of the B molecule, its distance from the hydroxyl oxygen is only 3.01 Å. The very slow rate of reaction observed may be due in part to the difficulty of redirecting the hydrogen bond from the carbonyl to the hydroxyl oxygen even though the distance appears short. An experiment in which initiation of the reaction was assisted by a little finely ground *p*-toluenesulfonic acid hydrate placed next to one of the end faces of the crystal of **1** did indeed accelerate the beginning of reaction, but the acceleration decreased as the reaction front moved away from the region of the crystal near the external acid.

In Figure 5 is shown the structural relationship between the starting material **1** and product **2** in the conformations found in their respective crystal structures. It will be noted that the conformation of **1** is not far removed from that required for a syn elimination about the N(1)-C(2) bond, insofar as the positions of C(1), C(3), and N(1) are concerned. The *HO*-C(2)-N(1)-*H*(N) dihedral angle is 36°. A major change in molecular shape is required during the elimination reaction because the indandione skeleton has to move into the plane of the C(2)=N(1) double bond.

Since no other studies of this type are available for comparison, the analysis of factors controlling rates of such reaction must await further experimental results. It appears that, with the present state of advance of x-ray crystallography and physical organic chemistry, this kind of study may open up a new area of solid-state organic chemistry.

Acknowledgment. We thank Dr. Karen Chiang, Miss Mary K. Greensley, and Mrs. Patti Eckert for their help in preparing the manuscript.

Supplementary Material Available: a listing of the observed and calculated structure factors (19 pp). Ordering information is given on any current masthead page.

References and Notes

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Proton Exchange in Benzyl Alcohols. Acid, Base, Intramolecular, and Bifunctional Catalyses

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Abstract: Acid, base, intramolecular, and bifunctional catalysis of OH proton exchange of benzyl alcohols in Me_2SO and benzene have been detected by DNMR methods. Base-catalyzed exchange in Me_2SO involves displacement of a solvation molecule from the alcohol followed by formation of ionic intermediates. Strong bases with respect to full proton removal are good catalysts, whereas strong hydrogen-bonding bases impede exchange. *n*-Butylamine in benzene appears to be able to exchange via a proton removal-delivery mechanism within an ion pair. Imidazole (but not 1-methylimidazole) catalyzes exchange by means of a process which is second order in amine. Phenols also catalyze exchange. The ortho hydroxy group of *o*-hydroxybenzyl alcohol is a powerful intramolecular catalyst for base-catalyzed (but not acid-catalyzed) exchange of the benzylic hydroxyl proton. By far the most effective intermolecular catalyst discovered was a combination of amine and amine salt. Thus, the monoperchlorate salt of *N,N,N',N'*-tetramethylethylenediamine is a 10^4 better catalyst than the free diamine. The efficiency of the monosalt probably stems from a concerted acid-base mechanism which averts charge formation.

Bioorganic mechanisms have progressed to a stage where they possess an awesome (and perhaps uncomely) complexity.[2,3] These mechanisms incorporate detailed descriptions of proton transfers from complicated intermediates of fleeting existence and uncertain structure. This is not to detract from the ingenuity of much bioorganic thought; considering the inherent limitations of chemical kinetics, the progress made with multistep processes has been remarkable. The present paper departs from current format. Rather than speculating about a catalyzed proton transfer from the hy-

droxyl of an unstable intermediate, we focus on the proton transfer of an ordinary alcohol. How is the proton exchange affected by acid-base catalysts? Bifunctional catalysts? Steric effects? Solvation? Answers to these and related questions are necessary to understand proton transfers which are coupled to formation and cleavage of carbon bonds.

We have measured the rates of OH proton exchange of benzyl alcohols using dynamic NMR methods. When proton exchange is slow relative to the NMR time scale, the methylene proton signal appears as a doublet owing to coupling with the OH proton. When OH proton exchange is fast, the spin-spin splitting vanishes, yielding a methylene singlet. At intermediate rates of exchange, the methylene signal is either a partially resolved doublet or a broadened singlet; these line shapes provided us with observed rate constants in the $1-10^2$ sec^{-1} range.

