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Quantum Mechanical Studies of Environmental Effects on Biomolecules

IX. Structure and Hydration of Thiourea

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SCF *ab initio* computations have been performed on the structure, molecular potential and hydration scheme of thiourea in view of a comparison with urea and more generally as a model of the conjugated S═CNH— group as compared to O═CNH—. In contrast to the carbonyl oxygen, both σ and π acceptor, the sulfur atom of the thiocarbonyl is a σ donor but a π acceptor and this results in an enhancement of the double-bond character of thiourea. The CN bond is less attractive for a proton than urea. The hydration scheme indicates a maximum number of four water molecules directly bound to thiourea.

Key words: Thiourea – Conjugated thiocarbonyl – Thioanalogs – Hydration of thiocarbonyls

1. Introduction

As a continuation of previous studies on the molecular structure and hydration properties of urea [1], acetamide [2], N-methylacetamide [3], and formamide [4, 5], we report presently the results of a similar investigation of the corresponding properties of thiourea, the thiocarbonyl analog of urea. This compound is one of the simplest molecules where a C═S double bond is part of a conjugated system involving the π lone-pairs of planar amine nitrogens. Thus, aside from its interest *per se* in comparison to urea [6, 7], thiourea provides also an appropriate model for the study of the properties of the S═C—NH— group, a fundamental building block in the chemical skeleton of thiopurines and thiopyrimidines. Some of these compounds, which differ from the usual natural bases of the nucleic acids only by substitution of the thiocarbonyl for the carbonyl double bond, have been found recently to occur naturally as minor components of the structure of transfer-

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RNA [8–10] with possible conformational implications. On the other hand, synthetic thioanalogs are known to act as antimetabolites [11,12] by replacing the corresponding normal bases and disrupting the course of normal biological processes. In spite of a considerable interest [13–19], the precise molecular mechanism of action of these analogs is not clear. A theoretical study of the fundamental analogies and differences between the S=C—NH and O=C—NH group may be helpful in this connection. To our knowledge there is no study at the *ab initio* level available on conjugated thio-carbonyl compounds.

2. Computational Details

As in the previous papers of this series, we use the *ab initio* SCF LCAO procedure with a Gaussian basis set. For C, N, O, H, we use the same (7*s*, 3*p*/3*s*) primitive set, contracted to minimal, as in Refs. [1–4]. For sulfur a corresponding (10*s*, 6*p*) atomic basis [20] has been adopted.

The bond lengths and angles (Fig. 1) of the molecule of thiourea have been recomputed from the X-ray crystallographic data [21].

The structural characteristics of the molecule have been explored in comparison to those of urea by an analysis of the Mulliken populations [22], and of the electrostatic molecular potential [23]. The hydration properties have been computed using the supermolecule procedure up to the completion of the first shell of bound water as in Ref. [1].

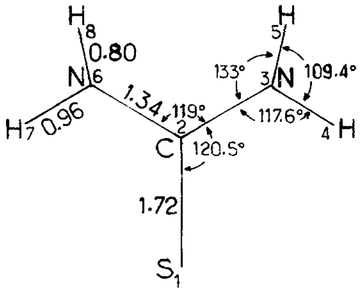


Fig. 1. Geometry of thiourea [21]

3. Results and Discussion

3.1. Structural Characteristics and Molecular Potential

The results of the Mulliken population analysis for thiourea are given in Fig. 2. In the diagram of the global charges, the polarity of the CS bond appears relatively small, a feature in apparent agreement with simple consideration of the global electronegativity values of carbon and sulfur, but in apparent contradiction with the rather large value of the observed dipole moment of thiourea (4.93 debye units [24], present computation: 4.88). In fact further analysis indicates that the global

