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STERIC FACTORS IN THE SHORT-RANGE SOLVATION OF SECONDARY AMINES*

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ABSTRACT

Steric aspects of the short-range solvation of proton transfer complexes between 2,4-dinitrophenol and various secondary amines was studied in benzene-DMSO and benzene-dioxane mixed solvent systems. Diisopropylamine was hindered when compared with diethylamine, and 2,2,6,6-tetramethylpiperidine was hindered when compared with 2,6-dimethylpiperidine in forming the proton transfer complex. The smaller electron-donating solvent dimethylsulfoxide was capable of solvating the more hindered amines, but the bulkier dioxane could only solvate diethylamine and dimethylpiperidine readily. Tetrahydropyran could solvate tetramethylpiperidine weakly, inferring that it did not solvate in precisely the same fashion as does dioxane. It is concluded that the solvation structure is sufficiently crowded as to be sensitive to small changes in the structures of the participants.

INTRODUCTION

Short-range solvation occurs when a solvent influences the chemical characteristics of a solute as a result of direct chemical interaction, usually by formation of hydrogen bonds. We are engaged in a study of the short-range solvation of aliphatic amines as they react with 2,4-dinitrophenol (DNP) to form proton transfer complexes in mixed solvents of benzene and small amounts of an electron-donating solvent [1]. Hydrogen bonds are formed between the amine protons of the primary and secondary amines and the electron-donating solvent. Such bonds partially withdraw the amine proton so that the electrons shared with the nitrogen move toward the nitrogen, increasing the basicity of the amine and thereby encouraging the formation of the proton transfer complex. Once the proton transfer complex is formed, the structure is stabilized by the dispersal of the positive charge on the ammonium ion caused by the withdrawal of the amine proton.

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Studies began using *p*-nitrophenol as the phenol in the complex [2] established by NMR that the solvent–solute hydrogen bonds did form, and showed that primary and secondary amines displayed this short-range solvation effect while tertiary amines, lacking the amine proton, did not. By using DNP, a stronger acid, the formation of the proton transfer complex can be observed in a pure benzene solvent, and the effect of very small additions of electron-donating solvent can be observed in the absence of large long-range (dielectric) solvation effects [3]. At that time the studies had focused on dimethylsulfoxide (DMSO) as the electron-donating solvent. The list of solvents was extended to a total of ten, representing a range of functionality [1,4].

The secondary amine common to all these studies was diethylamine (DEA). As the concentration of the electron-donating solvent was gradually increased and the equilibrium constant for the formation of the proton transfer complex (K_{PT}) was plotted versus the weight percent of the solvent, the constant is seen to increase rapidly with the first small additions of solvent, then to display an increase of much lower slope beyond a solvent concentration somewhere in the range of 1–2 wt.% (see Fig. 1). The region of high slope was interpreted to represent a range of concentration in which the solute–solvent hydrogen bond is forming. Once the bond is formed, any further increase in the equilibrium constant was attributed to long-range solvation. This interpretation was supported by the observation that solvents of high dielectric constant (DMSO, dimethylformamide) have a relatively steep slope at higher solvent concentration, while such solvents as dioxane, whose dielectric constant is approximately the same as that of benzene, display a slope of zero.

Extrapolating lines through the two linear portions of the plot, one may

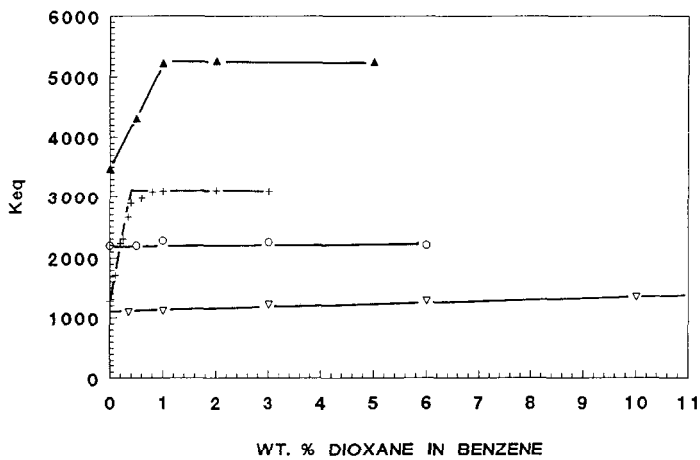

Fig. 1. Equilibrium constants for the formation of the proton transfer complex between DNP and the indicated amines in mixed benzene–dioxane solvents versus wt.% dioxane. +, DEA; ○, DIPA; ▲, DMP; ○, TMP.

assume the intersection to represent the concentration of electron-donating solvent that is sufficient to form the solute–solvent hydrogen bond completely. A plot of the log of the calculated ratio of hydrogen-bonded to non-hydrogen-bonded amine versus the log of the molar concentration of added solvent has the log of the equilibrium constant for the formation of the solute–solvent hydrogen bond (K_{sr}) as its Y intercept, and the number of solvent molecules hydrogen bonding to the amine proton as the slope.