Alcohols in $CDCl_3$ or CCl_4 may not always manifest H-C-O-H splitting unless the solvent has been carefully purified.[4] Acidic or basic impurities render exchange too fast for NMR measurement. However, splitting can often be detected with alcohols dissolved in dimethyl sulfoxide because Me_2SO strongly hydrogen bonds to the OH proton and impedes its exchange.[5,6] This article is concerned with how various intermolecular and intramolecular catalysts affect the methylene multiplicity of benzyl alcohols in Me_2SO. Although aqueous solutions might have been preferable from the point of view of a bioorganic chemist, we do not feel that use of a polar aprotic solvent seriously detracts from the relevance of the catalytic pathways developed in this article.[7,8]

Experimental Section

Materials. Benzyl alcohol (Aldrich Gold Label, 99+%) was distilled under vacuum through a 20-cm vacuum-jacketed Vigreux column. *o*-Aminobenzyl alcohol (Aldrich, 98%) was sublimed twice. *o*-Hydroxybenzyl alcohol (Aldrich, 97%) was crystallized twice, dried under vacuum, and sublimed. *p*-Chlorobenzyl alcohol (Aldrich, 99%) was sublimed at 55° and 3.5 mm.

n-Butylamine (Fisher reagent grade) was dried over KOH pellets and distilled through a spinning-band column. Triethylamine (Aldrich, 99%) was boiled under reflux with acetic anhydride for 3 hr and distilled. The material was redistilled over KOH twice, once with a Vigreux column and once with a spinning-band column. The hydrochloride salts of *n*-butylamine and triethylamine were prepared by passing HCl gas through ether solutions of the amines. The salts were recrystallized and carefully dried. Imidazole (Aldrich, 99%) was sublimed twice. 1-Methylimidazole (Aldrich, 99%) was purified by distillation over Na and a second time without Na. Aniline (Fisher reagent grade) was dried over KOH and distilled. The middle cut was redistilled over a small amount of Zn dust. 3-Dimethylaminopropylamine (Aldrich, 99%) was distilled over calcium hydride through a spinning-band column.

N,N,N',N'-Tetramethylethylenediamine (Aldrich, 99%) was purified by distillation from KOH. The monoperchlorate salt of this amine was prepared as follows. A solution of diamine (2.27 g, 0.0195 mol) in 25 ml of dried methanol was placed in a 100-ml flask equipped with a dropping funnel. Perchloric acid (2.738 g of 71% acid, 0.0193 mol) in 10 ml of methanol was added dropwise over 10 min while the reaction mixture was stirred magnetically. After 3 hr additional stirring, the solvent was removed and the residue crystallized twice from absolute ethanol. The monoperchlorate salt was dried over P_2O_5 under reduced pressure (0.1 min) for 3 days at 25°.

Phenol (Aldrich, zone refined, 99.9+%) was used as received. *p*-Nitrophenol was recrystallized twice and sublimed twice. Benzene (Fisher Spectranalyzed grade) was dried over Na wire and distilled over $LiAlH_4$.

The dimethyl sulfoxide used for the majority of kinetic runs was Fisher reagent grade material (0.10% water) which was dried over KOH pellets and fractionally distilled twice over calcium hydride at reduced pressures. The solvent was stored under nitrogen away from light.

Boiling points or melting points of the above compounds agreed with literature values.

Kinetics.[9a] The procedure is given here for one particular substrate and catalyst and is typical of that which we used throughout. Two stock solutions were prepared and stored under nitrogen: 0.20 *M* benzyl alcohol in Me_2SO and 0.20 *M* benzyl alcohol-0.020 *M* *n*-butylamine in Me_2SO. They were mixed in various ratios to prepare solutions 0.002-0.02 *M* in amine and 0.20 *M* in benzyl alcohol. Generally, solutions were used within 1 or 2 days of preparation, although there did not seem to by any detectable deterioration even after 2 weeks or more.

All NMR spectra were obtained with a Jeol JNM-MH-100 spectrometer equipped with a thermostated probe set at 25.0 ± 0.7° (as measured by the method of Van Geet[9b]). Samples were allowed to come to temperature within the probe for at least 15 min. The resolution was then optimized by adjusting the homogeneity control while observing a sharp peak which is not affected by exchange (e.g., the phenyl proton signal of benzyl alcohol). The methylene signal of benzyl alcohol was traced six to ten times using the following settings: rf field, 0.1 mG; filter bandwidth, 10 Hz; sweep time, 250 sec; sweep width, 54 Hz. Samples were examined randomly rather than with a uniformly increasing or decreasing *n*-butylamine concentration. A series of runs was always completed in one sitting during which the probe temperature was checked periodically.

