

form (for the previous synthesis see ref 6 and earlier papers therein cited). The transformations reported herein also mark the realization of the synthesis of the four primary prostaglandins, $F_{1\alpha}$, E_1 , $F_{2\alpha}$, and E_2 , from a single precursor, the intermediate **1**, a point of major practical importance.⁷

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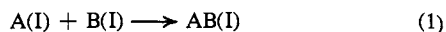
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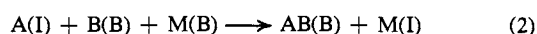
Calorimetric Determination of Heats of Formation of Hydrogen Bonds

Sir:

We wish to report the results of an investigation designed to test the reliability of heats of formation of hydrogen bonds determined by one of the calorimetric methods that have been devised in recent years.¹⁻³ While there are important differences in the thoroughness of the different techniques and in the reliability of the results obtained, the reported values refer to one of the two processes



or



In processes 1 and 2, the symbols A, B, AB, and I refer to the acid, the base, the hydrogen-bonded complex, and an inert solvent, respectively. The symbol M represents a "model" compound, which hopefully accounts for solvent-solute interactions other than hydrogen bonds between the acid and the solvents.³ Parentheses indicate that the preceding species is extremely dilute in the indicated solvent. The methods of Drago¹ and Lamberts² and Arnett's Method I³ may be represented by process 1; Arnett's Method II³ by process 2. Arnett has shown that the two methods give essentially the same results for hydrogen bonds between phenol and several bases with carbon tetrachloride as inert solvent. Drago and Epley⁴ have studied several acid-base pairs in different inert solvents, cyclohexane and carbon tetrachloride, and found that the results may be quite different. While we feel that their heats in cyclohexane are much less reliable than reported, as will be indicated later, the discrepancy between the heats of hydrogen bonding in the two solvents is probably real.

Studies of a hydrogen bond in different solvents and by the two methods can provide useful information regarding interactions in solution, providing the reliability limits of the methods can be established. It is apparent that no single study by either method could detect the existence of strong interactions between the "inert" solvent and either the acid or the base. A comparison of the values determined by the two methods using the same "inert" solvent should detect

(1) T. F. Bolles and R. S. Drago, *J. Amer. Chem. Soc.*, **87**, 5015 (1965).

(2) L. Lamberts, *J. Chim. Phys.*, **62**, 1404 (1965).

(3) E. M. Arnett, T. S. R. Murty, P. von R. Schleyer, and L. Joris, *J. Amer. Chem. Soc.*, **89**, 5955 (1967).

(4) R. S. Drago and T. D. Epley, *ibid.*, **91**, 2883 (1969).

such interactions between the solvent and the base, since in process 2 the two are never in contact. However, in the case of pyridine as base in carbon tetrachloride, where both Drago⁴ and Lamberts⁵ have suggested that such interactions exist, no discrepancy was noted between the values obtained by the two methods.³ This comparison could not possibly detect interactions between the acid and the solvent, since the species A(I) is common to both methods.

As a first step in establishing these reliability limits, we have investigated the effects of different inert solvents and model compounds on the heats calculated for process 2. The inert solvents are carbon tetrachloride, cyclohexane, and *n*-heptane; the model compounds involve the substitution of a methoxy group (M_1) or a methyl group (M_2) for the hydroxy group of the parent acid. The heats of solution of phenol and its model compounds, anisole and toluene, were determined in the three inert solvents and the basic solvents pyridine, tetrahydrofuran (THF), *p*-dioxane, and acetone. The calorimeter has been described elsewhere⁶ and experimental details will be given in a forthcoming paper.⁷ All of the heats of solution in basic solvents and those for the model compounds in inert solvents are relatively independent of concentration. The heat of solution of phenol in the hydrocarbon solvents is strongly dependent on composition ($\Delta H = 7.625 - 8.0 m \pm 0.02$ kcal mol⁻¹ between 0.004 and 0.03 *m* in cyclohexane). This concentration dependence, which is probably due to self-association of phenol, was not noted by Epley and Drago⁸ in their determinations of heats of hydrogen bonding in this solvent at even greater concentrations of phenol. Since the assumption of an ideal dilute solution is inherent in the treatment of data with process 1, the reliability limits on heats of formation of hydrogen bonds in this solvent must be regarded as questionable.

