Quantitative Study of Solvent Effects on the Menshutkin Reaction between 1,4-Diazabicyclo[2.2.2]octane and 2-Chloroethylbenzene, 2-Bromoethylbenzene, and 2-Iodoethylbenzene. Part 2.[1] Mixed Solvents

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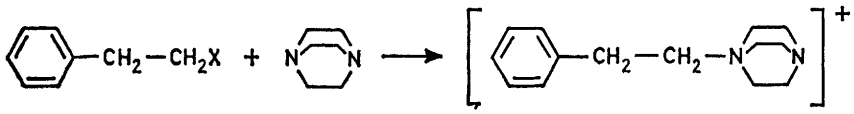
We have elucidated by kinetic studies the complex behaviour of the protic compounds at low concentration in various solvents for the Menshutkin quaternation reaction between 1,4-diazabicyclo[2.2.2]octane and 2-chloroethyl-, 2-bromoethyl-, and 2-iodoethyl-benzene. The variation of the reaction rate is interpreted on the basis of non-specific physical and specific chemical effects. The specific effects arise from the formation of hydrogen bonded complexes between the protic compound and the amine, the halide, and the basic solvent. The deactivation of the amine and the activation of the halide in the presence of added protic compound have been found to be a function of the basicity of the main solvent.

In Part 1, we showed that the effect of solvents on rates of reaction must be interpreted on the basis of two factors subject to the nature of the reaction partners.[1] The physical influence, resulting from polarity and polarizability of various species present in the medium, has a noticeable effect on reaction rates. The specific influence arises from the formation of complexes between protic compounds and the various species in the medium. In the Menshutkin quaternation reaction between 1,4-diazabicyclo[2.2.2]octane (DABCO) and 2-chloroethyl- (2CEB), 2-bromoethyl- (2BEB), and 2-iodoethylbenzene (2IEB), for example, we observe specific inhibition if a protic solvent forms hydrogen bonded complexes with the amine. Conversely upon association with the halide, the protic compound has a specific catalytic effect. The two effects are always in competition and the outcome is a function of the chemical nature of the reactants.

In order to elucidate the effects of protic compounds, we have added various species with active hydrogen in low concentration to various solvents. The chosen reactants were the same as in previous work, *i.e.*, 2CEB, 2DEB, 2IEB, and DABCO. The sole process that occurs with these reactants is the Menshutkin reaction (1).[1]



(1)

X = Cl, Br, I

RESULTS

Three distinctive protic compounds were chosen, methanol, phenol, and chloroform which can also form hydrogen bonded complexes.[2] Acetone, nitrobenzene, acetonitrile, nitromethane, and *NN*-dimethylformamide were chosen as main solvents owing to their greater effects. For a given solvent, the reaction rate increases *ca.* 10^3-fold on going from the DABCO–2CEB to the DABCO–2IEB pair and, for a given pair of reactants, *ca.* 10 times on going from the least active to the most active solvent. Results are in Tables 1—3.

To give a better understanding of the effect of protic compounds, the reaction rates of the DABCO–2BEB pair in acetone as main solvent were studied by adding 11 other aliphatic alcohols and eight substituted phenols. The results can be seen in Tables 4 and 5.