Observed rate constants were calculated using a computer program which varied τ (the reciprocal of k_{obsd}) such that the line width at half-height of a singlet or the peak-to-valley ratio of a doublet (averaged from the six to ten tracings) fit that of a theoretical spectrum. The program required the input of two static NMR parameters which were determined prior to each series of runs: the CH_2-O-H coupling constant, J, and the "natural" line width, $W_{1/2}$. The former was measured with a 0.20 *M* benzyl alcohol solution in Me_2SO containing no amine ($J = 5.7 \pm 0.1$ Hz). The latter was obtained with the aid of a mixture of 0.20 *M* benzyl alcohol and 1.23 *M* *n*-butylamine in Me_2SO ($W_{1/2} = 0.90$-1.20 Hz). When fast exchange could not be achieved with the catalyst and substrate under investigation, we used a sample consisting of the same substrate but a more powerful catalyst (usually *n*-butylamine).

Experimental Error. The accuracy of the data is limited by the usual assumption of a Lorentzian line shape, by the uncertainty in the effective relaxation time, T_2 (obtained from the natural line width), and by the uncertainty in the probe temperature. The error in k_{obsd} is estimated to be ±15%. Repeat runs with benzyl alcohol and *n*-butylamine in Me_2SO performed at six-month intervals agreed to within 8%. The catalysts and solvent in these repeat runs were from different batches. Repeat runs carried out by two different people also agreed well.

Results and Discussion

Our first concern was to determine the sensitivity of the system to impurities. We found that the rates of the *n*-butylamine-catalyzed proton exchange of benzyl alcohol in two different Me_2SO samples (one purifed with calcium hydride, the other with molecular sieve) differed by less than 5%. Moreover, "out of the bottle" Me_2SO and purified Me_2SO gave rate constants agreeing to within 20%. Saturating the Me_2SO with air instead of N_2 changed the rate 20%, barely larger than the experimental error. The effect of added water on the kinetics was complex and depended on the nature of the catalyst: the weaker the catalyst, the greater the enhancement by water. But even with a relatively weak catalyst, such as triethylamine, the perturbation by water was not substantial. Thus, addition of 0.011 *M* water to 0.20 *M* triethylamine and 0.20 *M* benzyl alcohol in Me_2SO increased the exchange rate threefold. This was not serious because the water content of purified Me_2SO is much less than 0.01 *M* and because no mechanistic conclusion in this paper is based on a small rate difference. As will be described shortly, impurities were in fact a problem with

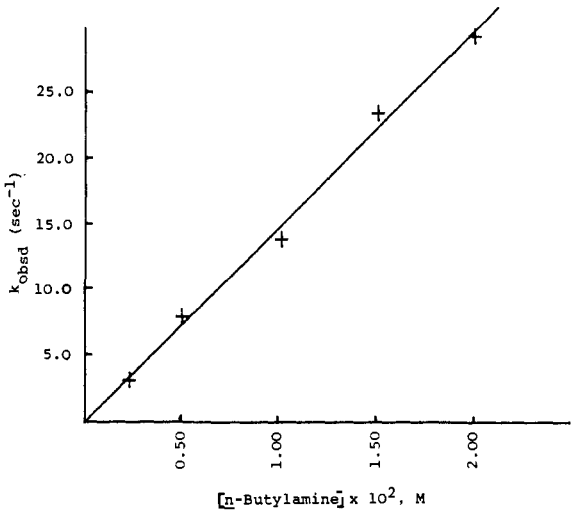


Figure 1. Plot of observed rate constants vs. concentration of *n*-butylamine for proton exchange of 0.20 *M* benzyl alcohol in Me_2SO at 25.0°.

highly reactive substrates such as *o*-hydroxybenzyl alcohol. On the other hand, benzyl alcohol (the primary substrate in this study) behaves ideally; it is reactive enough to respond to reasonable concentrations of catalysts, and yet it is sufficiently inert not to be affected by trace impurities.

