

Equilibrium Constants for the Interconversion of Substituted 1-Phenylethyl Alcohols and Ethers. A Measurement of Intramolecular Electrostatic Interactions¹

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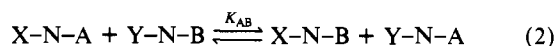
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Abstract: Equilibrium constants for the reactions of ring-substituted 1-phenylethyl alcohols with a series of aliphatic alcohols of pK_a 12.4–16 to form the corresponding ethers, and for interconversion of the ethers, have been determined in 50:45:5 HOH/CF₃CH₂OH/ROH (v/v/v), $\mu = 0.5$ (NaClO₄), at 25 °C. Formation of ethers from the alcohols is favorable, with values of $K = 3$ –74; replacement of water by methanol is favored by factors of 50–74. Equilibrium constants increase with increasing pK_a of the alcohol with values of $\beta_{eq} = \partial \log K / \partial pK_{ROH}$ in the range 0.17–0.27. This is attributed to hydrogen bonding of the alcohol to the solvent and to an electrostatic interaction between substituents on the alcohol and the aryl group. The contribution from hydrogen bonding to the solvent is estimated to be $\beta = 0.17$; for 90% HOH it is 0.25. An increase in β_{eq} with electron-withdrawing substituents on the benzene ring and a complementary increase in ρ_{eq} with electron-donating substituents on ROH are described by an electrostatic interaction coefficient $\tau = \partial \beta_{eq} / \partial \sigma = \partial \rho_{eq} / \partial pK_{ROH} = 0.10 \pm 0.01$. No change in τ for dipole–dipole interactions was observed with increasing water concentration in the range 50–90% (v/v). The electrostatic interactions that are described by τ can cause changes in structure–reactivity parameters, such as ρ or β , in the absence of changes in transition-state structure.

Changes in structure–reactivity parameters, such as Hammett ρ or Brønsted β values, are widely used as indicators of changes in transition-state structure, as described by Hammond, Marcus, and others.^{2,3} Hammett and Brønsted slopes are first derivatives of $\log k$, and changes in these slopes are second derivatives. These changes in slope are often estimated from the curvature of structure–reactivity correlations, but it is difficult to distinguish changes that represent changes in transition-state structure from other changes that arise from different chemical properties of the reactants or catalysts that are used for different parts of the curve and from other reasons for curvature. It is somewhat easier to evaluate changes in ρ or β in one series of reactants when the structure of a second reactant is changed. These changes may be described by cross coefficients such as q or p_{xy} (eq 1).^{3,4}

$$p_{xy} = \frac{\partial \beta}{-\partial \sigma} = \frac{\partial \rho}{-\partial pK_{HA}} \quad (1)$$

However, cross coefficients can also arise from simple electrostatic effects that change the energy of the transition state, in the absence of any change in the structure of the transition state.^{3,5} In fact, Hine has derived the Hammett equation from a treatment of electrostatic interactions across a rigid molecular framework.^{6,7} The changes in K_{AB} with changing substituents X, Y, A, and B in the reaction of eq 2 may be described by the interaction



(1) Supported in part by grants from the National Institutes of Health (GM 20888) and the National Science Foundation (PCM 81-17816). Dr. Richard was supported by a fellowship from the National Institutes of Health (AM 07251).

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(7) Hine, J. "Structural Effects on Equilibria in Organic Chemistry"; Wiley: New York, 1975; pp 58–65.

coefficient τ (eq 3). The first-derivative slopes ρ_{eq} and β_{eq} are

$$\log K_{AB} = \tau(\sigma_X - \sigma_Y)(pK_{BOH} - pK_{AOH}) \quad (3)$$

obtained from plots of $\log K$ against σ or pK with the other parameter held constant. The electrostatic interaction coefficient is then given by the slopes of plots of eq 4. These electrostatic

$$\tau = \partial \beta_{eq} / \partial \sigma = \partial \rho_{eq} / \partial pK_{ROH} \quad (4)$$

interactions can be mistakenly interpreted as evidence for changes in transition-state structure, if they have the same sign as an expected change, or can lead to an underestimation of such changes, if they have the opposite sign.³

The experiments described here were undertaken to estimate the magnitude of τ for dipole–dipole interactions of a reaction at equilibrium in a polar, largely aqueous medium. A knowledge of τ makes it possible to distinguish simple electrostatic interactions from structure–reactivity interaction coefficients that arise from changes in transition-state structure.

Experimental Section

Materials. Reagent grade chemicals, including 2,2,2-trifluoroethanol (TFE) (Aldrich, 99+% "Gold Label"), were generally used without further purification; other alcohols were redistilled. The preparation of 1-phenylethyl derivatives has been described previously.⁸ All substrates were shown to be $\geq 98\%$ pure by HPLC analysis.

Reaction Procedures. Reaction solutions containing HOH/TFE/ROH (50:45:5 v/v/v) at ionic strength 0.5 were prepared by mixing equal volumes of aqueous 1 M sodium perchlorate and 9:1 (v/v) TFE/ROH. The acid concentration was usually adjusted to 0.002–0.013 M with 1 M perchloric acid. Experiments with 4-methoxy-3-nitro- and 4-methoxy-3-bromo-substituted substrates were run in solutions containing 0.25 or 0.5 M perchloric acid, which were prepared by replacing an appropriate volume of 1 M sodium perchlorate by 1 M perchloric acid. Solutions with higher concentrations of water were prepared by replacing part of the TFE/ROH by water; the ionic strength was maintained at 0.5. Substrates were dissolved in acetonitrile, and an aliquot of $\leq 50 \mu\text{L}$ was added to 3 mL of reaction mixture to give a final concentration of ~ 1 mM. The reactions were incubated in a water bath at 25 °C.

Reactions of 1-(4-(dimethylamino)phenyl)ethyl alcohol were carried out in 0.025 M 4-morpholinioethanesulfonic acid buffer at a pH in which $\geq 96\%$ of the substrate was shown spectrophotometrically to be in the free base form. Reactions of the protonated species were carried out at an apparent pH about 3 units below its apparent pK_a of 5.5.⁸ Equilibrium constants for the free base species were obtained from the observed

(8) Richard, J. P.; Rothenberg, M. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1361–1372.