TABLE 1

Reaction between DABCO and 2CEB at 54.5 °C in mixed solvents

		Added compound											
		Cyclohexane			Methanol			Phenol			Chloroform		
Main solvent	k_0/l mol^{-1} min^{-1}	Conc. (M)	k_2/l mol^{-1} min^{-1}	k_r	Conc. (M)	k_2/l mol^{-1} min^{-1}	k_r	Conc. (M)	k_2/l mol^{-1} min^{-1}	k_r	Conc. (M)	k_2/l mol^{-1} min^{-1}	k_r
Acetone	7.06×10^{-4}	0.100	6.60×10^{-4}	0.935	0.203	8.66×10^{-4}	1.227	0.099	8.51×10^{-4}	1.205	0.097	9.04×10^{-4}	1.280
		0.300	5.70×10^{-4}	0.807	0.504	8.99×10^{-4}	1.273	0.178	8.05×10^{-4}	1.140	0.301	9.28×10^{-4}	1.315
								0.308	7.26×10^{-4}	1.028	0.495	9.33×10^{-4}	1.324
Nitrobenzene	1.83×10^{-3}	0.099	1.81×10^{-3}	0.989	0.186	1.84×10^{-3}	1.005	0.100	1.12×10^{-3}	0.601	0.097	1.95×10^{-3}	1.066
		0.294	1.70×10^{-3}	0.929	0.504	1.54×10^{-3}	0.841	0.189	8.35×10^{-4}	0.456	0.297	1.96×10^{-3}	1.071
								0.324	5.57×10^{-4}	0.304	0.492	1.91×10^{-3}	1.044
Acetonitrile	3.73×10^{-3}	0.103	3.65×10^{-3}	0.978	0.205	3.22×10^{-3}	0.863	0.119	2.87×10^{-3}	0.769	0.096	3.52×10^{-3}	0.946
		0.304	3.48×10^{-3}	0.933	0.508	2.04×10^{-3}	0.815	0.224	2.16×10^{-3}	0.579	0.291	3.51×10^{-3}	0.941
								0.299	2.00×10^{-3}	0.536	0.495	3.54×10^{-3}	0.949
NN-Dimethylformamide	4.54×10^{-3}	0.100	4.45×10^{-3}	0.981	0.201	4.60×10^{-3}	1.013	0.111	4.60×10^{-3}	1.013	0.102	4.75×10^{-3}	1.046
		0.297	4.28×10^{-3}	0.943	0.509	4.42×10^{-3}	0.974	0.207	4.47×10^{-3}	0.984	0.294	4.66×10^{-3}	1.029
								0.302	4.26×10^{-2}	0.938	0.492	4.43×10^{-3}	0.976
Nitromethane	6.88×10^{-3}	0.100	6.30×10^{-3}	0.915	0.200	5.75×10^{-3}	0.836	0.099	4.15×10^{-3}	0.603	0.100	6.64×10^{-3}	0.965
		0.301	5.96×10^{-3}	0.866	0.504	4.17×10^{-3}	0.685	0.214	2.51×10^{-3}	0.365	0.296	6.34×10^{-3}	0.921
								0.309	1.96×10^{-2}	0.285	0.497	6.21×10^{-3}	0.903

TABLE 2

Reaction between DABCO and 2BEB at 54.5 °C in mixed solvents

		Added compound											
		Cyclohexane			Methanol			Phenol			Chloroform		
Main solvent	k_0/l mol^{-1} min^{-1}	Conc. (M)	k_2/l mol^{-1} min^{-1}	k_r	Conc. (M)	k_2/l mol min^{-1}	k_r	Conc. (M)	k_2/l mol^{-1} min^{-1}	k_r	Conc. (M)	k_2/l mol^{-1} min^{-1}	k_r
Acetone	1.19×10^{-1}	0.104	1.13×10^{-1}	0.950	0.100	1.19×10^{-1}	1.000	0.100	1.04×10^{-1}	0.874	0.100	1.21×10^{-1}	1.017
		0.306	1.08×10^{-1}	0.908	0.277	1.17×10^{-1}	0.983	0.200	8.92×10^{-2}	0.750	0.302	1.28×10^{-1}	1.076
					0.505	1.07×10^{-1}	0.900	0.297	8.03×10^{-2}	0.675	0.500	1.19×10^{-1}	1.000
Nitrobenzene	2.16×10^{-1}	0.200	$2.07 \times 10^{-}$	0.958	0.102	2.18×10^{-1}	1.009	0.100	1.31×10^{-1}	0.606	0.101	2.40×10^{-1}	1.111
		0.403	1.99×10^{-1}	0.921	0.202	1.99×10^{-1}	0.921	0.200	7.48×10^{-1}	0.348	0.293	2.35×10^{-1}	1.088
					0.501	1.55×10^{-1}	0.718	0.300	4.76×10^{-2}	0.220	0.491	2.19×10^{-1}	1.014
Acetonitrile	3.70×10^{-1}	0.205	3.52×10^{-1}	0.950	0.100	3.87×10^{-1}	1.046	0.100	2.96×10^{-1}	0.800	0.103	3.94×10^{-1}	1.055
		0.412	3.33×10^{-1}	0.900	0.202	3.45×10^{-1}	0.932	0.200	2.21×10^{-1}	0.597	0.315	3.69×10^{-1}	0.977
					0.506	2.94×10^{-1}	0.795	0.300	1.89×10^{-1}	0.512	0.503	3.51×10^{-1}	0.949
Nitromethane	6.55×10^{-1}	0.203	5.62×10^{-1}	0.858	0.099	5.89×10^{-1}	0.899	0.100	3.70×10^{-1}	0.564	0.099	6.42×10^{-1}	0.981
		0.403	5.27×10^{-1}	0.805	0.205	5.38×10^{-1}	0.821	0.200	2.33×10^{-1}	0.356	0.302	6.26×10^{-1}	0.956
					0.506	4.30×10^{-1}	0.656	0.300	1.57×10^{-1}	0.240	0.500	6.02×10^{-1}	0.919
NN-Dimethylformamide	6.70×10^{-1}	0.204	5.91×10^{-1}	0.882	0.104	5.99×10^{-1}	0.894	0.100	5.78×10^{-1}	0.863	0.098	5.95×10^{-1}	0.888
		0.412	5.15×10^{-1}	0.769	0.207	5.70×10^{-1}	0.860	0.200	5.50×10^{-1}	0.821	0.283	5.56×10^{-1}	0.830
					0.506	5.40×10^{-1}	0.806	0.200	5.38×10^{-1}	0.806	0.500	5.33×10^{-1}	0.795

