourea are very interesting. It might be thought that these compounds would have lower moments than the parent compounds due to the cross conjugation between the main resonance and the ring resonance plus the possible opposition of the moment from the main resonance and the ring resonance. However, for all four forms to contribute, the molecule must be co-planar. A



study of the Fisher-Hirschfelder models reveals that the only way the molecule can get in a co-planar form is for the molecule to be arranged with the phenyl groups on the same side as the oxygen thus



in which case the moment from the ring— $\text{N}^+\text{H}$  resonance would be in a direction to augment the moment from the main resonance. Furthermore with a phenyl group on both nitrogens a new powerful resonance is possible between the following forms.



Here the ring resonance now supports the urea resonance in the other part of the molecule due to the conjugation, and the negative charge can oscillate from one phenyl group to the other while both nitrogens remain positively and the oxygen negatively charged. The contribution of these equivalent forms with separation of charges will raise the moment. Two symmetrically placed phenyl groups thus introduce factors which lower the moment and others which raise it and the factors balance one another so the moments of *sym*-diphenylurea and *sym*-diphenylthiourea are about the same as the moments of the parent compounds.

Although tetraethylurea and *sym*-dimethyl-diphenylurea are both symmetrical molecules, and therefore might be expected to have moments of about 4.6 these values are considerably less, 3.3 and 3.6, respectively. It is likely that steric hindrance in these tetrasubstituted compounds prevents their atoms from getting in a suitable position for the forms with a separation of charge to make an appreciable contribution. Examination of the models supports this view.

The new dipole moment values throw some light on the old controversy in regard to whether urea and thiourea are zwitterions. The use of the term "zwitterion" applied to these compounds

was first taken to mean the structure  $\text{H}_2\text{N}^+\text{C}(\text{O}^-)=\text{NH}$ . This structure has two things in common with a typical zwitterion, it has a separation of charge, and a shift of a proton is necessary to form it from the normal form. This structure, however, is very untenable and has been discarded in favor of the

structure  $\text{H}_2\text{N}^+=\text{C}(\text{O}^-)-\text{NH}_2$ , which also has a separation of charge but a shift of a proton is not necessary for its formation. The term "zwitterion" was carried over to this structure although it is a resonance hybrid and not a typical zwitterion. When we use the term "zwitterion" in the rest of this discussion we refer to a molecule with a complete separation of charge regardless of how it comes about. The dipole moments indicate very definitely that in dioxane these compounds are not chiefly in the zwitterion forms. The evidence for and against<sup>9</sup> the zwitterion structure has been summarized in "Sidgwick's Organic Chemistry of Nitrogen." One argument is that since amino

(9) Taylor and Baker, "Sidgwick's Organic Chemistry of Nitrogen," Clarendon Press, Oxford, 1937, p. 280.

acids are zwitterions and have high melting points, the high melting points of urea and thiourea suggest they are also zwitterions. The high melting points of urea and thiourea, however, can be accounted for on the basis of the number and strength of the hydrogen bonds that are formed between molecules in the solids. In fact, it is likely that with amino acids themselves the hydrogen bonds formed between molecules may be more responsible for the high melting points than is the zwitterion structure. The compound oxamide has a higher melting or decomposition point,  $420^\circ$ , than any of the amino acids and oxamide is most certainly not a typical zwitterion. However, each molecule in the solid has the possibility of being attached to the surrounding molecules by eight hydrogen bonds.

Another argument is that the short carbon-nitrogen distance of 1.37 Å. suggests a zwitterion structure. Pauling<sup>8</sup> has pointed out that this value for the carbon-nitrogen distance amounts to about 20% double bond character, hence the normal form makes a greater contribution to the structure than do the forms with a separation of charge.

Evidence considered most convincing for the zwitterion structure of urea and thiourea is the fact that these compounds and the aliphatic aminoacids raise the dielectric constant of water (have a positive dielectric increment) while most amides and other nitrogen compounds lower it. However amides in which a major portion of the molecule consists of the amide group such as formamide, malonamide and malamide have positive dielectric increments.<sup>9a,10</sup> The dipole moment of formamide<sup>11</sup> 3.68 is quite normal with respect to the moment of the other amides 3.7-3.9 and the moment value gives no evidence of formamide being a zwitterion.