Our heats of solution, extrapolated to infinite dilution, were combined to give the heats for process 2 listed in Table I, along with values that have been reported for process 1. These heats indicate that the heats of formation of hydrogen bonds determined by this method are strongly dependent on the choice of both the inert solvent and the model compound. Since there is apparently no basis for choosing one model compound as more appropriate than the other, there is no guarantee that the actual heat of formation of the hydrogen bond lies within the range of the values calculated for different combinations of inert solvent and model compound. The values determined with carbon tetrachloride as inert solvent are significantly lower (0.2-0.9 kcal) than corresponding values in the hydrocarbon solvents, which could indicate relatively strong interactions of the former solvent with phenol.

In calculating the heats for process 2, we realized that the disparities between the model compounds apparently arise in their heats of solution in the inert

(5) D. Neerincx and L. Lamberts, *Bull. Soc. Chim. Belges*, **75**, 473 (1966).

(6) G. L. Bertrand, R. D. Beaty, and H. A. Burns, *J. Chem. Eng. Data*, **13**, 436 (1968).

(7) In this paper, we will show that the heat determined for process 2 should refer to the heat of formation of the hydrogen bond with all species (A, B, and AB) at infinite dilution in pure base, assuming the acid is almost completely complexed.

(8) T. D. Epley and R. S. Drago, *J. Amer. Chem. Soc.*, **89**, 5770 (1967).

Table I. Effects of Model Compound and Inert Solvent on Heats of Formation of Hydrogen Bonds of Phenol with Various Bases, Calculated by Process 2

| Base | Inert solvent | $-\Delta H_2^a$, kcal mol ⁻¹ | $-\Delta H_2^b$, kcal mol ⁻¹ | $-\Delta H_1$, kcal mol ⁻¹ |
|-------------------|----------------------|--|--|--|
| Pyridine | Cyclohexane | 7.5 | 8.5 | 8.0 ^c |
| | <i>n</i> -Heptane | 7.7 | 8.6 | |
| | Carbon tetrachloride | 7.3 | 7.7 | 7.2 ^d |
| | | 7.3 ^d | | 6.6 ^e |
| THF | Cyclohexane | 5.9 | 6.9 | |
| | <i>n</i> -Heptane | 6.1 | 7.0 | |
| | Carbon tetrachloride | 5.7 | 6.1 | 5.3 ^c |
| | | 5.75 ^d | | 5.7 ^d |
| Acetone | Cyclohexane | 5.5 | 6.6 | |
| | <i>n</i> -Heptane | 5.7 | 6.7 | |
| | Carbon tetrachloride | 5.3 | 5.8 | 4.9 ^c |
| | | 5.6 ^e | | 4.6 ^f |
| <i>p</i> -Dioxane | Cyclohexane | 5.3 | 6.3 | |
| | <i>n</i> -Heptane | 5.5 | 6.4 | |
| | Carbon tetrachloride | 5.0 | 5.6 | |
| | | 5.1 ^h | | |

^a Model compound is anisole (M₁). ^b Model compound is toluene (M₂). ^c Reference 8. ^d Reference 3. ^e Reference 5. ^f Reference 2. ^g E. Mitchell, personal communication, 1970. ^h T. S. S. R. Murty, Ph.D. Thesis, University of Pittsburgh, 1967.

solvents. Since this heat has nothing to do with the actual formation of the hydrogen bond and enters the calculation primarily as an approximation, we wish to propose an alternate treatment by which this method can produce useful information.

By combination of eq 2 written for two different bases (B and B') with the same acid, we eliminate all species dissolved in the inert solvent, as in process 3.