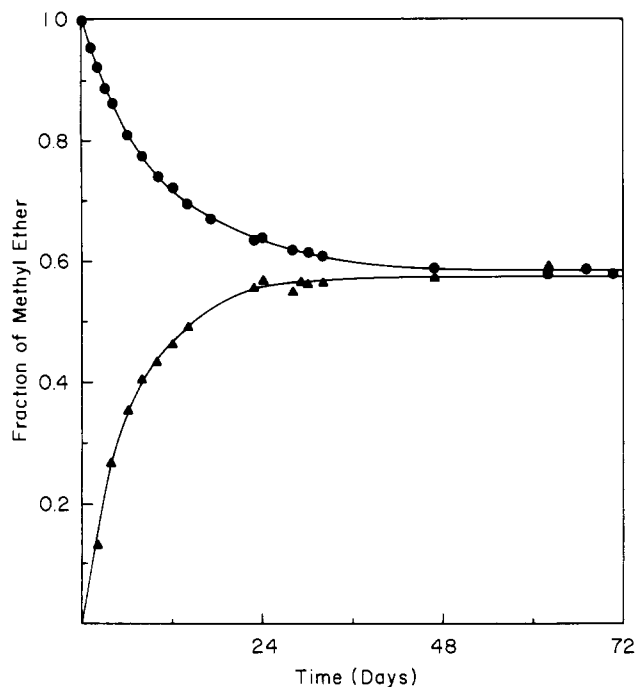


Figure 1. Approach to equilibrium for the reactions of 1-(3-nitro-4-methoxyphenyl)ethyl alcohol (▲) and the corresponding methyl ether (●) in HOH/TFE/MeOH (50:45:5) with 0.5 M perchloric acid at 25 °C.

equilibrium constants for the fully protonated and ~96% base species by a linear extrapolation of K_{obsd} to 100% base.

The propargyl ethers appeared to be stable under the conditions of the reactions, which is consistent with the small rate constant for acid-catalyzed hydration of 3-hexyne.⁹

Product Analysis. The equilibrium distribution of products was analyzed by HPLC as described previously.⁸ Solutions containing ≥ 0.1 M acid were neutralized with 1 M sodium bicarbonate before analysis. A large excess of sodium bicarbonate was added to samples containing 4-(dimethylamino)-substituted compounds in order to prevent further reaction during analysis. In the absence of sufficient base the methyl ether is formed during chromatography in methanol-water.⁸ The order of increasing retention times for most substrates was alcohol followed by 2-methoxyethyl, methyl, propargyl, ethyl, 2-chloroethyl, 2,2,2-trifluoroethyl, 3-chloropropyl, 2,2-dichloroethyl, *n*-propyl, and *n*-butyl ethers. The product ratios were determined from the integrated peak areas. The extinction coefficients of the alcohol and ether products do not differ significantly.⁸

1-(4-Methoxyphenyl)ethyl ethyl ether and the corresponding styrene were not separated on chromatography. Small amounts of styrene formation presented a problem because of its high extinction coefficient, especially in solvents of high water content. The formation of styrene was minimized (to <0.6% of the peak area for the ethyl ether, with which it coeluted) by determining equilibrium constants at low acid concentration. A correction was made for the contribution of styrene to the ethyl ether peak, from parallel runs that were carried out in the absence of ethanol. Traces of the acetophenone precursor of the alcohol, which eluted ~1 min after the alcohol, were identified in some analyses. The 4-methoxy-3-bromo substrate gave small amounts of unidentified decomposition products that increased to 9% of the total peak area after equilibrium had been reached and the experiment was terminated.

The concentrations of substrate (≤ 3 mM) and the injection volumes for HPLC were increased for reactions carried out at high concentrations of water. It was shown that Beer's law was followed at these substrate concentrations. Data from runs in 90% water showed alcohol:ether ratios as large as 50 and increased scatter of replicate determinations of equilibrium constants.

Results

The equilibrium distribution of reaction products was determined for a series of substituted 1-phenylethyl alcohols after equilibration in 50:45:5 HOH/TFE/ROH (v/v/v) at ionic strength maintained at 0.5 with sodium perchlorate, until all

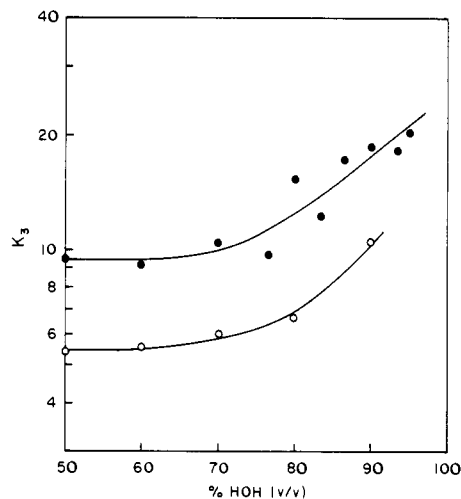
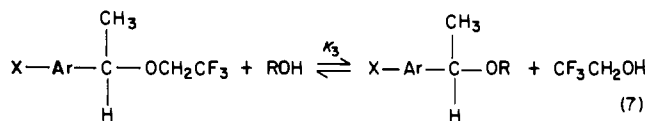
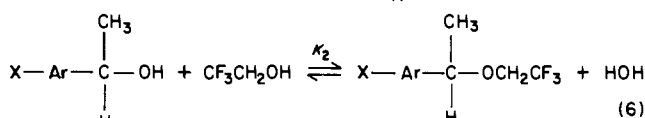
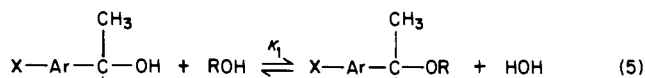


Figure 2. Dependence on solvent composition of $\log K_3$ for the conversion of trifluoroethyl to ethyl ethers of 1-(4-methoxy-3-nitrophenyl)ethyl (●) and 1-(4-methoxyphenyl)ethyl (○) ethers.

product ratios were constant. The approach to equilibrium of 1-(3-nitro-4-methoxyphenyl)ethyl alcohol and its methyl ether is shown in Figure 1. Equilibration was catalyzed by dilute perchloric acid, and the equilibrium constants were shown to be independent of the acid concentration in several cases. The equilibrium constants K_1 , K_2 , and K_3 for the reactions of eq 5-7 were calculated from the ratio of peak areas of the phenylethyl derivatives, after HPLC analysis of the equilibrated solutions, and the concentrations of ROH and HOH. The results are reported in Table I.



A limited series of results from determinations in 90:9:1 HOH/TFE/ROH (v/v/v) are given in Table II. These data are less accurate than those from experiments in 50:45:5 HOH/TFE/ROH because of the small concentration of ether products and the resulting large ratios of peak areas in HPLC analysis; however, they confirm the trends of the data in Table I. Figure 2 shows the effect of increasing water concentration on the equilibrium constant K_3 for the reaction of ethanol with 1-(4-methoxy-3-nitrophenyl)ethyl and 1-(4-methoxyphenyl)ethyl trifluoroethyl ethers.