We present below the major observations and their significance. Since far too many rate constants have been collected to include in a single article, we will merely summarize the results, cite specific values where appropriate, and refer the interested reader elsewhere[10] for complete listings of raw rate data.

(1) The rate of proton exchange of 0.20 *M* benzyl alcohol in Me_2SO at 25.0° shows a first-order dependency on *n*-butylamine and triethylamine. For example, a plot of k_{obsd} vs. [*n*-butylamine] is linear and has a zero intercept (Figure 1). Elevating the benzyl alcohol concentration from 0.20 to 0.40 *M* modifies the slope by only 17%, proving that alcohol-alcohol interactions are of little consequence at 0.20 *M* where most of the runs were performed. The exchange reaction is described by a simple rate equation (eq 1), where k_1

$$k_{obsd} = k_1[\text{catalyst}] \quad (1)$$

values for *n*-butylamine and triethylamine are 1.5×10^3 and 16 M^{-1} sec^{-1}, respectively. 3-Dimethylaminopropylamine, a diamine with a $k_1 = 1.6 \times 10^3$ M^{-1} sec^{-1}, possesses no special catalytic activity over and beyond that of an aliphatic primary amine.

(2) Pyridine, aniline, *N,N*-dimethylacetamide, and *N*-methylacetamide in Me_2SO possess no catalytic activity (i.e., do not perturb the methylene doublet) at concentrations below 0.8 *M*.[11] These results nicely illustrate the distinction between two classes of bases: the strong hydrogen-bonding bases and the strong proton acceptors. Amides, Me_2SO, etc., are good hydrogen-bonding bases but weak bases with respect to ion-pair formation (pK_{HB} values[12] are large and Δ values[13] are small). Members of this family impede exchange. Aliphatic amines, which are strong bases with respect to *full* proton removal (Δ values are large[13]), catalyze the exchange. We conclude that the base-catalyzed exchange involves ionic intermediates.

(3) *p*-Chlorobenzyl alcohol exchanges its proton five times faster than benzyl alcohol in Me_2SO solutions of *n*-butylamine ($k_1 = 7.2 \times 10^3$ M^{-1} sec^{-1}). This sensitivity to an electron-withdrawing substituent, corresponding to a $\rho = 3.1$, points further to formation of an oxygen bearing a substantial negative charge.

(4) Large rate enhancements were observed when the solvent was changed from Me_2SO to benzene. Thus, the k_1's for benzyl alcohol catalyzed by *n*-butylamine and triethylamine are about factors of 76 and 43 larger in benzene than in Me_2SO, respectively. Even aniline is a weak catalyst in benzene ($k_1 = 31$ M^{-1} sec^{-1} at 25.0°). This may seem surprising since we have argued above for the presence of ionic intermediates; formation of ionic species would be impeded in nonpolar solvents such as benzene. However, benzyl alcohol is tightly solvated in Me_2SO, and the catalyzing base must displace a solvent molecule prior to proton removal (eq 2). The preequilibrium should be more favorable in ben-

$$ROH\cdots Me_2SO + NH_2R \overset{K}{\rightleftharpoons} ROH\cdots NH_2R \xrightarrow{k_i} RO^{-}\overset{+}{H}NH_2R \quad (2)$$

zene, a weakly hydrogen-bonding solvent, than in Me_2SO. Apparently, this factor overrides the presumed retardation of the ionization step, k_i, in benzene.

One qualifying note should be mentioned with regard to proton exchange in benzene. The reaction is fast and sensitive to impurities; hence we confined our studies to a few experiments sufficient to provide an estimate of the solvent dependency of the proton exchange. We also shied away from benzene because we were uncertain how self-associated alcohol species, which are certainly present in benzene,[14] would perturb the kinetics. Since k_1 for *n*-butylamine is invariant with benzyl alcohol concentration ($k_1 = 1.13 \times 10^5$ M^{-1} sec^{-1} and 1.20×10^5 M^{-1} sec^{-1} at 0.20 *M* and 0.39 *M* benzyl alcohol, respectively), formation of hydrogen-bonded complexes may not be serious. The only hint of a problem in the benzene systems was noted with triethylamine whose linear k_{obsd} vs. [amine] plot had a small intercept; the origin of this deviation from normalcy is not clear.