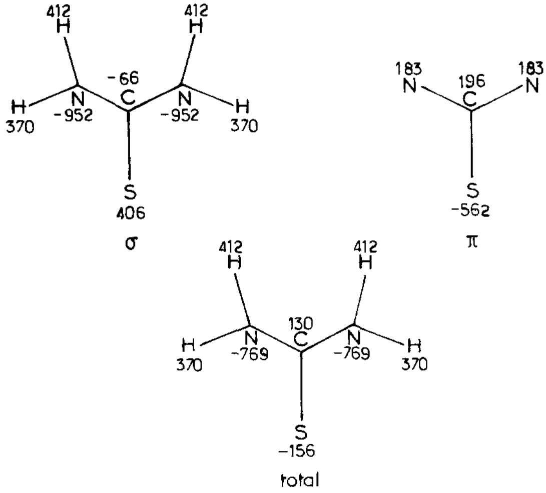


Fig. 2. Net charges in thiourea

polarity covers relatively strong *inverse* σ and π displacements: in the σ distribution, a drainage of electrons occurs toward the two strongly attractive nitrogens at the expense of the end sulfur atom whereas the two nitrogen π lone-pairs are appreciably delocalized toward the same atom. The comparison with the situation in urea and other amides (Table 1) indicates that this behavior is an essential element of the difference between the carbonyl and thiocarbonyl compounds: while the carbonyl oxygen is both a σ and a π electron acceptor, the thiocarbonyl sulfur is a σ donor but a π acceptor. A similar conclusion was obtained in *ab initio* computations on the simpler compounds H_2CS and H_2CO [25]. The fact that full nonempirical computations confirm the trends found earlier [26] by Del Re–Hückel computations based on orbital electronegativity values is interesting. Such trends in electron displacements appear as general characteristics of the type of conjugated thiocarbonyl/carbonyl compounds considered and are apparently closely related to the fact that the former have larger dipole moments than the latter [27].

Table 1. Comparison of the atomic σ and π net charges in formamide (F), acetamide (A), urea (U), and thiourea (T) $(10^{-3}e)$[a]

			N		C		O or S		C(CH$_3$)	
	H_c	H_t	σ	π	σ	π	σ	π	σ	π
F	337	321	−838	199	75	95	−89	−294		
A	352	335	−860	175	280	107	−97	−295	−508	−232
U	415	504	−1101	126	416	120	−51	−372		
T	370	412	−952	183	−66	196	+406	−562		

[a] A negative sign corresponds to an excess of electrons.

Table 2. Valence orbital populations on CS of thiourea (T) compared to CO of urea (U) (x is along the bond, z perpendicular to the molecular plane)

	T		U	
Orbital	S	C	O	C
s	1.817	1.067	1.807	0.875
p_x	0.852	1.147	1.326	0.852
p_y	1.959	0.842	1.920	0.858
p_z	1.568	0.804	1.372	0.880

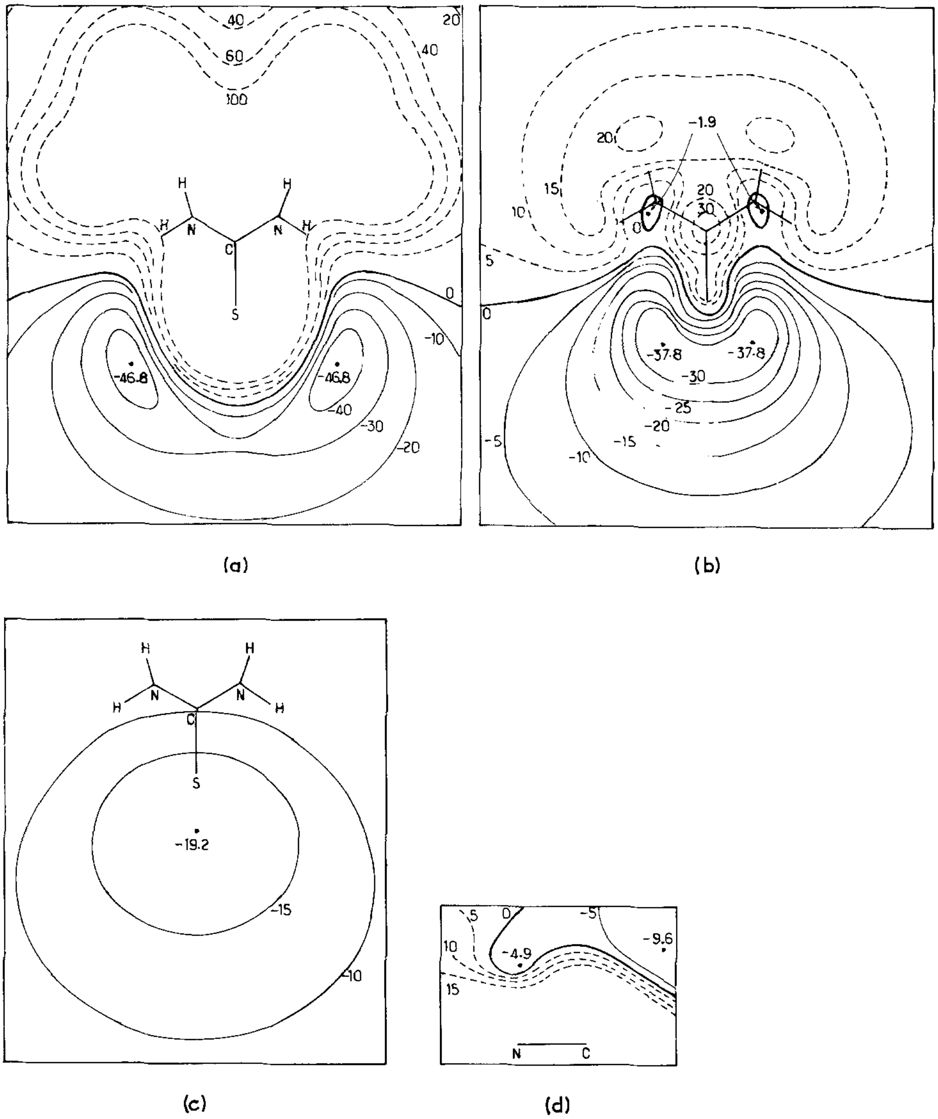
The valence orbital populations on sulfur and carbon in thiourea are given in Table 2 in comparison to the corresponding values on oxygen and carbon in urea. The p_y valence orbital of sulfur (perpendicular to the bond) is somewhat more populated than that of oxygen while the p_x orbital (along the bond) is depopulated in favor of carbon, the reverse effect being seen in the carbonyl compound. A localization by Boys' procedure [28, 29] yields two equivalent lone-pairs on sulfur which make an angle of 140.8°, somewhat larger than the corresponding angle in urea (135.6°).