In the earlier work, the calculation of K_{sr} was done such that the number of solute molecules per amine proton was not determined, and the assumption was made that this number was one. In fact, for all of the solvents studied with DEA as the amine it has since been found that two solvent molecules associate with the amine proton [1]. This requires the assumption of bifurcated hydrogen bonding in solution between the amine and the two solvent molecules.

It was assumed that K_{sr} would bear a simple relationship to Taft's beta value for the solvent, a constant that describes the ability of the solvent to donate electrons in solution [5]. In fact the relationship is very poor [1,4]. The situation is not the same here as in the model used by Taft to generate the constant. However, dioxane was found to have a very much higher value than would be anticipated, even if allowances are made for the difference in the models. In order to determine what structural aspect of dioxane was responsible for the very high K_{ar}, a study was made of cyclic and non-cyclic mono- and diethers. Only the cyclic diether dioxalane had a K_{ar} value similar to that of dioxane.

The discrepancy between the predictions of the Taft beta value and the actual value for K_{ar} is not explained by characteristics of the electron-donating molecule itself since the beta value is based on solution studies of hydrogen bonding with the actual molecule rather than on theoretical predictions based on functionality. Differences in the reaction situations must therefore be considered. First, in Taft's studies the proton donor in the formation of the hydrogen bond was uncharged, and here there is an ammonium ion in the proton transfer complex carrying a positive charge. The second obvious explantation lies in the possible existence of varying steric blockage of solvation hydrogen bond formation. That steric hindrance is a problem is made more likely by the fact that two solvent molecules must be accommodated on the amine proton. It is to investigate the possibility that crowding is a factor in this class of short-range solvation that this study was undertaken.

MATERIALS AND METHODS

DNP was Aldrich reagent grade. It was recrystallized twice from benzene, and was stored in a dessicator until used. The diethylamine (DEA), diisopropylamine (DIPA), 2,6-dimethylpiperidine (DMP), 2,2,6,6-tetramethylpiperidine (TMP), and tetrahydropyran were Aldrich reagent grade, and were distilled before use. The amines were stored in dark bottles under nitrogen gas

until used. The benzene, DMSO, and dioxane were Aldrich spectrophotometric grade, and were used without further purification.

Experimental methods and the methods of calculation used were exactly as described in the preceding paper [1].

RESULTS

All of the studies involved measuring K_{PT} between DNP and amines of varying steric requirement in solvents of benzene with a range of small concentra-

TABLE 1

Equilibrium constants for proton transfer complex formation at 25 °C between 2,4-dinitrophenol and various amines in benzene–dioxane mixed solvents

Dioxane (wt.%)	DEA	DIPA	DMP	TMP
0	1273 ± 44	1091 ± 29	3477 ± 103	2196 ± 43
0.1	1722 ± 123			
0.2	2228 ± 47			
0.25	2300 ± 83			
0.35	2661 ± 143			
0.4	2888 ± 126			
0.5			4310 ± 125	2195 ± 66
0.6	2971 ± 101			
0.8	3085 ± 71			
1.0	3097 ± 102	1109 ± 53	5222 ± 84	2274 ± 101
2.0	3110 ± 76		5262 ± 72	
3.0	3097 ± 114	1211 ± 22		2252 ± 66
5.0			5249 ± 77	
6.0		1278 ± 64		2201 ± 59
10		1343 ± 62		

TABLE 2

Equilibrium constants for proton transfer complex formation between 2,4-dinitrophenol and 2,2,6,6-tetramethylpiperidine at 25 °C in mixed solvents of benzene and tetrahydropyran or dimethylsulfoxide

THP in benzene (wt.%)	K_{eq} in THP	K_{eq} in DMSO
0.0	2196 ± 43	2196 ± 43
0.1		23 510 ± 1050
0.3		31 760 ± 1640
0.5	2507 ± 35	
1.0	2845 ± 54	40 770 ± 980
3.0	4206 ± 66	74 460 ± 1290
5.0		104 140 ± 6770
6.0	6206 ± 49	

tions of either DMSO, tetrahydropyran, or dioxane as the electron-donating solvent. The results of studies done in benzene–dioxane mixed solvents are summarized in Table 1, and in benzene–tetrahydropyran mixed solvents and benzene–DMSO mixed solvents in Table 2. These data are plotted in Figs. 1–3.

