these compounds do possess significant antibacterial activity, but this activity is noncompetitive in nature.

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Solubility Relationships in Urea–Water Systems

Keyphrases □ Urea–water systems—solubilization mechanism □ Solute–urea interaction effect—solubility □ Transfer, standard free energy—solute in urea solution, water

Sir:

Interpretations regarding the mechanisms of solution in cosolvent systems are facilitated if one can rely on various simplifying assumptions. In urea–water mixtures, for example, it would be convenient to assume that the interactions of the cosolvent with a given solute moiety are specific and predictable. Further, it would be of immeasurable aid if explanations of observed solubility phenomena were possible in terms of purely basic theoretical concepts. Therefore, as part of a larger study of solution properties, we investigated the potential usefulness of certain of these assumptions relative to compounds of intrinsic pharmaceutical interest.

The solubilities of compounds having various moieties in common were determined in water and in 5 *M* urea solutions at 30°. After equilibrating excess drug in both solvent systems, samples of the resulting solutions were withdrawn, and solubilities were determined spectrophotometrically. The standard free energies of transfer, $\Delta G_t°$, were then calculated according to the equation used by Wetlaufer *et al.* (1):

$$\Delta G_t° = -RT \ln C_u/C_w + RT \ln N_u/N_w \qquad \text{(Eq. 1)}$$

where C_u and C_w are the molar concentrations of drug in the urea and water solutions, respectively; and N_u and N_w represent the moles/liter summed over all components of solvent and solute for the urea and water solutions, respectively. In the present investigation, the free energy change is that which accompanies the transfer of 1 mole of drug from water to a 5 *M* urea solution. These data, along with the aqueous solubilities, are shown in Table I.

Table I—Standard Free Energy of Transfer, $\Delta G_t°$, from Water to 5 *M* Urea Solutions at 30°

Solute	Aqueous Solubility, moles/l. × 10^3	$\Delta G_t°$, cal./mole
Methyl *o*-methoxybenzoate	41.6	+621
Methyl paraben	19.2	−690
Methyl benzoate	17.8	−480
Methyl salicylate	6.27	−612
Ethyl paraben	5.85	−781
n-Propyl paraben	2.78	−645
n-Butyl paraben	1.34	−792

The results strongly suggest the following:

1. Moieties having the same chemical structure may not be expected to exhibit parallel interactions in solvent systems of similar composition. In all likelihood, these interactions are also a function of the chemical entity to which a given moiety is attached. This is in contrast to the interpretation by Nozaki and Tanford (2), who reported additive solubility effects for the hydrocarbon groups attached to various amino acids. The data in Table I show that this is not the case. For example, the difference in the standard free energy of transfer between methyl benzoate and methyl paraben is 210 cal./mole. The difference between phenylalanine and tyrosine is only 85 cal./mole for the same conditions of transfer (2).

2. The use of a simple homologous series gives no assurance of success in obtaining consistent resolution of solute–solvent interactions. As might be expected, the interactions observed on transferring alkanes from water to urea solutions vary as methane, ethane, propane, and butane (1). In contrast, the interactions of the parabens vary as propyl, methyl, ethyl, and butyl.

3. Relative hydrophobicity, as determined by a comparison of aqueous solubilities, may not be used to explain differences in enhanced solubilities in urea solutions. The data in Table I illustrate this point. For example, the aqueous solubility of methyl paraben is three times greater than methyl salicylate and seven times greater than propyl paraben, yet the transfer of methyl paraben to a 5 *M* urea solution is thermodynamically favored over either of these compounds.