As a result of the π-attractive character of the sulfur atom, the delocalization of the nitrogen π lone-pairs in thiourea is stronger than in urea. This results in a double-bond character of the CN bonds in thiourea stronger than in urea. The rotation barriers in thioamides are indeed larger than those of the corresponding amides [30]. Another confirmation of a greater π delocalization in thiocarbonyl compounds than in carbonyl compounds can be found in the analysis of the NMR spectra of several N-substituted pyridones and pyrithiones [31].

The trends observed in the computed net charges of thiourea and urea are in very good qualitative agreement with the trends of the peaks of electron density on the various atoms deduced from X-ray and neutron diffraction data [32]: nitrogen π lone-pair less populated in thiourea than in urea, global oxygen peak much larger than the sulfur peak, total nitrogen peaks rather close in the two molecules, hydrogens less depopulated in thiourea than in urea. Note that this last feature

Table 3. Energies of the three highest filled and of the two lowest empty molecular orbitals in thiourea and urea (a.u.)

Orbital	T	U
Occupied	−0.4754	−0.5494
	−0.3256	−0.4530
	−0.3224	−0.4299
Empty	+0.1245	+0.1962
	+0.3430	+0.4965



(a) (b)

(c) (d)

Fig. 3. Molecular electrostatic potential of thiourea in:
(a) the molecular plane;
(b) a plane parallel to it at 2.5 a.u.;
(c) *ibidem* at 5 a.u.;
(d) a plane perpendicular to the former ones, containing one CN bond

correlates with the observation that the acidic character of the amino group is smaller in thioamides than in amides [33, 34].

Another property of interest is the electron-donor and electron-acceptor ability of the thiocarbonyl group: from the point of view of the energies of the molecular orbitals in thiourea, this group appears as a much better electron donor and better electron acceptor than urea (Table 3).

A complementary aspect of the molecular structure of thiourea is given by its electrostatic molecular potential. Figure 3 (a–d) gives the isopotential contours in the most interesting planes. The most attractive region for a point positive charge is situated in the molecular plane with two distinct minima in directions making an angle of about 60 degrees with the CS bond. These minima of -46.8 kcal/mole are less deep than those obtained in formamide, N-methylacetamide, acetamide, and urea (-67.1, -66.5, -65.7, and -68.5 respectively). However their directionality is more marked in thiourea than in urea, where they are less separated. Thus, two distinct minima are still visible in thiourea in a plane parallel to the molecular plane at 2.5 a.u. from it (Fig. 3b), whereas the two corresponding zones are fused in urea in the similar plane. Fusion occurs in thiourea in the plane at 5 a.u. (Fig. 3c). Rather strong repulsive zones are seen above the CS bond at 2.5 a.u. and between the *trans* NH bonds, stronger than in urea. There appears a very small attractive zone above and below the amino nitrogens (Fig. 3d). This zone of a secondary minimum (a general characteristic of conjugated amino groups [1, 2, 35, 36]) is appreciably less attractive than in urea.