TABLE 3

Reaction between DABCO and 2IEB at 54.5 °C in mixed solvents

		Added compound											
		Cyclohexane			Methanol			Phenol			Chloroform		
Main solvent	k_0/l mol^{-1} min^{-1}	Conc. (M)	k_2/l mol^{-1} min^{-1}	k_r	Conc. (M)	k_2/l mol^{-1} min^{-1}	k_r	Conc. (M)	k_2/mol^{-1} min^{-1}	k_r	Conc. (M)	k_2/l mol^{-1} min^{-1}	k_r
Acetone	6.48×10^{-1}	0.099	6.30×10^{-1}	0.972	0.106	6.26×10^{-1}	0.966	0.087	5.61×10^{-1}	0.866	0.100	6.40×10^{-1}	0.980
		0.295	5.97×10^{-1}	0.921	0.505	5.53×10^{-1}	0.853	0.200	4.60×10^{-1}	0.710	0.302	6.31×10^{-1}	0.974
								0.303	4.00×10^{-1}	0.617	0.499	6.22×10^{-1}	0.960
Nitrobenzene	8.83×10^{-1}	0.100	8.79×10^{-1}	0.992	0.396	7.40×10^{-1}	0.838	0.100	4.37×10^{-1}	0.495	0.099	9.55×10^{-1}	1.081
		0.299	8.22×10^{-1}	0.931	0.489	5.19×10^{-1}	0.588	0.206	2.41×10^{-1}	0.273	0.306	8.58×10^{-1}	0.972
								0.307	1.62×10^{-1}	0.183	0.495	8.35×10^{-1}	0.946
Acetonitrile	1.44	0.101	1.27	0.854	0.195	1.06	0.736	0.100	9.53×10^{-1}	0.662	0.100	1.37	0.910
		0.299	1.09	0.757	0.295	9.86×10^{-1}	0.685	0.200	7.51×10^{-1}	0.521	0.269	1.25	0.868
					0.465	9.59×10^{-1}	0.666	0.300	6.38×10^{-1}	0.443	0.402	1.22	0.847
Nitromethane	1.61	0.099	1.56	0.969	0.195	1.31	0.814	0.098	8.90×10^{-1}	0.553	0.100	1.61	1.000
		0.299	1.44	0.894	0.474	1.10	0.683	0.200	5.83×10^{-1}	0.362	0.295	1.56	0.969
								0.306	4.18×10^{-1}	0.260	0.494	1.51	0.938
NN-Dimethylformamide	2.84	0.098	2.80	0.986	0.188	2.67	0.940	0.100	2.71	0.954	0.099	2.81	0.989
		0.294	2.69	0.947	0.471	2.60	0.915	0.201	2.58	0.908	0.297	2.76	0.972
								0.281	2.49	0.877	0.495	2.61	0.919

As the rate constants obtained for the three pairs under study are very different and in order to compare the kinetic effects produced by the addition of the protic compounds to the various main solvents, we introduce a relative constant (k_r) defined by equation (2) where k_2 is the second-order rate

$$k_r = k_2/k_0 \qquad (2)$$

constant observed in mixed solvents and k_0 the second-order rate constants observed in the pure main solvent.

