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Preferential solvation in *N*-methylthiourea

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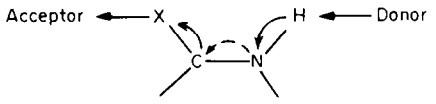
Abstract—The chemical shifts of the NH and NH_2 protons in *N*-methylthiourea dissolved in binary mixed solvents show a dependence on the solvent molar fractions typical of preferential solvation processes. The degree of preferential solvation determined from the N–H resonance depends mainly on the donor properties of the components of the mixture; however, those obtained from the NH_2 protons show also the influence of the solvent acceptor properties. These results, as well as some deviations from the general behaviour, are discussed considering the different degree of the electron delocalization along both branches of the thiourea.

INTRODUCTION

The influence of the solvent on some spectroscopic properties of amide [1–9] and thioamide [7–16] compounds has been frequently analysed by considering the Lewis acid and base properties of solvents. Thus, for instance, the application of the bond length variation rules [17] formulated within the framework of the donor acceptor concept, gives an understanding



of the increment of the energetic barrier for the rotation around the C–N bond when increasing the donor properties of medium as observed for acetamide [5]. The simultaneous influence of both donor and acceptor properties of solvents on the N–H and C–O vibrations in *N*-methylacetamide [6] has been also explained in this way. Although thiocompounds—for which planar structures similar to those in amide are also expected—show in general an analogous behaviour, some anomalous effects can be attributed to variations of the amide configuration have also been reported for thioacetamide [15] and for *N*-methylthiourea [16].

In order to extend our knowledge on the influence of media on the configuration of amide compounds (potentially useful as a model for more complex systems of biological interest) we have investigated the ^{1}H-NMR spectra of *N*-methylthiourea in various mixed solvents.

EXPERIMENTAL

N-methylthiourea (Aldrich) was recrystallized twice from an ethanol–ethylacetate mixture. Solvents were purified by standard techniques [18] and stored in a nitrogen atmosphere over molecular sieves. Purity was tested by running NMR spectra at the highest amplitude of our equipment.

The ^{1}H-NMR spectra were run on a Varian T-60 spectrometer using 5 mm o.d. tubes. The chemical shifts were determined using tetramethylsilane (TMS) as internal standard.

RESULTS

The solvation of *N*-methylthiourea (MTU) in the two components mixed solvents recorded in Table 1 was studied at 35°C by observing the dependence of the chemical shifts of the amidic protons, δ(N–H) and $\delta(N–H_2)$, on the solvent composition. Because the small concentration effect on δ observed in the pure solvents [16], no corrections for infinite dilution were considered. Despite the uncertainty in the measurement imposed mainly by the natural width of the N–H signals [4] and, in some cases, by the overlapping of the MTU signals with those of the solvent, most of the plots of δ against the molar fractions of the solvents in the mixture show patterns characteristic for preferential solvation. The results of an experiment with DMSO–NM solvent system are shown in Fig. 1. Nevertheless, anomalous appearances of maxima were observed in some cases. Some such deviations, more frequent in mixtures with HMPA, can be observed in Fig. 2 and, in the curve for $\delta(NH_2)$, in Fig. 1.

For measuring the degree of preferential solvation the composition of the bulk solvent at which the chemical shifts lies midway between the values for the pure solvents was used [19]. Assuming that the relative chemical shifts are proportional to the composition of the contact solvation shell, this point corresponds to the isosolvation point.