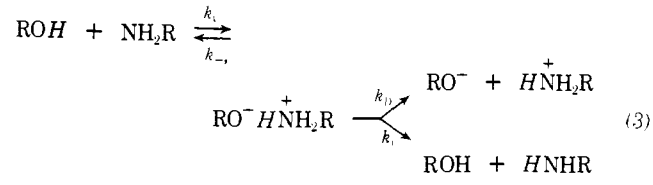
We have depicted the intermediate in eq. 2 as an ion pair although there is no evidence bearing on the degree of separation between the anion and cation. A more important issue relates to the source of the new proton which ultimately replaces the original one. Two pathways are possible with exchange reactions catalyzed by *primary* or *secondary* amines: (1) proton interchange between amine and alcohol may occur within an initially formed ion-pair; (2) the new proton may be derived from a species other than the base molecule responsible for abstracting the proton. This could happen in several ways. For example, two ion pairs may exchange their alkylammonium ions prior to proton delivery,[15] or the ion pairs could dissociate completely. In any event, *tertiary* amine catalysts must operate exclusively by mechanism 2 because they possess no labile proton of their own. Evidence that primary amines also function by the second pathway lies in the fact that k_1 for *n*-butylamine in Me_2SO is only 94 times larger than k_1 for triethylamine in Me_2SO. Since *n*-butylamine is 3.0 pK_a units more basic than triethylamine in Me_2SO,[16] the k_1 ratio is adequately explained by the greater basicity of *n*-butylamine. In other words, the lack of a special catalytic activity of *n*-butylamine in Me_2SO precludes the need to ascribe to the primary amine a mechanism not available to the tertiary amine.

The situation is different with proton exchange in benzene. *n*-Butylamine is a 170-fold better exchange catalyst than triethylamine despite triethylamine being more basic in nonpolar solvents. Thus, log *K* for formation of 1:1 salts composed of amine and acetic acid in CCl_4 is 0.12 unit larger for triethylamine than *n*-butylamine.[17] Even in acetonitrile the pK_a of triethylamine is 0.20 unit larger than that of *n*-butylamine.[18] The fast *n*-butylamine reaction can be explained by the first of the two mechanisms mentioned in the

Table I. Observed Rate Constants for the Imidazole-Catalyzed Proton Exchange of 0.20 M Benzyl Alcohol in Me_2SO at 25°

[Imidazole], M	k_{obsd}, sec^{-1}	[Imidazole], M	k_{obsd}, sec^{-1}
0.091	2.6	0.334	22
0.167	6.5	0.400	32
0.200	9.4	0.500	54

preceding paragraph: n-butylamine molecules return protons to the same alcohol from which they abstracted a proton (k_r step in eq. 3). Since proton return from tertiary ammonium ions within an ion pair is necessarily nonproductive ($k_r = 0$), triethylamine must exchange by a different and slower process. Conceivably, the alkoxide captures a new proton after ion pair dissociation (k_D in eq. 3) or after ion-pair interchange,[15] but we question the likelihood of these reactions in a nonpolar solvent.[19] The most attractive mechanism for triethylamine-catalyzed exchange in benzene involves an ion-paired alkoxide abstracting a proton from another alcohol molecule. Self-association of alcohols in benzene would promote such a transfer. This entire rationale is speculative (based on only two amines and two solvents) but reasonable. Nonpolar benzene favors formation of tight ion pairs; proton removal-and-delivery by one and the same n-butylamine molecule is enhanced in benzene relative to that in a dissociating solvent. Of course, in order for k_r to be kinetically significant, k_{-1} in eq 3 must be large, i.e., $k_{-1} \gg (k_D + k_r)$.