To show the specific action of the protic compounds, low concentrations of the inert solvent cyclohexane were added to the main solvent. Thus, we could plot dilution curves obtained with cyclohexane and then compare these with those for protic compounds. The dilution curves constitute the lower limit of the purely physical effects of dilution of the main solvent. The fact that the curves defined by the protic compounds lie below that of cyclohexane confirms the specific inhibitory effect of those compounds. Conversely if they lie above the dilution curve, the interpretation is more difficult. Indeed, the physical effects of polarity and polarizability may have to be added to the specific catalytic one. These non-specific physical effects will influence the rate constant favourably because cyclohexane is practically an inert compound.

TABLE 4

Reaction between DABCO and 2BEB at 54.5 °C in acetone with various substituted phenols added

Phenol	pK_a at 25 °C in water [a]	Conc. (M)	10^2 k_2/l mol^{-1} min^{-1}	k_r
o-Cresol	10.33	0.100	1.05	0.882
		0.303	9.88	0.739
m-Cresol	10.10	0.100	1.06	0.891
		0.295	0.90	0.756
p-Cresol	10.28	0.100	1.06	0.891
		0.300	0.96	0.807
m-Methoxyphenol	9.65	0.103	1.01	0.849
		0.305	0.83	0.697
p-Methoxyphenol	10.20	0.101	1.06	0.891
		0.300	0.95	0.789
m-Chlorophenol	9.12	0.105	0.89	0.748
		0.295	0.59	0.496
2,4-Dimethylphenol	10.49 [b]	0.105	1.06	0.891
		0.300	0.89	0.748
1-Naphthol	9.23	0.100	0.93	0.782
		0.300	0.73	0.613
2-Naphthol	9.46	0.100	1.05	0.882
		0.200	0.94	0.790

[a] Ref. 3. [b] Ref. 4.

DISCUSSION

The results show complex variation of the reaction rates depending on the nature of the protic compound, the halide, and the main solvent. Each of these variables is investigated starting with the nature of the protic compound.

Except for the DABCO–2CEB pair in acetone and in DMF, phenol has always a large inhibitory effect, methanol an effect very close of that of cyclohexane, and chloroform a very small effect on the rate constant but always favourable compared with that of cyclohexane. For the DABCO–2BEB pair in acetone, the inhibitory effect is proportional to the acidity of the added phenol (Table 4 and Figure 1). Compared with phenol (pK_a 9.99), *m*-chlorophenol (pK_a 9.12) and 1-naphthol (pK_a 9.23) have an inhibitory effect greater than *p*-cresol (pK_a

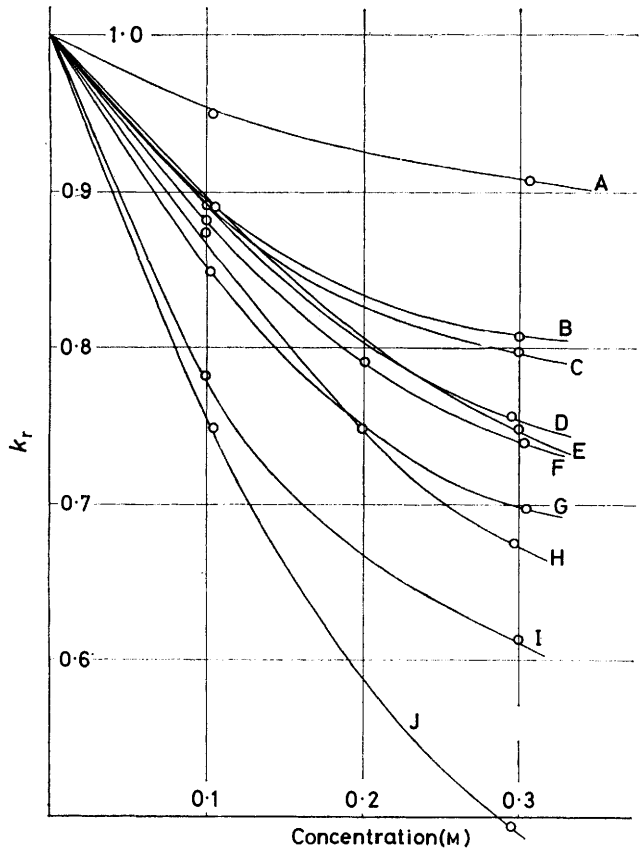


FIGURE 1 Kinetic effects of added phenols and cyclohexane on DABCO–2BEB in acetone: A, cyclohexane; B, *p*-cresol; C, *p*-methoxyphenol; D, *m*-cresol; E, 2,4-dimethylphenol; F, *o*-cresol and 2-naphthol; G, *m*-methoxyphenol; H, phenol; I, 1-naphthol; J, *m*-chlorophenol

10.28) and *p*-methoxyphenol (pK_a 10.20). However, the sequence is not exactly followed in the cases of *o*-cresol and 2-naphthol. This may be attributed to the fact that the pK_a values used were determined in water at 25 °C and the reaction studied in acetone at 54.5 °C. The effects of the 11 other alcohols are very small and <10% (Table 5). So no significant results can be observed, these compounds being less acidic with pK_a *ca.* 15.