FRANKEL *et al.* [20] devised a thermodynamical model of preferential solvation defining a value K that, similarly to the isosolvation point, allows to evaluate the degree of preference. Thus, for a given solute in a mixture of two solvents, A and B, K is related to the free energy change ΔG° associated with the exchange of A by B from the solvation shell without including contributions arising from changes in the configurational entropy:

$$\Delta G^\circ = -RT \ln K, \tag{1}$$

$$K = \exp\left(-\frac{\Delta G^\circ}{RT}\right) = \frac{y_A x_B}{y_B x_A}, \tag{2}$$

where y_A and y_B refer to the mole fraction of A and B in the solvation shell and x_A and x_B refer to the bulk

Table 1. K values and isosolvation points for N-methylthiourea in various solvents

Solvent system	N–H_2 K	N–H_2 Isosolvation point*	N–H K	N–H Isosolvation point*	AN†	DN‡
Dimethylsulfoxide-(DMSO)						
Acetone (Ac)	4.29	19.3	9.13	9.9	12.5	17.0
Acetonitrile (An)	4.00	20.0	14.5	6.5	18.9	14.1
Propanediolcarbonate (PDC)	4.14	19.5	10.67	8.5	18.3	15.1
Dichloromethane (DCM)	3.64	21.6	10.75	8.5	20.4	
Nitromethane (NM)	3.53	22.1	16.00	5.9	20.5	2.7
Chloroform	3.00	25.0			23.1	
Tributhylphosphate (TBP)	0.31	76	1.38	42.2	9.24	23.7
Hexamethylphosphoramide (HMPA)						
Acetonitrile (An)	12.5	7.5			18.9	14.1
Propanediolcarbonate (PDC)	17.67	5.4			18.3	15.1
Dichloromethane (DCM)	13.5	6.9			20.4	
Tributhylphosphate (TBP)	1.5	40	4.9	17.0	9.94	23.7
Dimethylsulfoxide (DMSO)			2.5	28.5	19.3	29.8
Trimethylphosphate (TMP)	8.5	10.5	14.0	6.7	16.34	23.0

*Equisolvation points in % DMSO or % HMPA.
†Acceptor numbers (AN) from [17] and [23], and from E. Spitzenberger, Dissertation, Vienna (1978).
‡Donor numbers (DN) from [17] and [21].

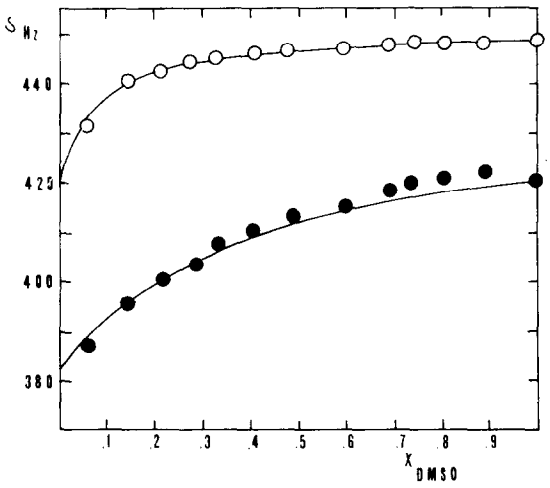


Fig. 1. The dependence of the chemical shifts of the N–H (○) and N–H_2 (●) protons in N-methylthiourea in DMSO–NM mixtures on the mole fraction of DMSO. Solid lines are drawn using the values of K obtained from the proper solvation isotherm as described by equation (2).