The overall weaker attractive character of the sulfur region in thiourea, as compared to that of the oxygen region in the carbonyl compounds, appears in agreement with the fact that the solution basicities of thioamides is weaker than that of the corresponding amides [37]. Similarly 2-pyridithione is less basic than 2-pyridone [31]. One must note, however, that gas-phase basicities appear to follow the inverse trends (2,4-dithiouracil larger than uracil [38]; thiocarbonic acid larger than carbonic acid [39]). This point will be discussed elsewhere in a more general perspective.

3.2. *Hydration Properties*

The results concerning monohydration are summarized in Table 4 and Fig. 4. To facilitate the comparison with urea, the same notations and conventions have been used: the position of the oxygen of water, O_w is defined by polar coordinates, R, θ, φ with respect to the nitrogen or the sulfur atom to which water is bound, the polar axis being either C—S or N—H. $\varphi = 0°$ or $180°$ when O_w is in the molecular plane. ξ, η, and ζ are local axes centered at O_w; η along the polar axis toward the

Table 4. Geometries and stabilization energy of the monohydrates of thiourea in the main favorable regions

Region	R	θ	φ	ξ	η	ζ	ΔE
I	3.30	90	0	0	0	0	-8.4
II	2.80	0	0	0	0	-60	-8.8
III	3.00	35.1	0	0	0	-22.6	-5.1
NH_t	2.80	0	0	0	0	0	-5.9
I/II[a]	—	—	–	–	–	—	-10.5

[a] S···O = 3.20 Å, N···O = 2.92 Å. The OH proton-donor bond is rotated by 40° from its position in I.

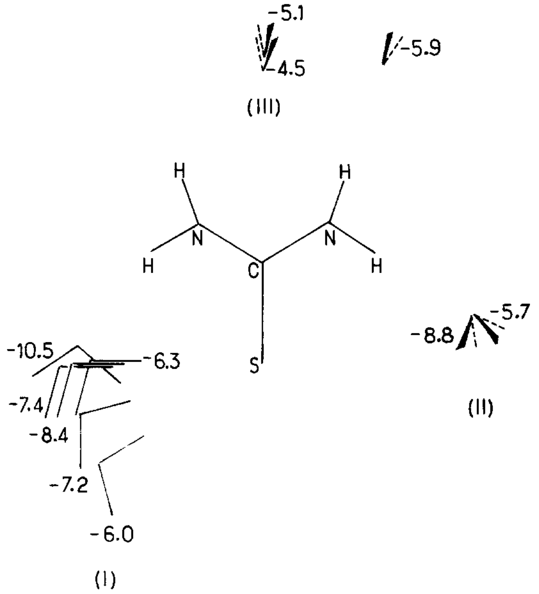


Fig. 4. In-plane monohydration of thiourea. Equilibrium positions and lability

sulfur or the nitrogen, ξ perpendicular to it in the plane of the solute, and ζ perpendicular to the $\xi\eta$ plane forming with them a direct system. For S—O binding, η is along one O_wH bond; for NH binding, it bisects the water molecule. The regions I, II, and III are defined like those of urea (see Fig. 4).

Mode I concerns water binding to sulfur: it corresponds to an appreciably stable hydrogen-bond ($\Delta E = -8.4$ kcal/mole) at an equilibrium distance ($S\cdots O$) of 3.3 Å, with the water molecule in the plane of thiourea, its proton-donor OH bond at 90° from the molecular axis. The corresponding adduct in urea was the most stable monohydrate, with an O—O distance of 2.80 Å and a smaller angle (75 degrees) with the molecular axis.

Mode II concerns the binding of water as a proton-acceptor to the *cis* NH proton of thiourea with an energy of -8.8 kcal/mole at an $N\cdots O$ distance of 2.80 Å, slightly more favorable than the corresponding position in urea, but with very similar characteristics (angularity, lability, position).

In fact a deeper exploration of the water–thiourea interaction hypersurface leads to find that a still more stable position for water exists (which we have labelled I/II in Table 4) in which the water molecule is rotated from position I about the middle of the proton-donor OH bond, by 40 degrees, thus turning its oxygen toward the NH_{cis} proton, in a sort of bridge position where the binding energy reaches -10.5 kcal/mole. Such a favorable bridge cannot be realized in urea: in the thioanalog, it results from the relative disposition of the most attractive zones for the proton and for the oxygen of water respectively (long optimal $S\cdots H$ distance and large SCH angle in I).