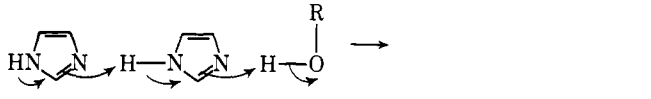


(3)

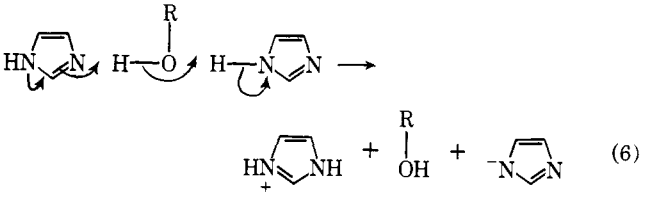
(5) Imidazole-catalyzed proton exchange of benzyl alcohol in Me_2SO displays both first- and second-order imidazole terms (eq 4, Table I).[20]

$$k_{obsd} = k_1[Im] + k_2[Im]^2 \quad (4)$$

From the linear plot of $k_{obsd}/[imidazole]$ vs. [imidazole], we calculated that $k_1 = 4.7\ M^{-1}\ sec^{-1}$ and $k_2 = 2.0 \times 10^2\ M^{-2}\ sec^{-1}$ at 25.0°. This means that at 0.50 M imidazole 96% of the reaction proceeds by the k_2 mechanism. In contrast, 1-methylimidazole-catalyzed exchange is purely first order in amine with a $k_1 = 5.5\ M^{-1}\ sec^{-1}$. Obviously the k_2 process of imidazole requires the presence of an NH proton, a fact consistent with several kinetically equivalent mechanisms, two of which are shown in eq 5 and 6. In an attempt



(5)



(6)

to distinguish the two mechanisms, we examined the imidazole-catalyzed proton exchange of p-chlorobenzyl alcohol. If eq 4 is correct, then the relatively acidic p-chlorobenzyl alcohol should react much faster than its unsubstituted counterpart (as it did with n-butylamine). If eq 5 is correct, then the favorable acidity change should be compensated in part by the decreased basicity of the alcohol oxygen, and the overall enhancement in k_2 could be small. This experiment was foiled by our finding that the imidazole-catalyzed exchange of p-chlorobenzyl alcohol possesses no second-order term. Remarkably, the k_1 value is 260 times larger than that of benzyl alcohol (corresponding to a $\rho = 11$). Likewise, 1-methylimidazole reacts 130 times faster with p-chlorobenzyl alcohol than it does with benzyl alcohol. Although the details of the k_2 mechanism remain uncertain, there is little doubt that the transition state of the k_1 process entails considerable charge separation. Furthermore, the similarity of k_1 for imidazole and 1-methylimidazole suggests that a single imidazole molecule does not serve the dual role of proton acceptor and proton donor.[21]

(6) Proton exchange in benzyl alcohol is subject to acid catalysis as well as base catalysis.[22] The rate increases linearly with phenol concentration (0.20–2.0 M), yielding a $k_1 = 10\ M^{-1}\ sec^{-1}$. p-Nitrophenol, 3 pK_a units stronger an acid than phenol, is only a fivefold more powerful catalyst than phenol. The relative ineffectiveness of acid catalysis probably stems from the catalysts themselves being strongly solvated by the Me_2SO.[23]

One of the more interesting observations of this work is the unusual reactivity of o-hydroxylbenzyl alcohol. Even when no catalyst is present, the methylene signal *is* a sharp singlet in Me_2SO (but not so in benzene, acetone, or dioxane).[24] The best explanation is that the substrate is particularly reactive and sensitive to a catalytic impurity in the Me_2SO. The impurity is believed to be a base for the following reason. Upon addition of extremely small amounts of an acid, p-nitrophenol, the rate *decreases* (i.e., the singlet separates into a doublet). As more p-nitrophenol is added, the rate reverses and increases linearly with p-nitrophenol, as would be expected for a typical acid-catalyzed exchange. The k_1 corresponding to this linear increase equals $65\ M^{-1}\ sec^{-1}$, quite similar to that for benzyl alcohol. By first neutralizing the basic impurity with p-nitrophenol, we managed to obtain a crude estimate of the triethylamine-catalyzed exchange of o-hydroxybenzyl alcohol. Thus, varying amounts of triethylamine were added to solutions 0.20 M in substrate and $3 \times 10^{-4}\ M$ in p-nitrophenol. The k_{obsd} vs. [triethylamine] plot, which was linear except for an initial convex region below $1.0 \times 10^{-4}\ M$ amine, yielded a k_1 value of $4.6 \times 10^4\ M^{-1}\ sec^{-1}$. This is three orders of magnitude larger than the k_1 for benzyl alcohol plus triethylamine. Despite the devious manner in which the rate constants were obtained, it is clear that the ortho hydroxyl group greatly accelerates base-catalyzed exchange but has virtually no effect on acid-catalyzed exchange. In the base-catalyzed process, either the phenolic OH group serves as an intramolecular general acid (eq 7), or else phenoxide assists in the removal of the benzylic OH proton (eq 8). We lean toward the general acid mechanism because in the next and final section we demonstrate the efficiency of joint acid–base catalysis.