Whether a compound raises or lowers the dielectric constant of water depends essentially on the number and size of the dipoles per unit volume compared with water. Or stated a bit differently it depends on whether the value of  $\mu\bar{\mu}/v$  for the compound is greater or less than its value for water where  $\mu$  is the dipole moment of a single molecule in the liquid,  $\bar{\mu}$  a related dipole moment<sup>12</sup> and  $v$  the molal volume. The value of this function for water is about 0.7 taking Kirkwood's value for  $\mu\bar{\mu}$  as  $3.55 \mu_0^2$  where  $\mu_0$  is 1.88 the dipole

moment of water in the vapor. The value of  $\mu_0^2/v$  for water is about 0.2. Using 44.3 cc.<sup>13</sup> for the apparent molal volume of urea and our value for the moment, the value of  $\mu^2/v$  for urea is about 0.48 considerably higher than the value of  $\mu_0^2/v$  for water. The larger value of  $\mu\bar{\mu}$  compared with  $\mu_0^2$  for water arises mainly from the hydrogen bonds that are formed between the water molecules in the liquid,<sup>12</sup> four such bonds being possible for each water molecule. An analogous effect would take place between urea and water with six possible hydrogen bonds for each urea molecule. Furthermore it is likely that some of these bonds are stronger than those in water due to the greater plus charge on the nitrogen resulting from the resonance.<sup>14,15</sup> The net effect would be to make the value of  $\mu\bar{\mu}/v$  for urea considerably larger than the corresponding value for water. Consequently these factors alone are sufficient to account for the positive dielectric increment of urea in water without making the assumption that the molecule is a zwitterion.

Evidence of a chemical nature pointing to structures of the type  $\text{HN}=\overset{\text{H}}{\underset{\text{S}}{\text{C}}}-\text{NH}_2$  can be accounted for just as well on a basis of a 20-30% contribution of forms  $\text{H}_2\text{N}^+=\overset{\text{S}^-}{\text{C}}-\text{NH}_2$ ,  $\text{H}_2\text{N}^+-\overset{\text{S}^-}{\text{C}}=\text{NH}_2$ .

Convincing evidence against the zwitterion structure for urea is that of Cohn, McMeekin, Edsall and Blanchard,<sup>13</sup> who found that the ratio of the solubility of urea in alcohol to its solubility in water is much higher for urea than for a typical amino-acid zwitterion. This points rather strongly to urea not being a zwitterion in alcohol. Our dipole moment data are definite evidence that urea and thiourea are not zwitterions in dioxane. The evidence in the solid state and in water solution does not demand the existence of urea as a zwitterion, but the facts can adequately be accounted for on the basis of factors such as the number and strength of dipoles per unit volume, hydrogen bonds, etc.

A consideration of all the available evidence thus leads to the conclusion that urea and thiourea are resonance hybrids with 20-30% contribution of the forms with a separation of charge and that this structure adequately accounts for their behavior whether in the solid state or in dioxane,

(9a) Ref. 9; p. 144.

(10) Wyman, *Chem. Rev.*, **19**, 213 (1936).

(11) Kumler, *THIS JOURNAL*, **57**, 600 (1935).

(12) Kirkwood, *J. Chem. Phys.*, **7**, 911 (1939).

(13) Cohn, McMeekin, Edsall and Blanchard, *J. Biol. Chem.*, **100**, Proc. XXVIII (1933).

(14) Kumler, *THIS JOURNAL*, **57**, 604 (1935).

(15) Lu, Hughes and Giguère, *ibid.*, **63**, 1507 (1941).

alcohol or water solutions. Their structure is essentially the same as that of the simple amides except for a higher contribution of the forms with a separation of charge.