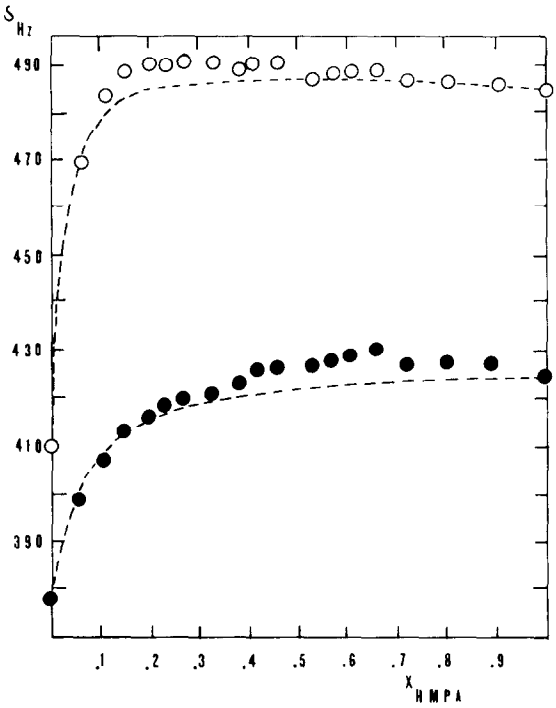


Fig. 2. The dependence of the chemical shifts of the N–H (○) and N–H_2 (●) protons in N-methylthiourea in HMPA–PDC mixtures on the mole fraction of HMPA.

solvents. The appropriate plots [according to equation (2)] for the mixed solvent DMSO–NM are presented in Fig. 3. The isosolvation points and the K values for the studied systems are reported in Table 1.

DISCUSSION

The chemical shifts of the amidic protons in thioamide compounds are not only determined by the substituents on the nitrogen and carbon atoms of the amidic backbone but also by intermolecular interactions with the medium. In solution, the interactions of the thioamide with donor molecules are expected to be strongly determinant "via" the formation of hydrogen bonds which, for a given thioamide, are principally governed by the donor strength of the solvent [15]. However, the chemical shifts of the N–H protons might also be influenced by the interaction of the sulfur atom with electrophilic sites of the solvent. The delocalization along the thioamide bond allows such interactions to have a measurable effect on the electron density at the N–H proton. In such a case the chemical

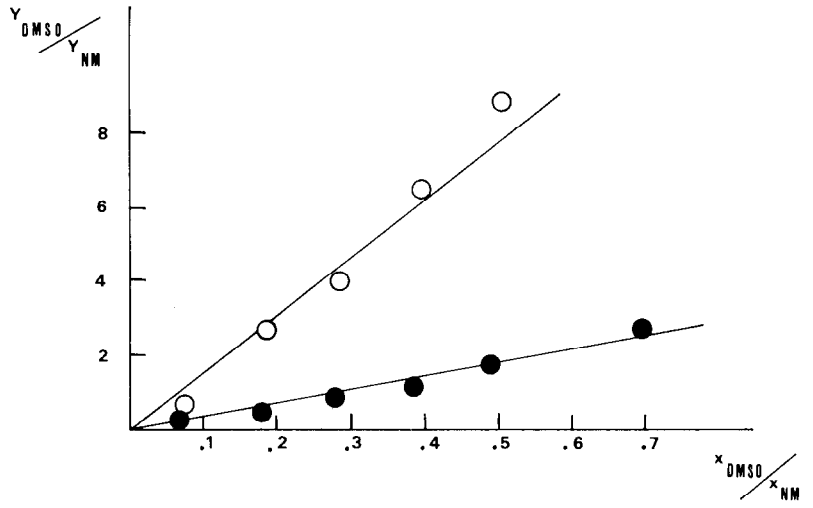
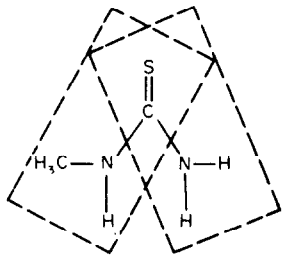


Fig. 3. Solvation isotherms [according to equation (2)] from the chemical shifts of the N–H (○) and N–H_2 (●) protons in *N*-methylthiourea in DMSO–NM mixtures.

shift will also reflect the strength of the Lewis acid properties of the media. For MTU both types of the interactions are possible, consequently they must be considered in the analysis of our results.

The MTU molecule can be imagined as formed by two thioamide like segments, I and II.