Discussion

Structure-Reactivity Correlations. Figure 3 illustrates the dependence of the equilibrium constants K_1 and K_3 ($\text{X} = 4\text{-NH}(\text{CH}_3)_2^+$) on the $\text{p}K_a$ of the alcohol, ROH. These equilibrium constants describe the replacement of the OH and OR groups of 1-(4-(dimethylammonium)phenyl)ethyl alcohol and its trifluoroethyl ether by a series of aliphatic alcohols (eq 5 and 7). The reactions are favored by increasing basicity of the alcohol. Brønsted slopes of $\beta = 0.25$ for K_1 and 0.26 for K_3 were calculated from the data for ethanol and 2-methoxy-, chloro-, dichloro-, and trifluoroethanol. Methanol and propargyl alcohol show positive deviations from this correlation of 2.5-fold and 3.7-fold, respectively, which presumably arise from less favorable steric effects or internal rotational entropy in the ethers formed from substituted

(9) Modena, G.; Rivetti, F.; Scorrano, G.; Tonellato, U. *J. Am. Chem. Soc.* **1977**, *99*, 3392-3395.

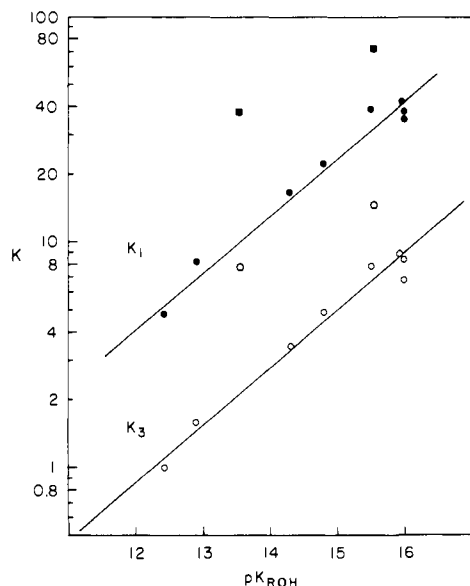


Figure 3. Dependence on pK_{ROH} of $\log K_1$ and $\log K_3$ for the formation of 1-(4-(dimethylammonium)phenyl)ethyl ethers in HOH/TFE/MeOH (50:45:5), ionic strength 0.5 (NaClO_4), at 25 °C. The squares represent equilibrium constants for the addition of propargyl alcohol and methanol.

ethanols. Space-filling molecular models show some restriction to rotation of the terminal methyl group in 1-phenylethyl ethyl ether; a π - π interaction with the benzene ring may also stabilize the propargyl ether. Similar, but smaller, deviations of the rate constants for reactions of these alcohols or their anions have been observed.^{10,11} The results for 1-(3-nitro-4-methoxyphenyl)ethyl alcohol (Table I) are very similar and give values of $\beta = 0.26$ for K_1 and $\beta = 0.27$ for K_3 .

The Brønsted slopes of $\beta = 0.25$ – 0.26 may be explained by relatively strong hydrogen bonding of the more acidic alcohols to the solvent, which is lost when the ether is formed, and by an unfavorable electrostatic interaction of electron-withdrawing substituents on the alcohol with the electron-withdrawing benzene ring and its 4-dimethylammonium ion substituent. Both of these effects are expected to make the equilibrium addition of acidic alcohols less favorable. The contributions to β of the electrostatic interactions with the substituent and the benzene ring are approximately 0.06 and 0.03, respectively,¹² which gives a value of $\beta = 0.26 - 0.09 = 0.17$ for breaking the hydrogen bonds of ROH to the solvent. The β values in the 90% aqueous solvent, from the data in Table II, are larger by an average of 0.08. This gives a value of $\beta = 0.25$ for breaking the hydrogen bonds of alcohols to this solvent. The data collected by Guthrie for replacement of the OH group of aldehyde hydrates and related compounds by ethanol or methanol in aqueous solution give a value of $\beta = 0.25$, for substituents on the carbonyl group.¹³

Electron-withdrawing substituents on the benzene ring have little or no effect on the equilibrium constants K_1 for formation of the methyl and ethyl ethers from 1-phenylethyl alcohols, as

(10) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1373–1383.

(11) Hupe, D. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 451–464.

(12) It is shown below that $\tau = \partial\beta/\partial\sigma = 0.10$ for substituents on the benzene ring. The contribution of the 4- $\text{NH}(\text{CH}_3)_2^+$ group is then $\Delta\beta = \tau\Delta\sigma = 0.10(0.56) = 0.06$. The electrostatic effect of the benzene ring may be estimated from the substituent effect for the Ph group, by correcting for the fact that it is closer to the alcohol than the substituents for which $\tau = 0.10$. Taking an attenuation factor for the benzene ring of 0.34, based on the ρ values for ionization of ArPhCOOH and ArCOOH (ref 7, p 162) and $\sigma^n = 0.10$ for Ph (ref 7, p 72), the increase in β that may be attributed to the electron-withdrawing effect of the benzene ring is $\Delta\beta = \tau\Delta\sigma = 0.10(0.10/0.34) = 0.03$.

(13) Guthrie, J. P. *Can. J. Chem.* **1975**, *53*, 898–906. Guthrie, J. P. *J. Am. Chem. Soc.* **1977**, *99*, 3991–4001. The equilibrium constants close to 1.0 M⁻¹ for the reactions of hydrates with MeOH or EtOH are based on a standard state of 1.0 for liquid water and correspond to values of $K_1 \sim 55$ for the dimensionless equilibrium constants described here.

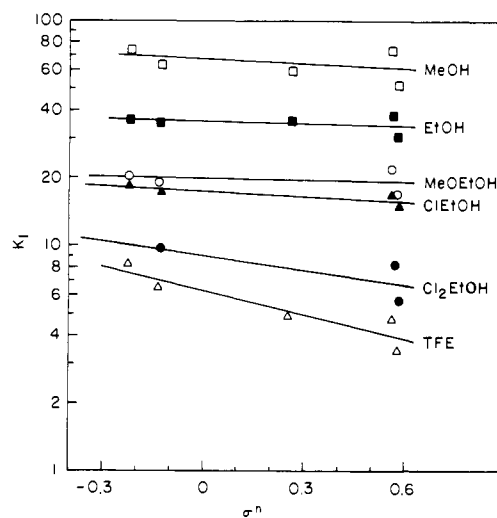


Figure 4. Dependence on σ^n of $\log K_1$ for the formation of 1-arylethyl ethers.