### Experimental

The measurements were carried out as was described in a previous paper.<sup>16</sup>

#### Materials

**Dioxane.**—The purification and constants of dioxane were as described previously.<sup>16</sup>

**Urea.**—A c. p. grade of urea was recrystallized twice from methyl alcohol, heated with pure dioxane to remove any alcohol; m. p. 132.6°.

**Thiourea.**—Eastman Kodak Co. best grade thiourea was recrystallized from methyl alcohol, heated with pure dioxane. The product gave no test for thiocyanate.

### Summary

The dipole moments of urea 4.56 and thiourea 4.89 have been measured in dioxane at 25°. Plots of the dielectric constants against weight fractions were linear, showing the molecules were not associated in these solutions.

The dipole moment values indicate that urea and thiourea are resonance hybrids with a 20–30% contribution from the forms with a separation of charge.

(16) Kumler and Halverstadt, *THIS JOURNAL*, **63**, 2182 (1941).

The magnitude of our values for these compounds together with those for substituted ureas appearing in the literature are correlated from the standpoint of resonance. Urea and thiourea have nearly the same moments as the corresponding symmetrical disubstituted compounds. All of these compounds have two equivalent forms with a separation of charge. The moments of the monosubstituted compounds in which the two forms with a separation of charge are not equivalent are smaller, and those of the unsymmetrical disubstituted compounds still less. The low moments of the symmetrical tetrasubstituted compounds are attributed to steric hindrance.

The evidence of the existence of urea and thiourea as zwitterions is examined and it is shown that all the evidence can be adequately accounted for by the resonance hybrid structure whether urea is in the solid state or in dioxane, alcohol, or water solutions.

The structure of urea and thiourea is not essentially different from that of the simple amides except for a somewhat larger contribution of the forms with a separation of charge.

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## The Dissociation Constant, Dipole Moment and Structure of $\alpha$ -Nitrotetronic Acid

By W. D. KUMLER

$\alpha$ -Nitrotetronic acid was originally assigned the isonitro form.<sup>1</sup> The structure of this compound is reconsidered here in the light of present day viewpoints. The dissociation constant and dipole moment have been measured and the results interpreted.

### Results

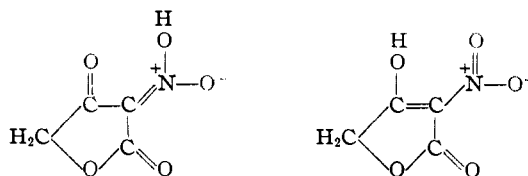
TABLE I

MEASUREMENTS IN WATER AT 25°						
<i>M</i>	% Neutralized	<i>pH</i>	<i>pK<sub>a</sub></i>	Average <i>pK<sub>a</sub></i>		
0.00875	40	2.40	1.63			
.00752	50	2.55	1.70	1.68		
.00710	60	2.67	1.70			
MEASUREMENTS IN DIOXANE AT 25°						
$\omega_2$	$\epsilon_{12}$	$\mu_{12}$				
0.0005308	2.2275	0.97349				
.0008488	2.2380	.97328				
.0012674	2.2507	.97315				
.0015091	2.2593	.97306				
$\epsilon_1$	$\nu_1$	$\alpha$	$-\beta$	<i>P<sub>20</sub></i>	<i>P<sub>E20</sub></i>	$\mu$
2.2100	0.97364	32.50	0.386	802	27	6.10

(1) Wolf and Lüttringhaus, *Ann.*, **512**, 133 (1900).

### Discussion

The possibilities for the structure are the isonitro and the enol.



The structure of analogous compounds suggests that the enol is by far the more stable structure. Thus tetronic acid and  $\alpha$ -halogen substituted tetronic acids are largely in the enol form<sup>2</sup> while no stable isonitro compound of any kind has been isolated. The isonitro compounds that have been obtained<sup>3</sup> change into the nitro form on standing. These facts in themselves suggest that the enol form is the more probable.

The structure of an isonitro compound is ana-

(2) Kumler, *THIS JOURNAL*, **60**, 857, 859 (1938).

(3) Hantzsch and Schultze, *Ber.*, **29**, 699, 2253 (1896).