(7) We have shown that both acids and bases catalyze proton exchange. How would proton exchange respond to the presence of *both* an acid and a base? To answer this question we studied systems containing an amine plus the conjugate acid of the amine. Use of an amine–amine salt combination (instead of, say, an amine and a phenol) precluded the need to evaluate complicated acid–base equilibria. Amine salt by itself has little effect on proton exchange; no catalysis was observed with 0.063 M n-butylamine hydrochloride or with 0.11 M triethylamine hydrochloride in Me_2SO. Yet tiny quantities of amine hydrochloride "catalyze the catalysis" of a basic species (Table II). For exam-

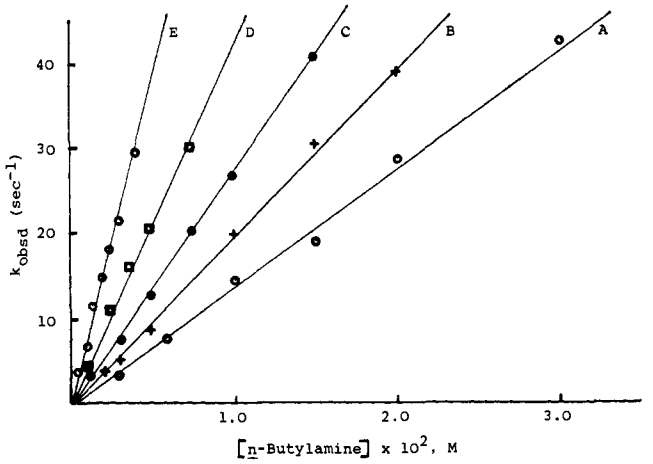
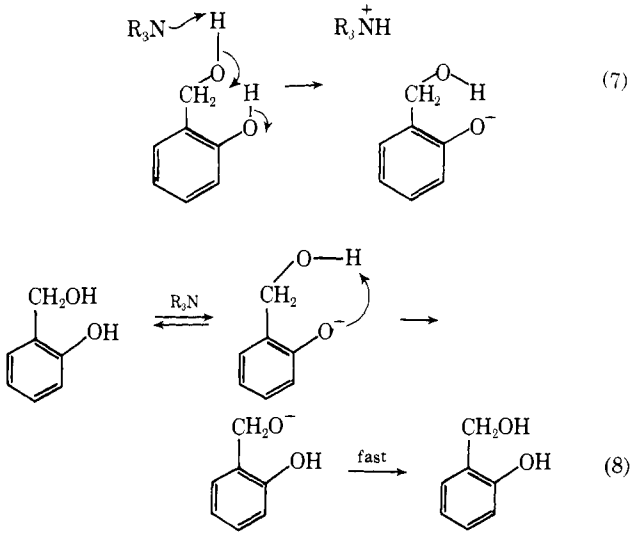


Figure 2. Plots of observed rate constants vs. *n*-butylamine concentration for the proton exchange of 0.20 *M* benzyl alcohol in Me_2SO at 25.0° in the presence of both *n*-butylamine and *n*-butylamine hydrochloride. The salt concentrations are (A), zero; (B), 6.4×10^{-5} *M*; (C), 1.3×10^{-4} *M*; (D), 2.5×10^{-4} *M*; and (E), 5.1×10^{-4} *M*.