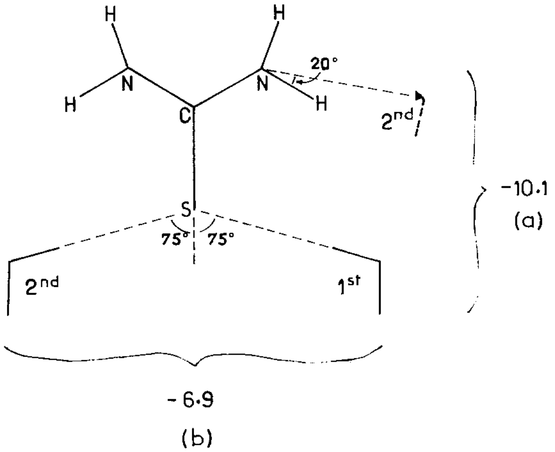


Fig. 5. Simultaneous placing of two water molecules. Binding energy (kcal/mole) per water molecule indicated for each dihydrate

Mode III in urea was a very stable hydrate with the water oxygen along the bissectrix of the NCN angle. This position in thiourea is much less favorable. The direct binding to the *trans* NH proton is somewhat more favorable but both binding energies are less than that of water–water interaction (−6.6 kcal/mole in the same basis set).

These results for monohydration of thiourea indicate that the formation of the first shell of bound water is likely to be somewhat different from what it is in urea.

As in our previous studies [1] we proceeded by adding the molecules of water stepwise using the information gained in the monohydration study. Considering the most stable monohydrate (I/II), it is clear that two molecules of this kind can be placed symmetrically with respect to the molecular axis: indeed a full computation of the dihydrate leads to a value of −10.45 kcal/mole per water molecule. We did not compute the dihydrates where two positions I or two positions II would be occupied simultaneously because the result can be easily foreseen. But we did consider the possibility of binding one water molecule as proton donor to sulfur and one water molecule as proton acceptor from the NH_{cis} on the same side as the first, each water molecule being somewhat displaced from its best monohydrate position so as to feel at best the attraction of the second one: we found that such a stable dihydrate exists (Fig. 5, case *a*) with a binding energy of −10.1 kcal/mole per water. (The distances $S \cdots O = 3.3$ and $N \cdots O = 2.8$ were kept constant; the CSO angle is 105°, the H_cNO angle is 20° toward H_t, $\xi = \pm 37.26°$, $\zeta = -77.5°$ for the N adduct.)

We tried further the possibility of fitting simultaneously two proton-donating water molecules bound to sulfur at an angle CSO + 105° (Fig. 5, case b). For $S \cdots O =$ 3.3 Å the binding energy of such a dimer is −6.9 kcal/mole. This indicates that it should be possible to place simultaneously symmetrically two dimers like that of

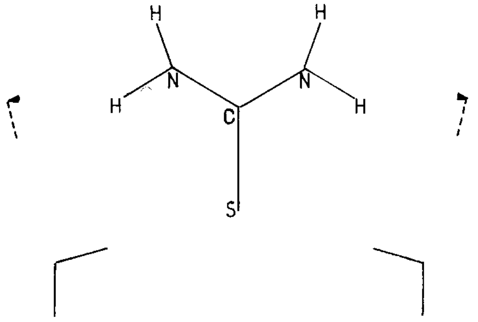


Fig. 6. The first layer of bound water around thiourea

Fig. 5, case a. This is indeed what shows the complete computation of the tetrahydrate (Fig. 6) for which we find $\Delta E = -9.9$ kcal/mole per water molecule (the distances have not been reoptimized). It appears that this tetrahydrate contains the maximum number of water molecules directly bound to thiourea. The corresponding maximum was five in urea with a ΔE per molecule of -9.15 kcal/mole.[1]

4. Conclusions

On the whole, thiourea can form individual monohydrates of stability comparable to that of the monohydrates of urea. However, the relative disposition of the stable sites is such that the first solvation shell of thiourea can comprise only four simultaneously bound water molecules instead of five in urea. It appears that the *trans*-NH bonds are not apt to disrupt the water–water bonds, a situation different from that encountered in urea: thus thiourea appears much less capable to disrupt the structure of water than urea, a feature which seems in agreement with the experimental knowledge concerning the solubility of these compounds and their effect on the movement of water in the renal tubules [6, 7, 40].

From the study of water binding, it appears that the doubly-bonded sulfur atom is capable of hydrogen-bonding with appreciable binding energy. The S···O distance of 3.3 Å found for water H-bonding is in reasonable agreement with the values 3.34–3.35 Å found for various OH···S bonds [15, 16, 41] in recent crystal structures. Not only is the H-bond longer than corresponding OH···O bonds, but the numerical values of the H-bond energies appear intrinsically smaller than the corresponding values for the C=O group, a feature in apparent agreement with the relatively scarce experimental evidence [42].

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[1] This number was erroneously stated as -7.4 in Ref. [1].

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