4. Direct urea–solute interaction is a significant factor in altering the solubility of drug species. Although this has been shown (3, 4), reports persist in which attempts are made to explain observations solely on the basis of solvent structuring. The latter approach was taken by Feldman and Gibaldi (5) in rationalizing the increased solubility of benzoic and salicylic acids in

urea solutions. In turn, Nogami *et al.* (6) analyzed the adsorption of tryptophan from urea solutions in much the same manner, using the Feldman and Gibaldi paper as a reference. There are implications of direct interaction in each of the results of the present investigation. Perhaps the most striking evidence of this interaction is that the introduction of methyl *o*-methoxybenzoate, a liquid, into a 5 *M* urea solution results immediately in the formation of a flocculent white precipitate, the composition of which is currently unknown.

These findings demonstrate the need for caution in interpreting solubility phenomena involving cosolvent systems, in general, and urea–water mixtures, in particular. At present, few, if any, simplifying assumptions appear to be valid for this purpose.

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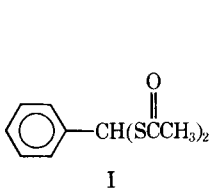
Preparation of Bis(acetylthiobenzyl)sulfide

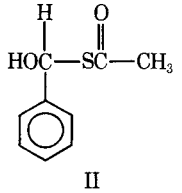
Keyphrases ☐ Bis(acetylthiobenzyl)sulfide—synthesis ☐ NMR spectroscopy—structure ☐ Mass spectroscopy—structure

Sir:

Bongartz (1), in 1886, obtained a product from the reaction of benzaldehyde and thioacetic acid, m.p. 147–148°, which he believed to be phenylmethanedithiol diacetate (I). In 1952, Cairns *et al.* (2) synthesized this compound from phenylmethanedithiol and found the melting point to be 37–38°.



I

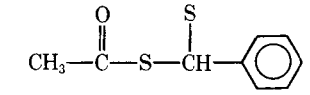


II

By utilizing the procedure of Böhme *et al.* (3) in the reaction of benzaldehyde and thioacetic acid to obtain the hydroxymethyl thioester (II), a small amount of a compound, m.p. 150–151°, which displayed the same properties as the material isolated by Bongartz (1), was obtained. The NMR spectrum showed absorption at 7.32δ, a singlet at 5.85δ, and a singlet at 2.29δ, having an integration ratio of 5:1:3. Mass spectral analysis indicated that the compound contained the following groups:

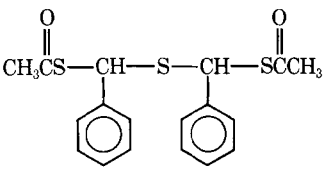
m/e		*m/e*	
15	CH_3	77	C_6H_5
28	CO	78	C_6H_6
32	S	90	C_6H_5CH
43	CH_3CO	105	OCSCHS
58	CH_2CS	121	C_6H_5CHS
60	COS	154	$SCH(C_6H_5)S$
75	CH_3COS	165	$CH_3COSCH(C_6H_5)$

From the NMR and mass spectral data, the following partial structure was assigned:



III

The elemental analysis and molecular weight indicate the compound to be $C_{18}H_{18}O_2S_3$. Thus, we propose the structure of the compound reported by Bongartz (1) as phenylmethanedithiol diacetate to be bis(acetylthiobenzyl)sulfide (IV).



IV

The reaction of benzaldehyde with thioacetic acid was conducted as follows. Benzaldehyde, 21.2 g. (0.2 mole), and thioacetic acid, 15.2 g. (0.2 mole), were mixed together and heated at 100° for 18 hr. After cooling, 1.6 g. of a white crystalline solid was obtained. The solid was recrystallized from methanol and then from petroleum ether (63–68°), and it was identified as bis(acetylthiobenzyl)sulfide (IV), m.p. 150–151°. The NMR and IR are in agreement with the assigned structure.

Anal.—Calcd. for $C_{18}H_{18}O_2S_3$: C, 59.63; H, 5.00; S, 26.54; mol. wt., 362. Found: C, 59.43; H, 5.02; S, 27.10; mol. wt., 361 (osmometer).

Mass spectral data were obtained from a Nuclide mass spectrometer.

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