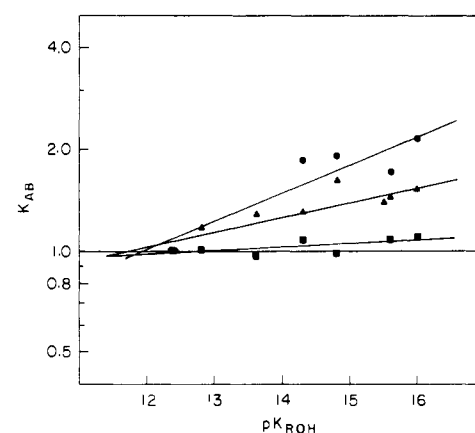
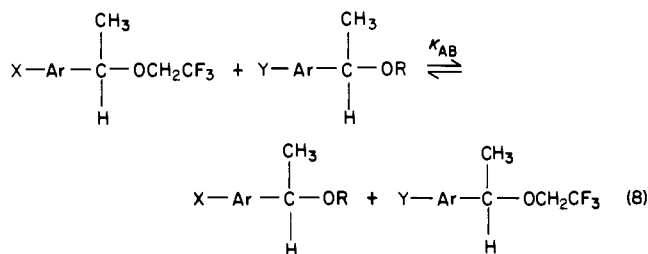


Figure 5. Dependence on pK_{ROH} of $\log K_{AB}$ for the interconversion of substituted 1-arylethyl ethers. The aryl substituents are X = 4- OCH_3 -3- NO_2 , Y = 4- $\text{NH}(\text{CH}_3)_2^+$ (■); X = 4- $\text{NH}(\text{CH}_3)_2^+$, Y = 4- OCH_3 (▲); and X = 4- OCH_3 -3- NO_2 , Y = 4- $\text{N}(\text{CH}_3)_2$ (●). The lines were calculated by least squares. The line of zero slope, for a reaction with X = Y and no interaction coefficient, is included for reference.

shown in Figure 4. However, ether formation is less favorable when electron-withdrawing substituents are added to both the aliphatic alcohol and the 1-arylethyl compound. The same trend is observed with the more limited data for formation of the *n*-butyl, 3-chloropropyl, and propargyl ethers and with the equilibrium constants K_3 for interconversion of substituted 1-phenylethyl ethers (Table I). There is a small but consistent increase in the equilibrium constants for ether formation from 1-(4-(dimethylammonium)phenyl)ethyl alcohol compared with the 4-methoxy-3-nitro compound. This is a specific effect on the replacement of OH by OR because these substituents have almost identical effects on the equilibrium constants for interconversion of ethers (K_3 , Table I). The closely similar effects of these substituents support the assignment of $\sigma^n = 0.56$ for the 4- $\text{NH}(\text{CH}_3)_2^+$ group,¹⁴ which is close to $\sum\sigma^n = 0.71 - 0.13 = 0.58$ for the 4-methoxy-3-nitro substituents (Table III).

Structure-Reactivity Interactions. The interaction between polar substituents on the aliphatic alcohol and the phenylethyl alcohol may be described by the equilibrium constants K_{AB} for interconversion of ethers with substituents in both positions, eq 8. When X is more electron withdrawing than Y the values of K_{AB} increase with increasing pK_a of the alcohol and plots of $\log K_{AB}$ against pK_{ROH} have slopes in the range 0.01–0.08. Figure 5 shows that for the systems X = 4- OCH_3 -3- NO_2 , Y = 4- $\text{N}(\text{CH}_3)_2$ and X =

(14) Hoefnagel, A. J.; Hoefnagel, M. A.; Wepster, B. M. *J. Org. Chem.* **1978**, *43*, 4720–4745.



4-NH(CH₃)₂⁺, Y = 4-OCH₃, the slopes are $\beta = 0.08$ and 0.04 , respectively. There is little or no change in K_{AB} for X = 4-OCH₃-3-NO₂, Y = 4-NH(CH₃)₂⁺, which have almost identical values of $\sum \sigma^n$ (squares, Figure 5).

Bronsted plots of $\log K_1$ and $\log K_3$ for the interconversion of 1-arylethyl alcohols and ethers with different aliphatic alcohols have slopes, β_1 and β_3 , in the range 0.17–0.27. Values of β and ρ are summarized in Table III. Figure 6A shows that the β_1 and β_3 values increase regularly with increasing σ^n for substituents on the 1-arylethyl ether. The slope of this line, τ , is the interaction coefficient that describes the polar interaction between substituents on the benzene ring and the aliphatic alcohol (eq 4). The value of τ is 0.10 ± 0.014 ($r = 0.982$) for β_1 and 0.10 ± 0.004 ($r = 0.998$) for β_3 ; the limits refer to the standard error.

There is a complementary increase in $-\rho_1$ and ρ_3 for the interconversion of different substituted 1-arylethyl ethers with increasing ΔpK_a of the aliphatic alcohols (eq 4), as shown in Figure 6B. The correlation is less good than that for the β values, but the increase with increasing alcohol basicity is certainly present. The slopes of the lines are $\tau = 0.081 \pm 0.019$ ($r = 0.883$) for $-\rho_1$ and $\tau = 0.088 \pm 0.016$ ($r = 0.927$) for ρ_3 . The same trend is followed by the limited data for 3-chloropropyl and *n*-butyl alcohols in Table I.

The slopes, β , of the two upper correlation lines of $\log K_{AB}$ and pK_a in Figure 5, divided by $\Delta \sum \sigma^n$, give values of $\tau = 0.11$ and 0.06 , respectively.

There is no indication of an effect of the composition of these highly polar solvents on τ for dipole–dipole interaction in the range 50–90% H₂O/TFE (v/v). The values of K_3 for the substitution of ethanol for trifluoroethanol increase over this range for both the 4-OCH₃ and the 4-OCH₃-3-NO₂ substituted phenylethyl ethers, as shown in Figure 2, but the ratio of the two equilibrium constants does not change significantly; the ratio is 1.7 in the 50% and 90% solutions. The increase of K_3 may be accounted for by the relatively strong hydrogen bonding of the released trifluoroethanol to the more basic water molecules in the more aqueous solvent.

The values of K_1 for substitution of OEt for OH decrease by factors of 2–3 when the water concentration is increased from 50% to 90% (Table II). This represents a relative destabilization of the phenylethyl ether and HOH relative to the phenylethyl alcohol and ROH with increasing water content of the solvent. The activity coefficients for simple ethers, alcohols, and water also indicate larger destabilization of ethers in water than might be expected from the stabilities of the reactants.¹⁵ The reason for this behavior is not clear to us. It does not represent an increase in the activity coefficient for water with increasing water concentration, because water–trifluoroethanol mixtures show positive deviations from Raoult's law.¹⁶

There is a larger decrease in K_2 with increasing water content (Table II) that presumably reflects the strong hydrogen bonding of trifluoroethanol to water that was noted above. Another consequence of this stabilization of trifluoroethanol is an increase in the β values for K_1 and K_3 by 0.06–0.09 units; the values of β for K_1 in the 90% aqueous medium are 0.28, 0.31, and 0.35 (2 points) for the 4-OCH₃, 4-NH(CH₃)₂⁺, and 4-OCH₃-3-NO₂ substituted compounds, respectively. Although the data are insufficient for a definite conclusion, the smaller difference in β of

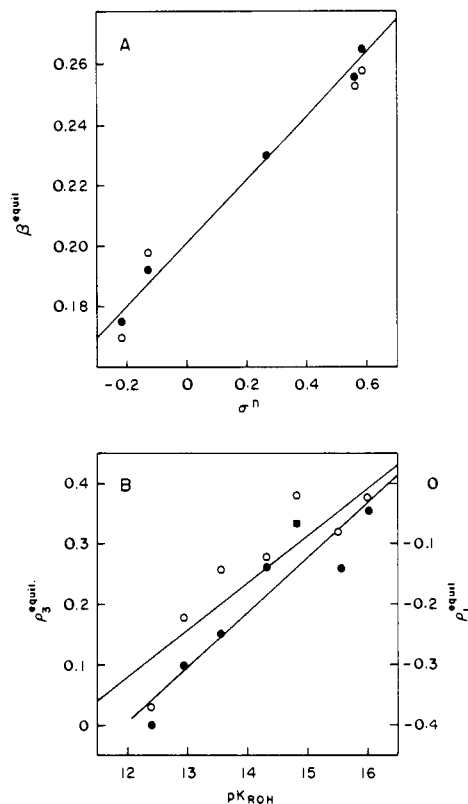
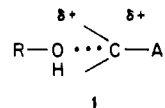


Figure 6. Dependence of β_1 (O) and β_3 (●) on σ^n (A) and $-\rho_1$ (O) and ρ_3 (●) on pK_{ROH} (B) for the formation of 1-arylethyl ethers.

0.03 for the 4-OCH₃ and 4-NH(CH₃)₂⁺ substituents compared with 0.06 units in the 50% aqueous medium suggests that the charge–dipole interaction may be smaller in the more aqueous medium. Charge–dipole and dipole–dipole interactions are expected to show differences in behavior, which may be solvent dependent.^{14,17}

Comparison with Other Interactions. Electrostatic interactions will perturb structure–reactivity coefficients that are used to characterize a transition state, in the absence of any change in transition-state structure. The resulting changes in structure–reactivity coefficients might be mistakenly interpreted as evidence for a change in transition-state structure. In the addition of alcohols to substituted 1-phenylethyl carbocations, for example, a value of $\tau = \partial\beta/\partial\sigma = \partial\rho/\partial pK_{\text{ROH}} = 0.10$ means that an electron-withdrawing group on Ar (increased σ) will interact with an electron-donating group on the alcohol (increased pK_a) to stabilize the transition state, **1**, and increase $\log k$. This will result



in an increased sensitivity of k_{obsd} to the pK_a of the alcohol, $\beta_{\text{nuc}} = \partial \log k / \partial pK_{\text{ROH}}$, with the electron-withdrawing substituent on the electrophile, σ_2 , in the absence of any change in transition-state structure, as shown by the arrow in Figure 7.

In fact, the reaction of substituted alcohols with these carbocations shows a normal “Hammond effect”, with a decrease in β_{nuc} for the more reactive cations that have electron-withdrawing substituents. This decrease may be described by the interaction coefficient $p_{yy'} = \partial\beta_{\text{nuc}}/\partial\sigma = \partial\rho/\partial pK_{\text{ROH}} = 0.1$. This is in the opposite direction from the electrostatic effect (τ and $p_{yy'}$ are defined with opposite signs). It suggests that the transition state for the more reactive carbocation has less bonding and charge development on the oxygen atom of ROH.¹⁰ Correction for the

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(16) Smith, L. S.; Tucker, E. E.; Christian, S. D. *J. Phys. Chem.* **1981**, *85*, 1120–1126.

(17) van de Graaf, B.; Hoefnagel, A. J.; Wepster, B. M. *J. Org. Chem.* **1981**, *46*, 653–657.

Table I. Equilibrium Constants for the Interconversion of Substituted 1-Phenylethyl Alcohols and Ethers in H₂O/TFE/ROH (50:45:5 v/v/v)^a

phenyl substituent	ROH	K ₁	K ₂	K ₃	phenyl substituent	ROH	K ₁	K ₂	K ₃
4-OCH ₃ -3-NO ₂	EtOH	30	3.2	9.5	4-OCH ₃	EtOH	36	7.1	5.1
		31	3.4	8.9			35	6.8	5.2
	CH ₃ OEtOH	17	3.5	4.8		38	6.9	5.6	
		17	3.6	4.6		37	6.3	5.8	
	ClEtOH	13.2	3.3	4.0		34	6.3	5.4	
		15	3.9	3.8		38	6.9	5.6	
	Cl ₂ EtOH	5.7	3.6	1.6		CH ₃ OEtOH	21	6.4	3.2
	MeOH	55 ^b	3.5 ^b	16 ^b			20	6.6	3.1
		49	3.1	16			20	6.6	3.1
	HC≡CCH ₂ OH	22	3.1	7.1			17	5.9	2.9
CF ₃ CH ₂ OH	26	3.5	7.5	18	6.5	2.8			
	3.4	3.4	1.0	20	6.5	3.0			
4-NH(CH ₃) ₂ ⁺	EtOH	38	4.1	9.2	ClEtOH	19	6.7	2.8	
		36	4.6	7.7		16	6.6	2.4	
		41	5.0	8.2		17	6.7	2.6	
		36	4.7	7.7		19	6.8	2.8	
		38	4.2	9.0		Cl ₂ EtOH	10	7.0	1.4
	CH ₃ OEtOH	24	4.7	5.2	9.3		7.2	1.3	
		22	4.4	4.9	MeOH	63	6.3	10	
		21	4.7	4.5		37	6.3	5.9	
	ClEtOH	17	4.9	3.6	38	6.4	5.9		
		16	4.6	3.6	ClCH ₂ CH ₂ CH ₂ OH	40	7.0	5.7	
16		5.1	3.1	37		6.8	5.4		
Cl ₂ EtOH	8.2	5.2	1.6	CF ₃ CH ₂ OH	6.6	6.6	1.0		
	MeOH	72	4.9		15	4-N(CH ₃) ₂ ^c	EtOH	36	8.7
38		4.7	8.0	34	8.1			4.2	
HC≡CCH ₂ OH	37	5.1	7.3	37 ^d	8.1 ^d	4.5 ^d			
	CH ₃ CH ₂ CH ₂ CH ₂ OH	42	4.8	8.8	CH ₃ OEtOH	20	8.1	2.5	
43		4.8	9.1	21		8.6	2.5		
CH ₃ CH ₂ CH ₂ OH	35	5.1	6.9	ClEtOH	18	8.6	2.1		
	ClCH ₂ CH ₂ CH ₂ OH	40	5.0		8.0	20	8.8	2.2	
38		5.0	7.7	MeOH	76	8.2	9.2		
CF ₃ CH ₂ OH	4.8	4.8	1.0		72	7.5	9.5		
	4-OCH ₃ -3-Br	EtOH				Butanol	43	9.2	4.6
46							9.7	4.8	
CF ₃ CH ₂ OH							8.5	8.5	1.0
							37	5.6	6.7
MeOH	33	5.0	6.6	EtOH	37	5.6	6.7		
	59	5.0	12		33	5.0	6.6		
60	5.2	11	MeOH	59	5.0	12			
5.2	5.2	1.0		60	5.2	11			
CF ₃ CH ₂ OH	5.2	5.2	1.0	CF ₃ CH ₂ OH	5.2	5.2	1.0		

^a At 25 °C, ionic strength 0.5 maintained with sodium perchlorate. ^b This reaction was started with 1-(4-methoxy-3-nitrophenyl)ethyl methyl ether. ^c In 0.025 M 4-morpholinoethanesulfonic acid buffer. ^d In 0.050 M buffer.

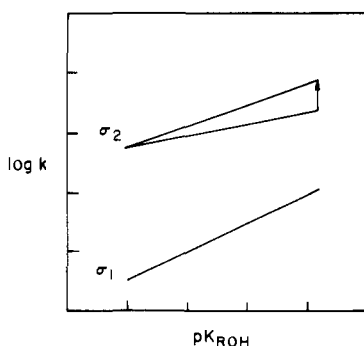
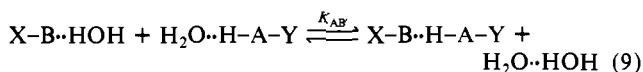


Figure 7. Schematic Brønsted plot to show how an electron-withdrawing group (σ_2) on the electrophilic reagent can increase β_{nuc} for the addition of substituted alcohols, as indicated by the arrow, by a favorable electrostatic interaction with an electron-donating group in the alcohol.

electrostatic contribution gives a value of $p_{yy} = 0.2$ for the change in β_{nuc} that is attributed to an increase in bond formation in the transition state. A more accurate correction would be slightly smaller because of the larger distance between the dipoles in the

transition state than in the product; a correction for this might be made from an estimate of the small difference in C–O bond lengths in the transition state and the product and the appropriate attenuation factor for polar substituent effects.¹⁸

It is of particular interest to compare this value of τ to τ' for the formation of hydrogen bonds between solutes according to eq 9 and 10, as described by Hine.¹⁹ A value of $\tau' = 0.024$ was



$$\log K_{\text{AB}} = \tau'(pK_{\text{AH}} - pK_{\text{HOH}})(pK_{\text{H}_3\text{O}^+} - pK_{\text{BH}}) - \log 55 \quad (10)$$

estimated for methanol, but a smaller value might be expected for an aqueous solvent. This coefficient differs from that for 1-arylethyl ethers in that pK_{a} values rather than σ were used as measures of the polar effects of the substituent, and the molecular

(18) The C–O bond length has been estimated to be 0.2–0.4 Å longer in the transition state than in the product for the addition of water to formaldehyde (Williams, I. H.; Spangler, D.; Femec, D. A.; Maggiora, G. M.; Schowen, R. L. *J. Am. Chem. Soc.* **1983**, *105*, 31–40).

(19) Hine, J. *J. Am. Chem. Soc.* **1972**, *94*, 5766–5771.

Table II. Equilibrium Constants for Interconversion of Substituted 1-Phenylethyl Alcohols and Ethers in H₂O/TFE/ROH (90:9:1 v/v/v)^a

phenyl substituent	ROH	K ₁	K ₂	K ₃
4-OCH ₃	EtOH	13	1.2	11
		14	1.4	10
	CH ₃ OEtOH	10	1.4	7.2
		9	1.2	7.6
		14	1.4	9.6
		13	1.5	8.8
	ClEtOH	7.4	1.5	4.8
		6.6	1.6	4.2
		8.1	1.6	5.1
	Cl ₂ EtOH	2.3	1.5	1.6
		2.9	1.5	1.8
	MeOH	24	1.3	18
		12	1.7	7.0
	CH ₃ CH ₂ CH ₂ OH	11	1.4	7.5
13		1.4	9	
ClCH ₂ CH ₂ CH ₂ OH	13	1.4	9	
	13	1.3	11	
CH ₃ (CH ₂) ₃ OH	14	1.2	11	
	14	1.2	11	
CF ₃ CH ₂ OH	1.4	1.4	1.0	
	1.4	1.4	1.0	
4-NH(CH ₃) ₂ ⁺	EtOH	12	1.1	11
		12	1.1	11
	CH ₃ OEtOH	9.5	1.0	9.4
		9.2	1.0	9.1
	ClEtOH	6.1	1.1	5.4
		6.0	1.1	5.7
	MeOH	22	1.0	22
		23	1.1	21
	CH ₃ (CH ₂) ₃ OH	8.7	1.1	7.7
		11	1.1	9.8
CF ₃ CH ₂ OH	1.1	1.1	1.0	
	1.1	1.1	1.0	
4-OCH ₃ -3-NO ₂	EtOH	13	0.7	18
	CF ₃ CH ₂ OH	0.7	0.7	1.0

^a At 25 °C, ionic strength maintained at 0.5 with NaClO₄.**Table III.** Structure-Reactivity Parameters for K₁ and K₃^a

phenyl substituent	∑σ ^{n,b}	β ¹ _{equil}	β ³ _{equil}
4-N(CH ₃) ₂	-0.22	0.17	0.18
4-OCH ₃	-0.13	0.20	0.20
4-OCH ₃ -3-Br	0.26	0.23	0.23
4-NH(CH ₃) ₂ ⁺	0.56 ^c	0.25	0.26
4-OCH ₃ -3-NO ₂	0.58	0.26	0.27
ROH	pK _a ^d	ρ ¹ _{equil}	ρ ³ _{equil}
EtOH	16.0	-0.02	0.35
MeOH	15.5	-0.08	0.26
CH ₃ OEtOH	14.8	-0.03	0.33
ClEtOH	14.3	-0.10	0.26
HC≡CCH ₂ OH	13.6	-0.14	0.15
Cl ₂ EtOH	12.9	-0.22	0.11
CF ₃ CH ₂ OH	12.4	-0.37	0

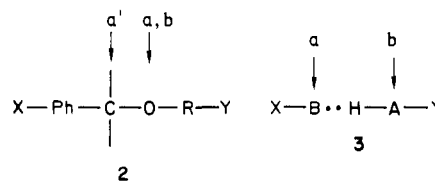
^a In H₂O/TFE/ROH (50:45:5 v/v/v) at 25 °C, ionic strength 0.5 maintained with sodium perchlorate. Calculated from the original data, using three significant figures. ^b Reference 7, pp 66–72. ^c Reference 14. The contribution of the Bjerrum field term, δ^B, is small at μ = 0.5 and is neglected. ^d Ballinger, P.; Long, F. A. *J. Am. Chem. Soc.* **1959**, *81*, 1050–1053; **1960**, *82*, 795–798.

framework of the two systems is different. The two coefficients may be compared in two ways.