Effects other than the nature of the protic compound interfere, especially the nature of the halide. For instance, the effect of the halide with nitrobenzene and acetone as main solvent can be seen in Figures 2 and 3. The influence of the halide is not pronounced although visible in nitrobenzene (Figure 2), nitromethane, and acetonitrile. The inhibitory effect of phenol is greater for DABCO–2IEB than for DABCO–2BEB and DABCO–2CEB. So in addition to a specific inhibitory effect of phenol there is a specific catalytic effect of the protic compound on the halide, all the more important as the halogen become more electronegative or decreases in size. This effect has already been observed for pure solvents.[1]

The effect of the nature of the halide seems more important for DABCO–2CEB in acetone and in DMF as main solvent. Maxima of variable importance can be seen in Figure 4. From all results, the two effects of

TABLE 5

Reaction between DABCO and 2BEB at 54.5 °C in acetone with various alcohols added

Alcohol	Conc. (M)	$10^2\ k_2$/l mol^{-1} min^{-1}	k_r
Cyclohexanol	0.175	1.22	1.025
	0.300	1.18	0.991
	0.468	1.12	0.941
Butan-1-ol	0.210	1.18	0.991
	0.312	1.17	0.983
	0.503	1.12	0.941
t-Butyl alcohol	0.099	1.20	1.008
	0.294	1.20	1.008
	0.498	1.11	1.933
Allyl alcohol	0.105	1.16	0.975
	0.204	1.11	0.933
	0.510	0.98	0.824
Cinnamyl alcohol	0.195	1.18	0.991
	0.430	1.13	0.950
	0.465	1.12	0.941
Benzyl alcohol	0.103	1.23	1.043
	0.300	1.19	1.000
	0.507	1.07	0.899
Water	0.123	1.18	0.991
	0.306	1.15	0.966
	0.446	1.14	0.958
Ethane-1,2-diol	0.308	1.18	0.991
	0.446	1.14	0.158
	0.530	1.09	0.916
	0.204	1.11	0.933
Pentane-1,5-diol	0.222	1.15	0.966
	0.347	1.11	0.933
	0.520	1.05	0.882
4-Hydroxy-4-methylpentan-2-one	0.196	1.23	1.034
	0.304	1.21	1.017
	0.520	1.14	0.958
3-Chloropropanol	0.103	1.23	1.034
	0.303	1.31	1.101
	0.508	1.25	1.050

phenol, deactivation of the amine and activation of the halide, are always in competition; moreover the nature of the main solvent is very important for that competition.

Figure 5 illustrates the variation of k_r with the con-

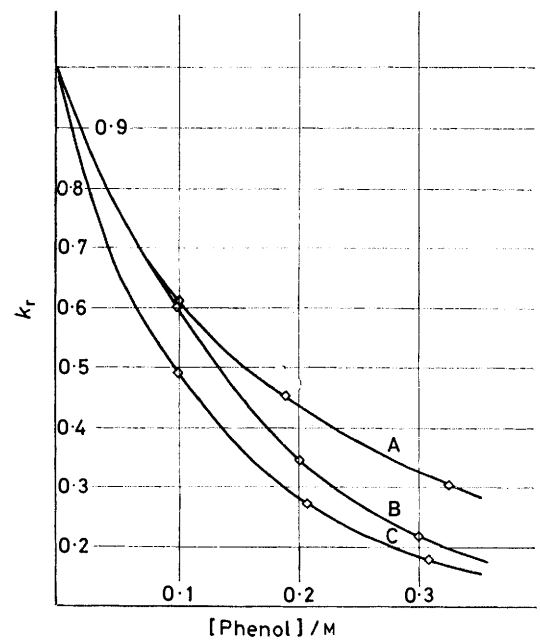


FIGURE 2 Kinetic effect of phenol in nitrobenzene on A, DABCO–2CEB; B, DABCO–2BEB; C, DABCO–2IEB