Table II. Sample Rate Data for the Proton Exchange of 0.20 *M* Benzyl Alcohol in Me_2SO at 25.0° in the Presence of Either Triethylamine, Triethylamine Hydrochloride, or a Combination of the Two

[Triethylamine], *M*	[Triethylamine Hydrochloride], *M*	k_{obsd}, sec^{-1}
0.25		3.8
0.50		8.0
	0.11	NR[a]
0.12	1.1×10^{-3}	17
0.12	2.7×10^{-3}	38

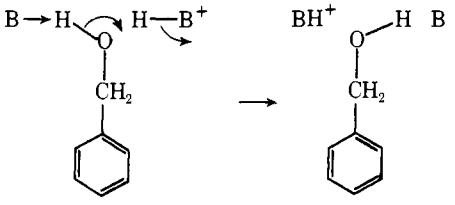
[a] No reaction (exchange is too slow to measure by NMR).



ple, 5.1×10^{-4} *M* *n*-butylamine hydrochloride induces a 5.0-fold increase in the *n*-butylamine-catalyzed exchange of benzyl alcohol in Me_2SO. As predicted by the rate equation describing the "amine plus amine salt" reaction (eq 9),[25]

$$k_{obsd} = k_1[B] + k_2[B][BH^+] \quad (9)$$

plots of k_{obsd} *vs.* [*n*-butylamine] at constant values of [*n*-butylamine hydrochloride] are straight lines passing through the origin (Figure 2). The k_2 value, calculated by averaging the (slope $- k_1$)/[BH^+] for lines B, C, D, and E of Figure 2, is $10.2 \pm 1.2 \times 10^6$ M^{-2} sec^{-1}. A similar treatment led to a $k_2 = 11.4 \pm 0.3 \times 10^4$ M^{-2} sec^{-1} for triethylamine-triethylamine hydrochloride in Me_2SO. Since the *n*-butylamine to triethylamine k_2 ratio nearly equals the corresponding k_1 ratio (89 and 94, respectively), acid catalysis is as effective for primary amines as for tertiary amines. Catalysis by the salts must be ascribed to the alkylammonium ions and not to their anionic counterion, because the methylene NMR signal of benzyl alcohol remains a doublet in the presence of 0.06 *M* tetrabutylammonium chloride or a mixture of 3.7×10^{-3} *M* *n*-butylamine and 0.06 *M* tetrabutylammonium chloride (compare these high concentrations with those in Figure 2). A likely mechanism for the amine-amine salt catalysis is presented in eq 10. Its



efficiency stems from the concerted acid-base catalysis which averts formation of high-energy ionic intermediates.[26]

In this paper we have only touched upon base catalysis, acid catalysis, intramolecular catalysis, and bifunctional catalysis. Each of the catalytic modes warrants a much more thorough investigation. Although this would require considerable effort (rate constants based on NMR are more difficult to secure than spectrophotometrically based rate constants), our mechanistic framework could be expanded and perhaps modified. For the moment a rather pleasant simplicity pervades the present level of understanding.

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References and Notes

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(11) Slow exchange was observed even with 0.20 *M* *o*-aminobenzyl alcohol in Me_2SO. This contrasts with the results of Bass and Sewell[6] who found no spin–spin coupling with this compound at much higher concentrations. Although these authors concluded that an aromatic amine destroys the diagnostic value of the Chapman–King test for alcohols,[5] this is probably not the case if the Me_2SO is carefully purified and the concentrations are kept low.
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(22) OH-proton exchange of phenol in methanol is catalyzed by HCl: M. S. Puar and E. Grunwald, *Tetrahedron*, 2603 (1968).
(23) A plot of k_{obsd} vs. acetic acid concentration shows a marked convex curvature which may stem from traces of basic impurities in the Me_2SO. Addition of acids to the Me_2SO could give rise to termolecular catalysis as described in section 7 of this article.
(24) A collapsed doublet was *not* observed with 0.20 *M* benzyl alcohol plus 0.20 *M* phenol in Me_2SO.
(25) A termolecular reaction of this type has been also observed in *tert*-butyl alcohol: M. Cocivera and E. Grunwald, *J. Am. Chem. Soc.*, **87**, 2070 (1965).
(26) Linking an amine with an amine salt creates a powerful bifunctional catalyst. Thus, the monoperchlorate salt of *N,N,N′,N′*-tetramethylethylenediamine is a 10^4 more powerful catalyst than the free diamine (whose $k_1 = 56\ M^{-1}\ sec^{-1}$). Only minute quantities (10^{-5} *M*) of monosalt are required to bring the observed exchange rates into the "NMR window". We presume that the mechanism is an intramolecular version of eq 10: