

## THE CONFORMATION OF SUBSTITUTED HYDROXYUREAS AND HYDROXYTHIOUREAS IN SOLUTION\*

Jiří MOLLIN<sup>a</sup>, Pavel FIEDLER<sup>b</sup>, Václav JEHLIČKA<sup>c</sup> and Otto EXNER<sup>b</sup>

<sup>a</sup> Department of Inorganic and Physical Chemistry,  
Faculty of Natural Sciences, Palacký University, 771 46 Olomouc,

<sup>b</sup> Institute of Organic Chemistry and Biochemistry,  
Czechoslovak Academy of Sciences, 166 10 Prague 6 and

<sup>c</sup> Department of Physical Chemistry,  
Prague Institute of Chemical Technology, 166 28 Prague 6

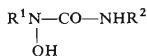
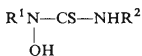
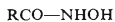
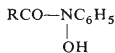
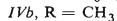
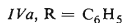
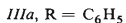
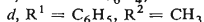
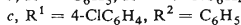
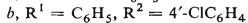
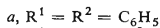
Received August 23rd, 1978

The conformation of 1,3-disubstituted 1-hydroxyureas *Ia-d* and 1-hydroxythioureas *IIa-d*, mostly with aromatic substituents, was investigated by means of dipole moments in dioxan solution and by infrared spectroscopy. The results are concordant for the two classes of compounds. The most populated conformation is near to the planar *Z, E, ap* form (*A*), or possibly with the hydroxyl hydrogen out of the N—C—N—O plane (between *A* and *B*). This finding from the analysis of dipole moments is corroborated by the presence of the amide-II band and absence of intramolecular hydrogen bonds. While the conformation of hydroxyureas seems to be virtually uniform, in the case of hydroxythioureas a less abundant rotamer may be present in nonpolar solvents, possibly the *E, E, sp* (*G*) or *E, E, ap* (*F*) form. The conformation found (*A*) is not explicable in terms of hydrogen bonds and/or steric factors when compared to symmetrically substituted ureas (thioureas) and to N-alkylhydroxamic acids.

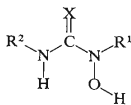
The conformation of substituted hydroxyureas *I* and hydroxythioureas *II* represents a complex problem since rotation around three axes must be taken into account: two C—N bonds and one N—O bond. We may start with the hypothesis that the two amide-like groups are approximately planar, similarly as in true amides<sup>1</sup>. As regards the conformation around the N—O bond, there is no particular reason for a planar arrangement; of simpler molecules with the same grouping hydroxamic acids *III* are probably nonplanar<sup>2,3</sup> and even the dipole moments<sup>4</sup> of N-arylhydroxamic acids *IV* could be interpreted in terms of nonplanar forms as well as of a mixture of the planar ones<sup>4</sup>. Nevertheless, we considered the planar conformations even around the N—O bond as possible limiting forms, so that there are on the whole eight possibilities (*A-J*). The task is to decide which of them may be present in a significant amount in solution, bearing in mind that actual energy minima can be

\* Part XXI in the series Acyl Derivatives of Hydroxylamine; Part XX: This Journal 43, 2740 (1978).

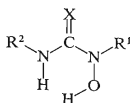
situated between the forms *A-B*, *C-D*, *F-G*, and *H-J*, respectively, and that considerable oscillations around the N—O bond take place.

*I**II**III**IV*

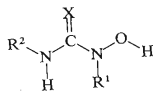
The actual conformation of 1,3-diaryl-1-hydroxythiureas has been recently dealt with in two papers<sup>5,6</sup>. A discussion of possible hydrogen bonds and of the IR spectra in the solid state preferred a form<sup>5</sup> near to *B* for *IIa* but the weak intramolecular bonds were overestimated and intermolecular bonds not taken properly into account<sup>6</sup>. A study of dipole moments and IR spectra of several hydroxythiureas in solution lead to the conclusion that the conformation is sensitive to substitution<sup>6</sup>, the preferred forms of *IIa* and *IId* being *G* and *D*, respectively. However, the discussion of dipole moments was only qualitative and the significant H—O bond moment was completely neglected.



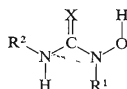
*Z, E, ap*  
*A*



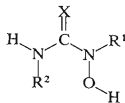
*Z, E, sp*  
*B*



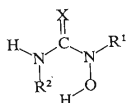
*Z, Z, ap*  
*C*



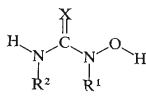
*Z, Z, sp*  
*D*



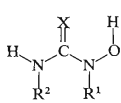
*E, E, ap*  
*F*



*E, E, sp*  
*G*



*E, Z, ap*  
*H*



*E, Z, sp*  
*J*

Under these circumstances we felt that a reinvestigation is necessary. In the study of dipole moments we took into account all the bonds present and tried to assign proper values even to the mesomeric moment. We further exploited the substitution

in the two *para* positions and evaluated the results by means of the graphical method<sup>7</sup>. When interpreting the IR spectra, we paid proper attention to the concentration dependence and distinguishing of monomers and associated forms. We always compared hydroxythioureas *II* with the corresponding hydroxyureas *I* which have an advantage of being more stable in dilute solutions. The conformation of the latter could be also discussed referring to 1,3-disubstituted ureas which were investigated both spectroscopically<sup>8-10</sup> and on the basis of dipole moments<sup>11,12</sup> more thoroughly than 1,3-disubstituted thioureas<sup>13-15</sup>.

## EXPERIMENTAL

### Materials

Melting points were determined on the Kofler block and not corrected; they are rather approximate due to considerable decomposition. The purity of all compounds was checked by elemental analyses and thin-layer chromatography.

The 1,3-disubstituted 1-hydroxyureas were prepared by mixing equimolar amounts of aryl (alkyl) isocyanate and substituted N-phenylhydroxylamine in benzene solutions and heating to 40°C. 1,3-Diphenyl-1-hydroxyurea (*Ia*) m.p. 129°C (literature<sup>16</sup> 125°C). 1-Phenyl-3-(4-chlorophenyl)-1-hydroxyurea (*Ib*) m.p. 163°C (ethanol); for C<sub>13</sub>H<sub>11</sub>ClN<sub>2</sub>O<sub>2</sub> (262.7) calculated: 59.43% C, 4.24% H, 10.65% N; found: 59.78% C, 4.29% H, 10.77% N. 1-(4-Chlorophenyl)-3-phenyl-1-hydroxyurea (*Ic*) m.p. 158°C (ethanol); for C<sub>13</sub>H<sub>11</sub>ClN<sub>2</sub>O<sub>2</sub> (262.7) calculated: 59.43% C, 4.24% H, 10.65% N; found: 59.18% C, 4.15% H, 10.97% N. 1-Phenyl-3-methyl-1-hydroxyurea (*Id*) m.p. 128°C (literature<sup>17</sup> m.p. 129–130°C).

1,3-Disubstituted hydroxythioureas were prepared from the pertinent isothiocyanate and N-arylhydroxylamine in ether at room temperature. They are recrystallized from ether-hexane at the same temperature, any heating was avoided even in preparing solutions. 1,3-Diphenyl-1-hydroxythiourea (*IIa*) m.p. 108°C (ref.<sup>16</sup> 111°C). 1-Phenyl-3-(4-chlorophenyl)-1-hydroxythiourea (*IIb*) m.p. 109°C; for C<sub>13</sub>H<sub>11</sub>ClN<sub>2</sub>OS (278.8) calculated: 56.01% C, 3.99% H, 10.04% N; found: 55.87% C, 4.23% H, 10.08% N. 1-(4-Chlorophenyl)-3-phenyl-1-hydroxythiourea (*IIc*) m.p. 127°C (ref.<sup>18</sup> 126°C). 1-Phenyl-3-methyl-1-hydroxythiourea (*IId*) m.p. 147°C (ref.<sup>16</sup> 146°C). N-Phenylacethydroxamic acid<sup>19</sup> (*IVb*) m.p. 67°C in agreement with the literature<sup>19</sup>.

### Physical Measurement

Dipole moments in dioxan solution were measured by the standard method<sup>20</sup> as described recently in detail<sup>21</sup>. When calculating the molar refraction from increments<sup>22</sup>, the value of 4.35 cm<sup>3</sup> was used for the CO groups in hydroxyureas, which is based on tertiary amides<sup>23</sup>. The increment of 13.07 cm<sup>3</sup> for the CS group has been determined on xanthates<sup>22</sup>. The results are collected in Table I. The infrared absorption spectra were registered on a Zeiss UR-20 instrument, calibration was made with polystyrene foil. The most important bands are listed in Tables II and III.

### Calculations

The dipole moments anticipated for the individual conformations *A* – *J* were calculated by vector addition of standard bond moments<sup>24</sup> (in D units): H—C<sub>ar</sub> 0.3, H—C<sub>ar</sub> 0, C=O 2.5, C=S 2.95,

C—N 0.45, N—O 0.3, H—N 1.31, H—O 1.51; the conjugation N—C=X was expressed by mesomeric moments of 0.3 along each N—C bond and in addition twice 0.3 along the C=O or C=S bond. The angles on the central carbon atom, N—C—N = 118° and N—X=C = 121°, agreed with the crystal structure of 1,3-diethyl-1,3-diphenylurea<sup>25</sup>, while the angles on nitrogen, equal to 120°, and the angle N—O—H = 105° were assumed. The calculated values are represented graphically in Figs 1, 2 and listed in Table I, last column only for the assumed actual conformations.

## RESULTS AND DISCUSSION

Amides bearing unsubstituted hydrogen atoms are known to form hydrogen bonded dimers of polymers in solution, which can depreciate the experimental values of dipole moments<sup>26</sup>. Since our compounds *I*, *II* have two active hydrogen atoms,

TABLE I  
Polarization and Dipole Moments of Substituted Hydroxyureas and Hydroxythiureas *I* and *II* (dioxan, 25°C)

Compound	X	R <sup>1</sup> R <sup>2</sup>	$\alpha^a$ $\beta^a$	$P_2^0, \text{cm}^3$ $R_D^b, \text{cm}^3$	$\mu(5)^b, \text{D}$ $\mu(15)^c, \text{D}$	$\mu_{\text{cal}}^d, \text{D}$
<i>Ia</i>	=O	C <sub>6</sub> H <sub>5</sub>	10.5	446	4.30	4.20
		C <sub>6</sub> H <sub>5</sub>	-0.197	65.5	4.26	
<i>Ib</i>	=O	C <sub>6</sub> H <sub>5</sub>	12.6	600	5.06	5.52
		4'-ClC <sub>6</sub> H <sub>4</sub>	-0.243	71.5	5.02	
<i>Ic</i>	=O	4-ClC <sub>6</sub> H <sub>4</sub>	11.8	555	4.84	4.71
		C <sub>6</sub> H <sub>5</sub>	-0.382	71.5	4.80	
<i>Id</i>	=O	C <sub>6</sub> H <sub>5</sub>	12.5	380	4.03	3.99
		CH <sub>3</sub>	-0.180	45.8	4.00	
<i>IIa</i>	=S	C <sub>6</sub> H <sub>5</sub>	12.8	569	4.90 <sup>e</sup>	4.63
		C <sub>6</sub> H <sub>5</sub>	-0.198	74.2	4.85	
<i>IIb</i>	=S	C <sub>6</sub> H <sub>5</sub>	15.2	749	5.70	5.90
		4'-ClC <sub>6</sub> H <sub>4</sub>	-0.340	80.2	5.66	
<i>IIc</i>	=S	4-ClC <sub>6</sub> H <sub>4</sub>	11.6	589	4.97	5.15
		C <sub>6</sub> H <sub>5</sub>	-0.271	80.2	4.93	
<i>IId</i>	=S	C <sub>6</sub> H <sub>5</sub>	16.6	539	4.85 <sup>e</sup>	4.42
		CH <sub>3</sub>	-0.190	54.5	4.82	

<sup>a</sup> Slopes of the plots  $\epsilon_{12}$  vs  $w_2$  and  $d_{12}^{-1}$  vs  $w_2$ , respectively; <sup>b</sup> calculated from Vogel's increments<sup>22</sup> and the value of 4.35 cm<sup>3</sup> for the CO group; <sup>c</sup> correction for the atomic polarization 5% or 15%, respectively; of the  $R_D$  value; <sup>d</sup> calculated for the conformation *A* as given in Experimental; <sup>e</sup> the values of 4.47 and 5.20 D were found<sup>6</sup> for *IIa* and *IId*, respectively, by the Guggenheim method in benzene solution.

TABLE II  
The Main Infrared Frequencies of Substituted Hydroxyureas Ia-d (cm<sup>-1</sup>)

Compound	Solvent	Amide II		Amide I		ν(OH)		ν(NH)		ν(OH) monomer
		monomer	dimer	dimer	monomer	dimer	monomer	dimer	monomer	
Ia	CCl <sub>4</sub> <sup>a</sup>	b	b	1 666	1 710	3 190 vb	3 413	3 413	3 439	3 532 b
	CDCl <sub>3</sub> <sup>c</sup>	1 533	1 541 sh	1 663	1 694	3 195 vb	3 416-3 430 <sup>d</sup>	3 416-3 430 <sup>d</sup>	3 439	3 517 b
	CHCl <sub>3</sub> <sup>e</sup>	1 520 sh	1 539	1 661	1 695	3 200 vb	3 417-3 431 <sup>d</sup>	3 417-3 431 <sup>d</sup>	3 430	3 518 b
	CHCl <sub>3</sub> <sup>f</sup>	1 521 sh	1 534	1 664	1 689 sh	3 205 vb	3 418 <sup>d</sup>	3 418 <sup>d</sup>	3 430	3 511 b
	+2% dioxan									
	CHCl <sub>3</sub> <sup>g</sup>	1 521 sh	1 539 sh	g	1 693	3 225 vb	3 425 <sup>d</sup>	3 425 <sup>d</sup>	g	g
	dioxan 1:1	1 527	1 540 sh	g	1 695	3 240 vb	3 425 sh	3 425 sh	—	—
Ia-d <sub>2</sub>	KBr disc	—	1 537	1 652 sh 1 659	—	3 155 vb	3 414	—	—	—
	CDCl <sub>3</sub> <sup>h</sup>	1 412	1 418 sh	1 665 sh	1 695	2 395 vb	2 532 sh	2 547	2 602	2 602
Ib	CCl <sub>4</sub> <sup>i</sup>	b	b	—	1 717	—	—	—	3 437	3 530 b
	CDCl <sub>3</sub> <sup>i</sup>	1 530	1 541 sh	—	1 703	—	—	—	3 430	3 516 b
	KBr disc	—	1 552 1 540 sh	1 645 1 651 sh	—	3 175 vb	3 399	—	—	—
Ic	CCl <sub>4</sub> <sup>i</sup>	b	b	g	1 714	g	—	—	3 438	3 528 b
	CDCl <sub>3</sub> <sup>i</sup>	1 533	1 542 sh	g	1 703	g	—	—	3 430	3 513 b
	KBr disc	—	1 551 1 540 sh	1 643 1 650 sh	—	3 155 b	3 412	—	—	—
Id	CCl <sub>4</sub> <sup>a</sup>	b	b	1 660	1 706	3 180 vb	3 460 sh	3 473	3 538 b	3 538 b
	CHCl <sub>3</sub> <sup>j</sup>	b	1 539 b	1 660	1 689	3 190 vb	3 464-3 469 <sup>d</sup>	3 464-3 469 <sup>d</sup>	3 527 b	3 527 b
	KBr disc	—	1 549 1 539 sh	1 623	—	~3 150 vb	3 377	—	—	—
	KBr disc	—	1 551 1 540 sh	1 643 1 650 sh	—	3 155 b	3 412	—	—	—

<sup>a</sup> Concentration 0.0002-0.001M; <sup>b</sup> solvent absorptions; <sup>c</sup> concentration 0.004-0.1M; <sup>d</sup> not resolved; <sup>e</sup> concentration 0.001-0.13M; <sup>f</sup> concentration 0.09-0.13M; <sup>g</sup> traces; <sup>h</sup> concentration 0.01M; <sup>i</sup> saturated solution; <sup>j</sup> concentration 0.001-0.02M.

we thought it necessary to estimate the population of monomer and associated forms under the conditions of dipole moment measurement. In tetrachloromethane and chloroform solutions of hydroxyureas *Ia-d* two OH bands are observed (Table II) assigned according to the concentration dependence to the monomer ( $3515$  to  $3532\text{ cm}^{-1}$ ) and associate (c.  $3200\text{ cm}^{-1}$ ). The carbonyl band (amide I) is similarly doubled ( $1657-1664$  and  $1690-1714\text{ cm}^{-1}$ ) while the two NH bands are rather close and were clearly distinguished only in tetrachloromethane. By adding dioxan into chloroform solutions all the bands pertinent to dimers are gradually weakened but some of them are still perceptible in pure dioxan at a concentration of  $0.09\text{M}$ . Since the concentration during the dipole moment measurements was  $0.003-0.03\text{M}$ , we believe that the amount of dimer was negligible and could not affect the values obtained.

The above reasoning applies without change also to hydroxythioureas *IIa-d* whose spectra were studied less thoroughly (Table III) owing to their easy decomposition to aryl isothiocyanate and N-arylhydroxylamine in dilute solutions. Some of

TABLE III  
The Main Infrared Frequencies of Substituted Hydroxythioureas *IIa-d* ( $\text{cm}^{-1}$ )

Compound	Solvent	Thioamide I	$\nu(\text{NH})$	$\nu(\text{OH})$
<i>IIa</i>	$\text{CCl}_4^{a,b}$	<sup>c</sup>	3 388, 3 410 sh, 3 430 sh	3 528 b
	$\text{CDCl}_3^{b,d}$	1 526 b, 1 540 sh	3 381, 3 408 sh	3 504 b
	KBr disc	1 541	3 350	3 206 b
<i>IIb</i>	$\text{CCl}_4^{a,b}$	<sup>c</sup>	3 381, 3 411, 3 430 sh, 3 442 sh	?
	$\text{CDCl}_3^{b,d}$	1 525, 1 540 sh	3 373, 3 406	?
	KBr disc	1 540 sh, 1 549	3 356	3 238 vb
<i>IIc</i>	$\text{CCl}_4^{a,b}$	<sup>c</sup>	3 389, 3 408	3 527 b
	$\text{CDCl}_3^{b,d}$	1 520, 1 451 sh	3 382, 3 404	3 502 b
	KBr disc	1 540	3 357	3 266 b
<i>IIId</i>	$\text{CCl}_4^{e,f}$	<sup>c</sup>	3 420	3 533 b
	$\text{CDCl}_3^{d,f}$	1 534, 1 543 sh	3 415	3 515 b
	$\text{CHCl}_3^{f,g}$	<sup>c</sup>	3 415	3 513 b
	KBr disc	1 540, 1 551	3 316	vb

<sup>a</sup> Concentration  $0.0003\text{M}$ ; <sup>b</sup> rapid decomposition to N-arylhydroxylamine and aryl isothiocyanate; <sup>c</sup> solvent absorption; <sup>d</sup> concentration  $0.01\text{M}$ ; <sup>e</sup> saturated solution; <sup>f</sup> little decomposition; <sup>g</sup> concentration  $0.001\text{M}$ .

the bands quoted in the literature belong in fact to N-phenylhydroxylamine, viz. the  $3580\text{ cm}^{-1}$  band of *Ila* (ref.<sup>5</sup>), or the  $3580\text{ cm}^{-1}$  band of 1-phenyl-3-(2,6-dimethylphenyl)-1-hydroxythiourea<sup>6</sup>. We were able to record parts of the spectra of *Ila-d* in freshly prepared solutions since the OH ( $3583\text{ cm}^{-1}$  in  $\text{CCl}_4$ ,  $3581\text{ cm}^{-1}$  in  $\text{CHCl}_3$ ), and NH ( $3319\text{ cm}^{-1}$  in  $\text{CCl}_4$ ,  $3322\text{ cm}^{-1}$  in  $\text{CHCl}_3$ ) bands of N-phenylhydroxylamine can be easily identified. In 0.02M dioxan solution the decomposition is much slower. Hence the compounds are sufficiently stable under the conditions of dipole moment measurement.

Before comparing the experimental and calculated dipole moments two problems must be dealt with: the mesomerism within the amide groups and the influence of dioxan solvent. The standard bond moments<sup>24</sup> for the C=O and C—N bonds have been derived from ketones and amines, respectively; hence they cannot be expected to reproduce well the dipole moment of the amide group. The pertinent correction may be called the mesomeric moment and expressed formally either as two vectors in the directions N—C and C=O, or as one vector directed approximately from N to O. In the literature there is no agreement about the magnitude of this correction and even about its necessity. It depends much on the system of bond moments used on the one hand, and on the quality and number of experimental data on the other; just for amides and ureas quite systematic data are lacking. We used previously the system of two vectors<sup>27</sup>, 0.45 D each, derived on aliphatic derivatives like acetamide and N,N-dimethylacetamide. This correction agrees essentially with the original values of Lumbroso<sup>28</sup> (one vector of 0.73 D for secondary amides, or 1.09 D for tertiary amides), which were later replaced by less probable higher values<sup>29</sup>. In the molecule of carbamates the carbonyl group is conjugated simultaneously with one nitrogen and one oxygen atom, hence we used a smaller correction of two vectors, 0.3 D each; this agreed well with the rather systematic experimental data<sup>30</sup>. A similar crossed conjugation is encountered in hydroxyureas. We thus adopted the same values for each moiety, it means that the C—N bond moments are finally reduced to 0.15 D and the C=O moment increased to 3.1 D. Of course, such a correction is rather arbitrary and its final confirmation was achieved from the experimental values of substituted ureas with an unambiguous conformation. Tetramethylurea can possess only one planar conformation and even the rotation around the C—N bonds does not affect the dipole moment value; our calculated value 3.70 D agrees fairly with the experimental one, 3.49 D in dioxan<sup>11</sup>.\* For 1,1-diethylurea

\* In the literature the dipole moment of tetramethylurea was either discussed in terms of distorted planarity and restricted conjugation<sup>11</sup>, or taking resort to quite improbable nonplanar conformations<sup>12</sup>. Our set of bond moments agrees reasonably with all the data for substituted ureas (moderately well even for urea itself<sup>33</sup>) and could be used in reexamining their conformation. We feel, however, that before doing so the *para*-substituted derivatives should be investigated similarly as in this paper or in ref.<sup>30</sup>.

and 1,1-diphenylurea we calculate 4.03 and 3.92 D, respectively, found<sup>11</sup> 4.08 and 4.11 D. For 1,3-dimethyl-1,3-diphenylurea whose *E, E* conformation is established<sup>31</sup> we calculate 3.12 D; found<sup>11</sup> 3.27 D.

In the case of hydroxythioureas we applied the same mesomeric correction as for hydroxyureas. Although it may be somewhat underestimated and not applicable *e.g.* for simple thioamides<sup>32</sup>, it corresponds to the difference in our experimental values between the two classes of compounds. Dipole moments of thiourea derivatives with unambiguous conformation are not available; for thiourea itself we calculated 4.74 D, found<sup>33</sup> 4.89 D. In addition to the conjugation N—C=X in the compounds *I, II* the *n*- $\pi$  conjugation of the nitrogen atoms with the phenyl rings may be also taken into consideration. We introduced no particular moment to account for it, the main reason being that the rings are with all probability not coplanar with the N—C bonds, see *e.g.* the X-ray structure of 1,3-diethyl-1,3-diphenylurea<sup>25</sup>. The same reasoning was used previously in the case of other N-phenyl derivatives and was confirmed experimentally (*e.g.*<sup>34</sup>).

As far as the influence of solvent is concerned, it is true that standard bond moments<sup>24</sup> have been determined from measurements in benzene and cannot reflect specific solvent effects of dioxan. The differences between the two solvents are usually unimportant for solutes which cannot act as proton donors, *e.g.* for tetraalkylureas<sup>11</sup>. However, for primary and secondary amides these differences amount<sup>26,35</sup> up to 0.5 D. The higher dipole moments in dioxan were assigned to a hydrogen bond with the solvent<sup>26</sup> but there is another explanation that the values in benzene are too low owing to the formation of symmetrical dimers. The 1,1-dialkylureas quoted above were also investigated in dioxan<sup>11</sup> and the agreement with our calculated values was reasonable. Hence we use our experimental results in this solvent without any correction. In our opinion dioxan is a more suitable solvent than benzene<sup>6</sup> for this particular problem, since the most important objective is to minimize dimerization.

According to the foregoing discussion we believe that we can predict the dipole moments expected for individual conformation with a usual or only slightly impaired accuracy, *i.e.* better than to 0.5 D. This accuracy might be sufficient to find the most populated conformation. The graphical comparison<sup>7</sup> of calculated and found dipole moments is carried out in Fig. 1 for hydroxyureas and in Fig. 2 for hydroxythioureas. Both figures yield the same picture: the true conformation is near to *A* or between *A* and *B*. The conformation of methyl derivatives *Id, IId* seems to be not different (Table I). On the basis of dipole moments one cannot decide whether there is a certain admixture of the form *B* to *A*, or only one form present, similar to *A*, with the hydroxyl hydrogen distorted in the direction to *B*. The latter possibility seems more probable since planar conformations around the N—O bond are not particularly stabilized. Any other reasonable hypothesis cannot be formulated, even if equilibrium of several forms were admitted. Note still that the dipole moments of *D* and *J* might be affected by an intramolecular hydrogen bond. This effect, however, can be never so large<sup>21</sup> to match even approximately the observed values.



When the dipole moments have revealed the main, most populated conformation, the IR spectroscopy may be applied to confirm this finding and/or to detect minor forms possibly present in equilibrium. The first relevant finding is the presence of a strong amide-II band in the  $1500\text{--}1550\text{ cm}^{-1}$  region of the spectra of *Ia-d*. It was found in  $\text{CHCl}_3$  and dioxan solutions and even at high dilution in  $\text{CDCl}_3$ , its assignment was confirmed by deuteration experiments. This band arises by mixing the C—N stretching and N—H bending modes and appears in this region only at the antiperiplanar position of the C=O and N—H bonds<sup>9,36</sup>. Hence its finding proves the presence of some of the forms *A-D* in appreciable amounts; of course, it does not exclude the presence of some others. In the crystalline state the molecules *Ila-d*

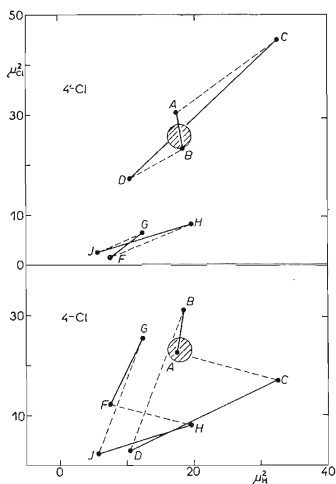


FIG. 1

Graphical Comparison of Squared Dipole Moments of 1,3-Diphenyl-1-hydroxyurea *Ia* (*x*-axis), and Its Derivatives *Ib* and *Ic* (*y*-axis)

Shown are experimental values (hatched circles) and those calculated for the conformations *A-J* (full points). Full lines represent rotation around the N—O bond, broken lines around the C—N(3) bond.

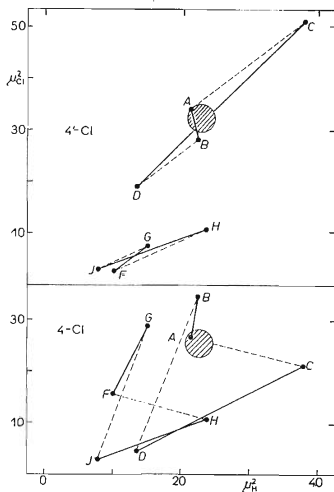


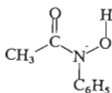
FIG. 2

Graphical Comparison of Squared Dipole Moments of 1,3-Diphenyl-1-hydroxythiourea *IIa* (*x*-axis) and Its Derivatives *IIb* and *IIc* (*y*-axis)

See Fig. 1 for descriptive details.

must exist in one of the forms *A–D*. The corresponding band of thioureas, called Thioamide *I*, was observed (Table III) but it is of no diagnostic value for the conformation.

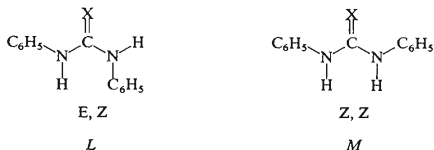
We further investigated the hydrogen bonds, intramolecular and intermolecular, on the OH group. A strong intramolecular bond as postulated in the formulae *D* and *J* can be disproved with certainty, according to the O—H as well as the C=O frequency. This reasoning applies to both hydroxyureas and hydroxythioureas in tetrachloromethane or chloroform solutions; the less are forms *D* or *J* possible in dioxan. As a reference compound we chose *N*-phenylacetylthioamic acid (*IVb*) which exists in  $10^{-3}$ M- $\text{CCl}_4$  solution quite predominantly in the conformation *K* with a strong intramolecular hydrogen bond,  $\nu(\text{OH})$   $3254\text{ cm}^{-1}$ ,  $\nu(\text{CO})$   $1651\text{ cm}^{-1}$ . Broad bands between  $2850$  and  $3200\text{ cm}^{-1}$  in the spectra of hydroxythioureas were assigned<sup>6</sup> to O—H... $\pi$  bonds and consequently claimed to prove the conformation *G*. The large shift is, however, *a priori* incompatible with such a weak bond. In our opinion this interpretation is disproved by comparing the diphenyl derivatives *Ia*, *Ila* to the corresponding methyl derivatives *Id*, *Ild* which are unable to form any  $\pi$  bond and exhibit the same frequency with still a higher intensity. Finally, our dilution experiments in both  $\text{CCl}_4$  and  $\text{CHCl}_3$  have shown that this band is due to association. On the other hand the O—H frequency of the true monomeric form of hydroxyureas and hydroxythioureas as well ( $3500$ — $3540\text{ cm}^{-1}$ ) is lower than expected for a completely free hydroxyl group. A weak intramolecular hydrogen bond is thus to be assumed, but  $\pi$ -electrons as proton acceptor do not come into consideration for the same reason as above: there is only a negligible difference of  $6$  or  $9\text{ cm}^{-1}$  (in tetrachloromethane and chloroform, respectively) between the frequencies of *Ia* and *Id*, similarly for *Ila* and *Ild*. A possible explanation would be a weak interaction with the free electron pair on nitrogen in a nonplanar conformation near to *B*. It means that in chloroform and tetrachloromethane solutions the conformation would be distorted more in the direction to *B* than in dioxan. A hydrogen bond O—H...N was already postulated in the crystalline state<sup>5</sup>, but without good grounds, and was later rejected<sup>6</sup> as impossible in principle. We think that a weak interaction can account for the observed shift, although it cannot be classified as an actual hydrogen bond.



K

Finally, we have searched for a weak hydrogen bond of the NH hydrogen which could perhaps be present in the forms *C*, *D* with  $\pi$ -electrons as proton acceptor, or in the forms *A*, *F* with the hydroxyl oxygen as acceptor. No evidence of such bonding was obtained but additional NH bands were detected which may be assigned to the presence of further, less populated rotamers. It is only in this point that the results for hydroxyureas and for hydroxythioureas differ: In the spectra of hydroxyureas *Ia–d* under different conditions, there is only one NH band of the monomer, assigned according to the foregoing discussion to a conformation between *A* and *B*. In order to reveal a possible interaction with the hydroxyl oxygen, we tried to refer to 1,3-diphenylurea as a possible model compound without that oxygen. This com-

compound exhibit two N—H bands (in  $\text{CCl}_4$  3430 and 3442  $\text{sh cm}^{-1}$  in agreement with ref.<sup>8</sup>, in  $\text{CHCl}_3$  3426, 3436  $\text{sh cm}^{-1}$ ) assigned<sup>8</sup> to forms *L* and *M*; the assignment is, however, not unambiguous as there are three different N—H bonds and two observed bands. If the higher frequency corresponds to the free N—H in *M*, there is almost no difference as compared to *Ia*. Any N—H...O bond was thus not detected.



In the spectra of hydroxythioureas *Ila-c* the main NH band is accompanied by a shoulder, in  $\text{CCl}_4$  even by more shoulders (Table III) which could indicate the presence of an additional, less populated rotamer. Multiple NH bands were observed in the spectra of several 1,3-disubstituted thioureas<sup>13,15</sup>, in the case of 1,3-diphenylthiourea the two bands (3382 and 3414  $\text{cm}^{-1}$  in  $\text{CCl}_4$ , ref.<sup>13</sup>) were assigned<sup>13</sup> to the two hydrogens in the formula *L*. The lower of them corresponds nearly to the main maximum of *Ila-c*, so that one cannot decide whether there is a very weak interaction N—H...O in the latter. The higher frequencies in 1,3-diphenylthiourea and in *Ila-c* are also very close, one can assign the latter tentatively to the form *F* or *G* with a reversed conformation in the amide-like group. Note that *IId* shows only one maximum, hence the reversal of conformation, if it takes place, could be facilitated by the hydrogen bond in *G*. This bond is, however, not manifested in the OH frequency. The existence of less abundant forms, *F* or *G*, of hydroxythioureas thus remains only a possibility which cannot be evidenced with more reliability at present. Their presence in dioxan in appreciable amounts is not compatible with the dipole moment data (Fig. 2). Note still that the differences between hydroxyureas and hydroxythioureas exist only in solution, in the crystalline state they have most probably the same conformation.

Summarizing we can state that a conformation near to *A* is virtually the only one present in dioxan solution; in chloroform and tetrachloromethane its distortion in the direction toward *B* is possible. In the case of 1,3-diphenyl-1-hydroxythiourea (*Ila*) and its derivatives *Ilb,c* a less abundant form *G* or *F* may be also present. The conformation *A* is now to be compared with simpler compounds, 1,3-disubstituted ureas or thioureas on the one hand and with hydroxamic acid derivatives on the other. As mentioned, 1,3-diphenylureas<sup>8</sup> and 1,3-diphenylthiourea<sup>13</sup> prefer the unsymmetrical conformation *L*, the latter almost exclusively. The conformation is probably controlled by the N—H... $\pi$  hydrogen bond since it is no more uniform in the case of 1,3-dialkylated ureas<sup>9,10</sup> and thioureas<sup>13,15</sup>. The OH group on nitrogen is able to

reverse the conformation so that the form *A* (or *B*) is preferred against *C* or *D* in which the mentioned hydrogen bond is retained. The driving force could be the weak interaction  $\text{N}-\text{H}\cdots\text{O}$  in *A* or  $\text{O}-\text{H}\cdots\text{N}$  in *B*, but either is evidently insufficient. The comparison with *N*-substituted hydroxamic acids *IV* affords similar problems. The compound *IVb* exists mostly in the form *K* according to our spectroscopic investigation. The same form was claimed to be the prevailing one for *IVa* and its derivatives on the basis of dipole moments<sup>4</sup> and for *N*-alkylformthiohydroxamic acids on the basis of NMR spectra<sup>37</sup>, in all the cases it is evidently stabilized by the hydrogen bond. Even the unsubstituted hydroxamic acids have the *Z* conformation around the  $\text{C}-\text{N}$  bond in the solid state<sup>38</sup> and probably also in solution<sup>2</sup> but a notable exception is just hydroxyurea in crystal<sup>39</sup>. The  $\text{NH}_2$  group is thus able to overcome the hydrogen bond and reverse the conformation; the same occurs with the derivatives *I* and *II*. Hence the stability of conformation *A* results from several factors which cannot be easily resolved.

*Thanks are due Mrs M. Kuthanová, Prague Institute of Chemical Technology, and to Mr P. Formánek, Institute of Organic Chemistry and Biochemistry, Prague, for skilful technical assistance, further to Dr M. Dzurilla, P. J. Šafárik University, Košice, for a gift of 4-chlorophenyl isothiocyanate. The elemental analyses were carried out in the Analytical Laboratory, Institute of Organic Chemistry and Biochemistry, Prague, and in the Department of Analytical Chemistry, Palacký University, Olomouc.*

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Translated by the author (O. E.).