(1) The ρσ and β-pK_a scales may be interconverted by using the value of ρ = 1.1 for the acid dissociation of trifluoroacetophenone hydrates²⁰ and protonated benzylamines.²¹ This shows

(20) Stewart, R.; Van der Linden, R. *Can. J. Chem.* **1960**, *38*, 399–406.

that the development of charge at position a of 1-arylethyl ethers, 2, may be measured by ΔpK = 1.1 Δσ. This gives τ = 0.10/1.1



= 0.09 for this system if the polar substituents X are calibrated by their effects on charge development at position a as measured by pK_a. The effects of polar substituents Y are calibrated by the pK_a of the alcohol YROH, which is a measure of charge development at position b of 2.

The effects of polar substituents on the stability of hydrogen bonds are calibrated by their effects on charge development at positions a and b of 3, as measured by the pK_a values of YAH and XB. The positions a and b in a hydrogen bond are separated by 2.8–3.0 Å, which is approximately twice the C–C bond distance of 1.54 Å.^{22,23} The attenuation factor for dipole–dipole interactions is not known, but a value of 0.4 may be estimated from a value of 0.5 for pole–dipole interactions and an equation described by Hine, using exponents of 3 and 2, respectively, for the dependence of the two kinds of interactions upon distance.²⁴ This gives a corrected value of τ = 0.4 × 0.4 × 0.09 = 0.014, which may be compared with an estimated value of τ = 0.013²⁵ and a measured value of τ = 0.014 for hydrogen bonding in water.²⁶ The agreement is better than might have been expected, in view of the approximations in the calculation.

(2) The ρ value for the effect of substituents X on charge development at position a of 1-arylethyl ethers, 2, may be converted to the β-pK_a scale by using values of ρ = 2.7 for the dissociation of phenols in 49% EtOH, ρ = 2.5 for thiophenols in 49% EtOH, and ρ = 3.0 for anilinium ions in 50% ethanol.²⁷ A value of ρ = 2.7 gives ΔpK = 2.7Δσ and τ = 0.10/2.7 = 0.037, based on the pK_a scale. In 1-arylethyl ethers the interacting groups are separated by the covalent C–O bond, 1.43 Å.²³ Correction for the additional 1.37–1.57 Å separation in the hydrogen bond, using the fall-off factor of 0.4 for the 1.54-Å distance of the C–C bond, gives τ = 0.015. This agrees with the above estimate.

Water vs. Alcohols. The replacement of water by an alcohol in the 1-phenylethyl system at equilibrium is favored by large factors of 52–74 for methanol and 30–37 for ethanol (Table I). Similar factors of up to 73 for methanol and 47 for ethanol favor the rate constants for addition of alcohols compared with water to 1-arylethyl carbocations, although the selectivity decreases with increasing reactivity of the carbocation.¹⁰ Analogous behavior has been observed for many other systems, but the differences are usually smaller when electron-withdrawing substituents are present in the compound undergoing substitution.¹³ For example, replacement of water by alcohol in pyridine-4-aldehyde hydrate is favored by 20-fold for methanol and 10-fold for ethanol.²⁸ In the 1-phenylethyl system the behavior of water is not very different

(21) Blackwell, L. F.; Filscher, A.; Miller, I. J.; Topsom, R. D.; Vaughan, J. *J. Chem. Soc.* **1964**, 3588–3591.

(22) Pimentel, G. C.; McClellan, A. L. "The Hydrogen Bond"; W. H. Freeman and Co.: San Francisco, 1960; p 289.

(23) Hine, J. S. "Physical Organic Chemistry", 2nd ed.; McGraw-Hill: New York, 1962; p 28.

(24) The average attenuation factor for a CH₂ group is 0.53, based on ionization constants of substituted phenylacetic and phenylpropionic acids in 10, 50, and 75% ethanol and rate constants for alkaline hydrolysis of the corresponding ethyl esters (Hoefnagel, A. J.; Wepster, B. M. *J. Am. Chem. Soc.* **1973**, *95*, 5357–5366). Conversion from a pole–dipole to a dipole–dipole interaction gives an attenuation factor of 0.39, using an equation proposed by Hine (ref 7, p 96).

(25) Funderburk, L. H.; Jencks, W. P. *J. Am. Chem. Soc.* **1978**, *100*, 6708–6714.

(26) Stahl, N.; Jencks, W. P., in preparation.

(27) Wells, P. R. *Chem. Rev.* **1963**, *63*, 171–219. The dielectric constants of ethanol and trifluoroethanol are almost identical (Mukherjee, L. M.; Grunwald, E. *J. Phys. Chem.* **1958**, *62*, 1311–1314). Ehrenson, S.; Brownlee, R. T. C.; Taft, R. W. *Prog. Phys. Org. Chem.* **1973**, *10*, 1–80.

(28) Sander, E. G.; Jencks, W. P. *J. Am. Chem. Soc.* **1968**, *90*, 6154–6162.

from that of trifluoroethanol for both rate¹⁰ and equilibrium constants; at equilibrium the trifluoroethyl ether is only 3-9 times more stable than the alcohol in the 50% aqueous solvent and is equally stable in 90% water.

This behavior may be described in terms of a relatively large carbon basicity of RO⁻ compared with HO⁻.¹⁵ The reason for this is not clear to us, although it is possible that dispersion interactions stabilize the ether compared with the phenylethyl and aliphatic alcohols. It is not simply a hydrophobic effect, because ether formation is *less* favorable when the water content of the solvent is increased (Tables I and II). It is conceivable that it involves solvophobic interactions with both the fluorocarbon component of the solvent²⁹ and water.