This necessarily removes any contribution of the inert solvent to the results. In the same way that the heat of process 2 can be considered as the heat of formation of the hydrogen bond in pure base, the heat of process 3 can be considered to represent the difference in heats of formation of hydrogen bonds of the acid with the two different bases. The heat for this process is calculated from the heats of solution of the acid and the model compound in the two basic solvents. With elimination of the inert solvent, the method can now be extended to acids for which strong self-association prevents accurate determination of standard heats of solution in inert solvents. To illustrate this point, we have also measured the heats of solution of acetic acid, benzoic acid, and their model compounds methyl acetate, acetone, methyl benzoate, and acetophenone, respectively. We have chosen THF as the reference base (B') and report heats for process 3 in Table II as the heat of transfer of the hydrogen bond of the acid from THF to the other bases. These heats are shown to be virtually independent of the choice of model compound. In fact, acetophenone or methyl benzoate could have been used as the model compound for phenol without changing the calculated heats by more than 0.1 kcal.

The difference in the heats of formation of hydrogen bonds between an acid and different bases may also be calculated from the difference in heats determined

Table II. Heats of Transfer of Hydrogen Bonds from THF (B') to Other Bases, Calculated by Process 3

| Acid | Base (B) | ΔH_3 , kcal mol ⁻¹ | |
|--------------|-------------------|---------------------------------------|----------------------|
| | | Model M ₁ | Model M ₂ |
| Phenol | Pyridine | -1.58 | -1.60 |
| | <i>p</i> -Dioxane | +0.67 | +0.57 |
| | Acetone | +0.43 | +0.27 |
| Acetic acid | Pyridine | -1.77 | -1.79 |
| | <i>p</i> -Dioxane | +0.77 | +0.64 |
| | Acetone | +0.79 | +0.81 |
| Benzoic acid | Pyridine | -2.08 | -1.96 |
| | <i>p</i> -Dioxane | +0.92 | +0.98 |
| | Acetone | +1.09 | +1.18 |

for process 1. The contribution of the inert solvent is not necessarily eliminated in this combination. From Lamberts' data^{2,5} we calculate 2.0 kcal for the difference between the phenol-pyridine and phenol-acetone interactions with carbon tetrachloride as solvent, compared with an average value of 1.94 kcal calculated by combination of our data for pyridine and acetone in Table II. Using his Method I, Arnett obtained a difference of 1.5 kcal between phenol-THF and phenol-pyridine in carbon tetrachloride compared with our average value of 1.59 kcal.

From this study we conclude that "absolute" heats of formation of hydrogen bonds determined by process 2 may be in considerable error relative to reported uncertainties, but relative heats determined by this process are at least as reliable as, and possibly more accurate than, those determined by process 1. Heats of formation of hydrogen bonds determined by process 2 with carbon tetrachloride as "inert" solvent might more properly be considered in terms of process 3 with carbon tetrachloride as the reference base. Because of their greater dependence on the model compound, these heats should be recognized as somewhat less accurate than those determined with stronger bases.

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The Structure of Mitromycin

Sir:

Mitromycin, a compound of unknown structure in the mitromycin class of antibiotics I-IV,^{1,2} was isolated and described in 1962.¹ From combustion analysis and ir, uv, and nmr spectra mitromycin was indicated to have the molecular formula C₁₆H₁₉N₃O₈, the same as I and II, the same chromophore as I and II, and functional groups 1 OMe, 1 NMe, and 1 CMe. Careful examination of the nmr spectra in the presence of CD₃OD also indicated two or three of the 19 protons readily exchanged with deuterium. Although one active proton was assigned as NH the remaining exchangeable protons were not unambiguously defined.

(1) D. V. Lefemine, M. Dann, F. Barbatschi, W. K. Hausmann, V. Zbinovsky, P. Monnikendam, J. Adam, and N. Bohonos, *J. Amer. Chem. Soc.*, **84**, 3184 (1962).

(2) J. S. Webb, D. B. Cosulich, J. H. Mowat, J. B. Patrick, R. W. Broschard, W. E. Meyer, R. P. Williams, C. F. Wolf, W. Fulmor, C. Pidacks, and J. E. Lancaster, *ibid.*, **84**, 3185 (1962).