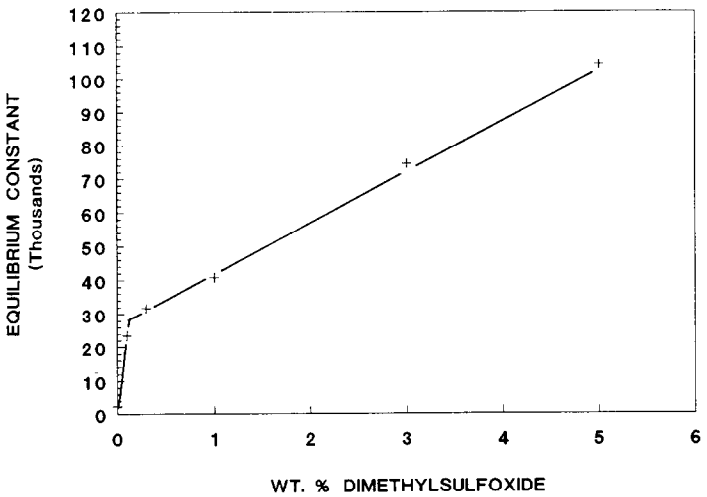

Fig. 2. Equilibrium constants for the formation of the proton transfer complex between DNP and TMP in mixed benzene-DMSO solvents versus wt.% DMSO.

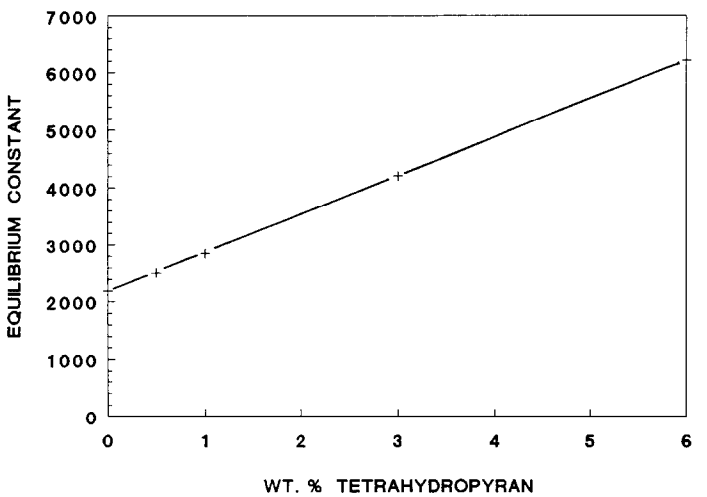

Fig. 3. Equilibrium constants for the formation of the proton transfer complex between DNP and TMP in mixed benzene-tetrahydropyran solvents versus wt.% tetrahydropyran.

DISCUSSION

General principles

The first objective is to determine whether or not there is steric crowding in the solvation structure. There are a number of factors to consider when interpreting the results.

(1) The study has been confined to secondary aliphatic amines. In all of these, there is only one amine proton to solvate. In addition the pK_a values of these amines are all close to 11. Thus, all of the compounds under study start at a common point.

(2) There are two sources of blockage. One relates to the ability of the amine proton to be reached as a result of substitutions on the amine. The other has to do with the ability of the electrons of the electron-donating solvent to reach the proton as a result of the shape of the solvent molecule. We have selected for this study two solvents of differing steric demand and two pairs of amines of differing steric demand.

(3) Although the amines are secondary, they are all accepting a proton from DNP, so that they have a third large attachment to the nitrogen atom. Therefore, solvating the proton transfer complex is similar sterically to solvating a tertiary ammonium ion. Tertiary amines have been described as having one of the three alkyl groups forced toward the pair of electrons, which in this case would mean closer to the proton to be solvated [6].

(4) The cyclic compounds should be less hindered than corresponding noncyclic compounds because the amine alkyl groups are rigidly held back from the proton in the cyclic structure.

TABLE 3

Basicity data and equilibrium constants for proton transfer complex formation with 2,4-dinitrophenol at 25 °C in benzene

Amine	pK_a at 25 °C[a]	Gas-phase basicity[b]	K_{eq}
n-Butylamine	10.66	214.3	75
Diethylamine	10.97	221.8	1273
Diisopropylamine	11.13	226.0	1091
Triethylamine	10.75	228.0	2930
Piperidine	10.97		2800[c]
2,6-Dimethylpiperidine	10.92		3477
2,2,6,6-Tetramethylpiperidine	11.18		2196

[a]Ref. 8.
[b]Ref. 9.
[c]Ref. 10.

(5) Alkyl groups raise the electron density on adjacent structures (the inductive effect). For this reason tertiary amines are more basic in non-polar solvents than secondary amines, which in turn are more basic than primary amines [7] (example in Table 3). In the same fashion, having a branched alkyl group next to a nitrogen should result in a greater increase in the electron density of the nitrogen than would be produced by the corresponding normal chain.

(6) The aqueous pK_a represents the reactivity of the base toward a very small acid, the hydronium ion, in the presence of a very small electron-donating solvent (water). In effect, this is a sterically unhindered solvated amine model.