I II

In a first approximation, they can be considered to act independently of each other. Thus, we can discuss separately the results obtained by observing each signal N–H or N–H_2 as being originated from derivatives of the methylthioacetamide and thioacetamide respectively. Each segment will have fundamentally two active sites [15] for interacting specifically with the solvent. In a pure solvent both sites, sulfur atom and amidic proton, are solvated by the same solvent. However, a competition for the interaction sites on the thioamide will be established by adding a second solvent. In the binary mixture, the actual solvation of these sites will be then determined by the relative energies for the transfer of the solvent molecules from solvation sites at the thioamide to the bulk. Therefore there will be a relationship between the composition of the solvation shells in the segments I and II and the molar fraction of the mixture. This relationship should be determined by the equilibrium constant of the solvent exchange on each of the interactions sites. On the other hand, for a given thioamide the transfer energies as well as the corresponding equilibrium constants will be determined by the strength of both donor and acceptor properties of the solvent.

The dependence of the chemical shifts of the N–H protons on the mixture composition should be mainly determined by the competition between the solvents for the amidic protons sites. However, this dependence could also be affected by the solvent exchange at the sulfur atom. The extent of this effect depends on the planarity of the thioamidic structure. The comparison of the isosolvation points or of the *K* values, obtained from I by observing the N–H protons resonance, with donor and acceptor properties of the solvents shows that for most of the studied mixtures they are mainly determined by the relative donor strength of the components, DN [17, 21] (Fig. 4 illustrates this tendency). Mixtures with large DN-values, HMPA–PDC and DMSO–NM, escape this trend.

Data obtained from segment II show a more complex pattern. In this case, no simple relationship between log *K* and the basic properties of the solvent is observed (Table 1). However a nearly linear relationship of log *K* with the acceptor numbers [17, 22] of the cosolvents was observed for sets of mixtures having a common solvent. This behaviour is shown for mixtures with DMSO in Fig. 5. In these cases, the isosolvation points are certainly reflecting the competition between the solvents for solvating the sulfur atom. Nevertheless, this tendency can be observed only when the preference of the N–H protons towards one of the solvents is sufficiently large to maintain these protons solvated preferentially by the same solvent virtually over the whole range of molar fractions. When the difference between donor strengths of the mixtures components decrease, a more complex pattern for the preferential solvation must occur and deviations from

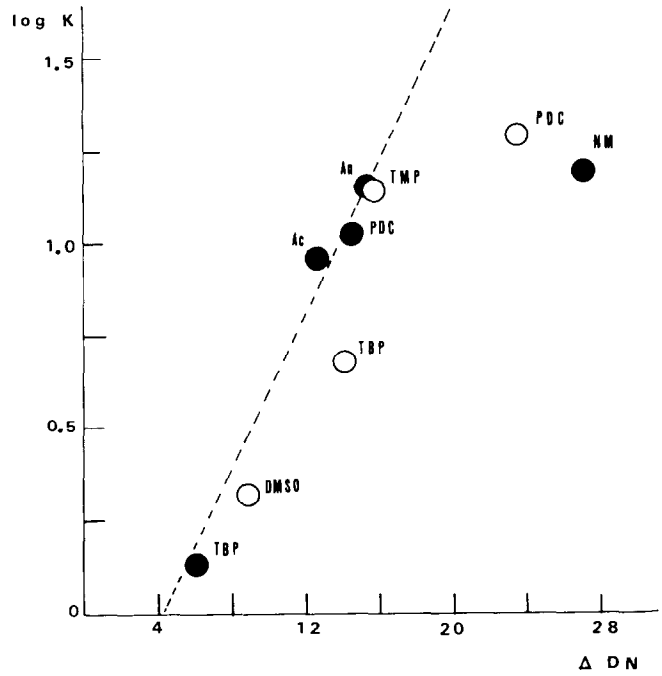


Fig. 4. Relationship of the logarithm of the K values corresponding to the N–H protons in *N*-methylthiourea with the difference of donicity (ΔDN) between the solvent components for mixtures with HMPA (○) and DMSO (●).