Registry No. EtOH, 64-17-5; CH₃O(CH₂)₂OH, 109-86-4; Cl(C₂H₅)₂OH, 107-07-3; Cl₂CHCH₂OH, 598-38-9; MeOH, 67-56-1; HC≡CCH₂OH, 107-19-7; CF₃CH₂OH, 75-89-8; Me₂N-*p*-C₆H₄CH(OH)-CH₃·HClO₄, 94670-01-6; CH₃(CH₂)₃OH, 71-36-3; CH₃(CH₂)₂OH, 71-23-8; Cl(CH₂)₃OH, 627-30-5; Me₂N-*p*-C₆H₄CH(CH₃)OEt·HClO₄, 94670-03-8; Me₂N-*p*-C₆H₄CH(CH₃)O(CH₂)₂OMe·HClO₄, 94670-05-0; Me₂N-*p*-C₆H₄CH(CH₃)O(CH₂)₂Cl·HClO₄, 94670-07-2; Me₂N-*p*-C₆H₄CH(CH₃)OCH₂CHCl₂·HClO₄, 94670-09-4; Me₂N-*p*-C₆H₄CH-

(CH₃)OMe·HClO₄, 94670-11-8; Me₂N-*p*-C₆H₄CH(CH₃)OCH₂≡CH·HClO₄, 94670-13-0; Me₂N-*p*-C₆H₄CH(CH₃)O(CH₂)₃CH₃·HClO₄, 94670-15-2; Me₂N-*p*-C₆H₄CH(CH₃)O(CH₂)₂CH₃·HClO₄, 94670-17-4; Me₂N-*p*-C₆H₄CH(CH₃)O(CH₂)₃Cl·HClO₄, 94670-19-6; MeO-*p*-C₆H₄CH(CH₃)OH, 3319-15-1; MeO-*p*-C₆H₄CH(CH₃)OEt, 67233-95-8; MeO-*p*-C₆H₄CH(CH₃)O(CH₂)₂OMe, 94670-20-9; MeO-*p*-C₆H₄CH(CH₃)O(CH₂)₂Cl, 94670-21-0; MeO-*p*-C₆H₄CH(CH₃)OCH₂CHCl₂, 94670-22-1; MeO-*p*-C₆H₄CH(CH₃)OMe, 77525-91-8; MeO-*p*-C₆H₄CH(CH₃)OCH₂C≡CH, 94670-23-2; MeO-*p*-C₆H₄CH(CH₃)O(CH₂)₃Cl, 94670-24-3; Me₂N-*p*-C₆H₄CH(CH₃)OH, 5338-94-3; Me₂N-*p*-C₆H₄CH(CH₃)OEt, 94670-02-7; Me₂N-*p*-C₆H₄CH(CH₃)O(CH₂)₂OMe, 94670-04-9; Me₂N-*p*-C₆H₄CH(CH₃)O(CH₂)₂Cl, 94670-06-1; Me₂N-*p*-C₆H₄CH(CH₃)OMe, 94670-10-7; Me₂N-*p*-C₆H₄CH(CH₃)O(CH₂)₃CH₃, 94670-14-1; Me₂N-*p*-C₆H₄CH(CH₃)OCH₂CF₃·HClO₄, 94670-30-1; MeO-*p*-C₆H₄CH(CH₃)OCH₂CF₃, 94670-31-2; Me₂N-*p*-C₆H₄CH(CH₃)OCH₂CF₃, 94670-29-8; 1-(4-methoxy-3-nitrophenyl)ethanol, 67223-02-3; 1-(4-methoxy-3-nitrophenyl)ethyl ether, 94669-95-1; 1-(4-methoxy-3-nitrophenyl)ethyl 2-methoxyethyl ether, 94669-96-2; 1-(4-methoxy-3-nitrophenyl)ethyl 2-chloroethyl ether, 94669-97-3; 1-(4-methoxy-3-nitrophenyl)ethyl 2,2-dichloroethyl ether, 94669-98-4; 1-(4-methoxy-3-nitrophenyl)ethyl methyl ether, 94669-99-5; 1-(4-methoxy-3-nitrophenyl)ethyl prop-2-yn-1-yl ether, 94670-00-5; 3-bromo- α -methyl-4-methoxybenzenemethanol, 94670-25-4; 1-(3-bromo-4-methoxyphenyl)ethyl ether, 94670-26-5; 1-(3-bromo-4-methoxyphenyl)ethyl methyl ether, 94670-27-6; 1-(4-methoxy-3-nitrophenyl)ethyl 2,2,2-trifluoroethyl ether, 94670-28-7; 1-(3-bromo-4-methoxyphenyl)ethyl 2,2,2-trifluoroethyl ether, 94670-32-3.

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Preparation and Dimerization of 1,2,4,6-Thiatriazinyl Radicals: Crystal and Molecular Structure of Bis(3,5-diphenyl-1,2,4,6-thiatriazine)

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Contribution from the Guelph Waterloo Centre for Graduate Work in Chemistry, Guelph Campus, Department of Chemistry and Biochemistry, University of Guelph, Guelph, Ontario, N1G 2W1 Canada, and the Department of Chemistry, University of Arkansas, Fayetteville, Arkansas 72701. Received September 7, 1984

Abstract: The reduction of Ph₂C₂N₃SCI, prepared from the reaction of benzamidine with S₃N₃Cl₃, with triphenylantimony yields the 3,5-diphenyl-1,2,4,6-thiatriazinyl radical Ph₂C₂N₃S·, whose ESR signal in CH₂Cl₂ consists of a seven-line pattern with equal hyperfine coupling constants to all three nitrogen atoms ($a_N = 0.397$ mT, $g = 2.0059$). In the solid state the radical forms a dimer, whose crystal structure has been determined by X-ray diffraction. Crystals of (Ph₂C₂N₃S)₂ are triclinic, space group *P*1̄, $a = 8.894$ (3) Å, $b = 11.058$ (3) Å, $c = 12.814$ (5) Å, $\alpha = 81.76$ (2)°, $\beta = 86.75$ (3)°, $\gamma = 76.00$ (2)°, $V = 1209.9$ Å³, and $Z = 2$. The structure was solved by direct methods and refined by Fourier and full-matrix least-squares techniques to give a final $R = 0.050$ and $R_w = 0.056$ for 1125 reflections with $I > 2\sigma I$. The solid-state structure of the dimer consists of a pair of cofacial Ph₂C₂N₃S rings with a dihedral angle of 14° between their respective mean planes. The closest interring contact is between two sulfur atoms (2.666 (3) Å). The electronic structures of the radical and the dimer are discussed in the light of MNDO molecular orbital calculations on related model compounds.

The possibility of emulating the electronic properties of the (SN)_x polymer² by incorporating carbon atoms into conjugated sulfur-nitrogen chains has provided a stimulus for research in organothiazyl chemistry. As a result the preparation and characterization of a variety of novel heterocyclic thiazyl compounds have recently been reported.³⁻⁸ In principle at least these com-

pounds combine the structural stability of carbocyclic π systems with the interesting redox properties of sulfur-nitrogen linkages. In this latter context the generation of planar ring systems which can exist in a variety of stable oxidation states (cation, anion, and radical) is a particularly appealing target. The importance of such

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