DEA versus DIPA

Because DIPA has a branched alkyl group it should be slightly stronger as a base than DEA, and it should be somewhat harder to approach. Both the gas-phase basicity and the pK_a confirm that DIPA is a stronger base (Table 3). However, the K_{PT} values in benzene indicate that the steric blockage resulting from the extra methyl group overcomes the greater basicity (Table 3). The study to compare the effects of DMSO as an electron-donating solvent on DEA and DIPA has already been reported [3], and it reveals that solvation occurs freely on both amines. When the bulkier electron-donating solvent dioxane is used, dioxane is able to reach the amine proton of DEA successfully ($K_{sr}=630$), and on average 1.7 dioxanes are reaching the proton. The bonding here is in fact exceptionally strong, such that the solvation is completed with only slightly more than 0.5 wt.% dioxane present in solution. The equilibrium constant for the formation of the proton transfer complex increases from 1200 to 3100 as a result of this solvation. By contrast, very little solvation of DIPA by dioxane occurs (Fig. 1). Based on the DEA model, the equilibrium constant for proton transfer complex formation would be expected to rise from 1100 to a value in excess of 2500, and even with the addition of 10 wt.% dioxane it has only risen to about 1350 (Table 1).

DMP versus TMP

The significance of 2,6-disubstitution in six-membered nitrogen heterocycles was explored by Brown and Kanner [11]. Gas-phase basicity values are not available for DMP and TMP, but the pK_a values (Table 3) indicate that these amines have a relationship similar to that of DIPA and DEA. The parallel continues as the K_{PT} values are compared. DMP is more reactive than piperidine, the result of extra basicity without serious steric blockage. However, the TMP is clearly less reactive in spite of a further increase in basicity, which must be attributed to steric factors. TMP displays the effects of short-

range solvation by DMSO (Fig. 2). However, with the bulkier dioxane, DMP solvated with a K_{sr} value of 501, and an indication that on average two molecules of dioxane bond to the amine proton (Fig. 1). The dioxane seems to be incapable of hydrogen bonding to the amine proton of TMP at all, with no change in the K_{PT} value occurring in concentrations of dioxane up to 6 wt.% (Fig. 1). In summary, the evidence supports the concept that the solvation structures under study are crowded to the point that small increases in the steric demand block the solvation reaction.

The nature of dioxane solvation

The second objective of this study was to consider further the special nature of dioxane as an electron-donating solvent. One hypothesis to explain the very high values obtained for the K_{sr} for 1,4-dioxane and 1,3-dioxalane solvating the DNP–DEA proton transfer complex is that in the solvation complex both oxygens of the cyclic diether are interacting with the amine proton in a bifurcated hydrogen bond structure. This explanation follows readily from the observation that monoethers do not bond as readily to diethylamine. That the non-cyclic diether 1,2-dimethoxyethane is no more effective than a monoether could be explained in terms of the difficulty of moving the second oxygen into place near the amine proton in a crowded solvation structure. Since the cyclic diethers are rigid structures, it is no more difficult to move both oxygens into the vicinity of the proton than it is to move one. Such a bifurcated bond has been observed as an intramolecular structure. Jochims and Kobayashi reported an internal hydrogen bond in 1,3-dioxane-5-ol in which the proton of the alcohol was equally shared by the two ring oxygen [12].

We have seen that the fit of dioxane to the amine proton is such that a small increase in the steric demand of the amine blocks the entry of the dioxane. If the dioxane is hydrogen bonding to the amine by only one of the two oxygens, then tetrahydropyran and dioxane should display identical patterns of steric blockage. When TMP was studied in mixed benzene–tetrahydropyran solvents, it showed a steady increase in the K_{PT} value from 2200 at 0 wt.% to 6200 at 6 wt.% (Fig. 3). The ability of tetrahydropyran to fit where dioxane does not lends support to the hypothesis that dioxane is attaching to the amine proton in a different fashion, perhaps by a bifurcated bond involving both dioxane oxygens.

SUMMARY

A study has been made of the solvation of proton transfer complexes between 2,4-dinitrophenol and various secondary amines in benzene–DMSO and benzene–dioxane mixed solvent systems. In the interpretion of the results, emphasis was placed on steric factors both in the formation of the proton transfer

complex and in the solvation reaction. Diisopropylamine was hindered when compared with diethylamine, and 2,2,6,6-tetramethylpiperidine was hindered when compared with 2,6-dimethylpiperidine in forming the proton transfer complex. The smaller electron-donating solvent dimethylsulfoxide was capable of solvating the more hindered amines, but the bulkier dioxane could only solvate diethylamine and dimethylpiperidine readily. Tetrahydropyran could solvate tetramethylpiperidine weakly, inferring that it did not solvate in precisely the same fashion as does dioxane.

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