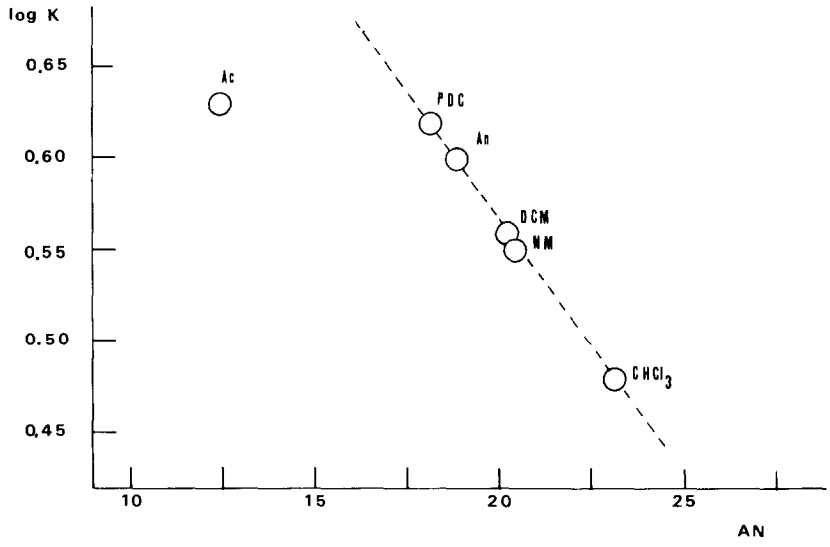


Fig. 5. Relationship of the logarithm of the K values obtained from the resonance of the $N-H_2$ protons in *N*-methylthiourea with the acceptor number (AN) of the co-solvent in mixtures with DMSO.

the simple relationship in Fig. 4 are observed. Such requirements should be more widely met by the NH than by the NH_2 protons, since the greater the intrinsic acidity of the amidic proton the stronger will be the solvation by a donor solvent. However, the effect of the interactions through the sulfur atom is not any more clearly observed in the chemical shifts of the N–H protons in segments I; on the contrary, the dependence of the log K on DN shown in Fig. 4 is not restricted to mixture with a common solvent, indicating a relatively high independence of the NH protons in I on the influence of the rest of the thiourea molecule, i.e. pointing to a lower delocalization degree along this thioamide segment than along segment II.

The non-planarity implied in the different behaviour observed for both segments, I and II should be possible

by some additional stabilization reached in donor solvents by a rotated configuration. Such effect should counterweigh the destabilization caused by lowering the electron delocalization. The effect of the pure solvents on the stretching frequencies, $\delta(NH_2)$ for MTU [16] as well as on the chemical shifts $\delta(NH_2)$ for thioacetamide [15] could also be interpreted by considering a lower degree of coplanarity for the NH_2 group in the solvents with higher donicity. Consequently, MTU should have a lower degree of delocalization in the pure solvents, DMSO and HMPA, than in their mixtures with poor donor cosolvents. Non-planar conformations, called "trans-out" conformations, have also been detected in small amounts, in solutions of some ureas and thioureas in poor donor solvents [23, 24].

The anomalies observed in some of the plots of δ against molar fraction, in which larger effects on δ are observed for some mixed solvents than for the pure solvents (see Fig. 2 and plots for $\delta(NH_2)$ in Fig. 1), could correspond to a synergic effect caused by mixed solvations of the thioamide, i.e. a different composition of the solvation shell at both sites, sulfur atom and N–H protons. However, an alternative, or perhaps complementary, explanation for such anomalous behaviour could be that dependence of the configuration on solvent composition that has been discussed previously, i.e. the configurational rearrangements induced by the various stabilization possibilities existing in the different media.

Thus, it is apparent from these results that some fundamental properties of thioamide compounds as the strength of the C–N bond, the acidity of the N–H protons, the basic properties of the sulfur atom and the configuration of the molecule could be regulated, at least in principle, by adjusting the coordinative properties of the medium.

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