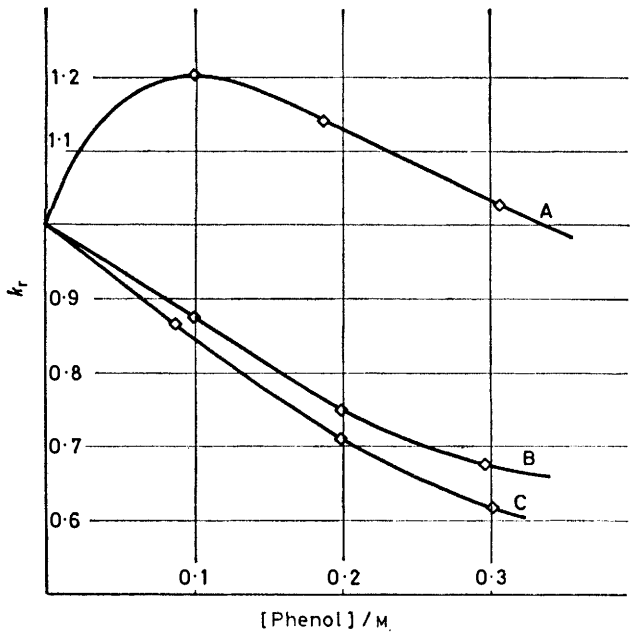


FIGURE 3 Kinetic effect of phenol in acetone on A, DABCO–2CEB; B, DABCO–2BEB; C, DABCO–2IEB

centration of phenol in the five main solvents for DABCO–2IEB. A diminution of k_r is always observed

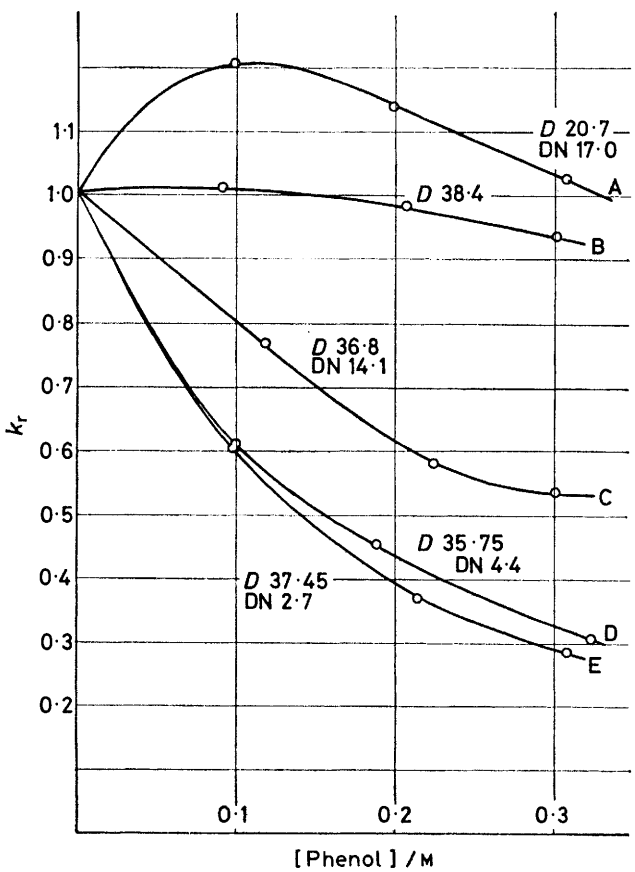


FIGURE 4 Kinetic effect of phenol in A, acetone; B, *NN*-dimethylformamide; C, acetonitrile; D, nitrobenzene; E, nitromethane for DABCO–2CEB

which is dependent on the nature of the solvent. The lowering is very small in acetone and in DMF but greater in nitromethane and nitrobenzene. The variation of the rate is independent of the dielectric constant. Thus the polarity as well as the polarizability have no influence on the deactivation of the amine since phenol causes practically the same deactivation in nitromethane and nitrobenzene.

On the contrary, the slopes of the k_r curves for a given concentration of phenol increase on going from a very basic solvent such as DMF to the less basic solvents nitromethane and nitrobenzene. So it is the basicity of the solvent that determines the deactivation by phenol. By forming a hydrogen bonded complex with the protic

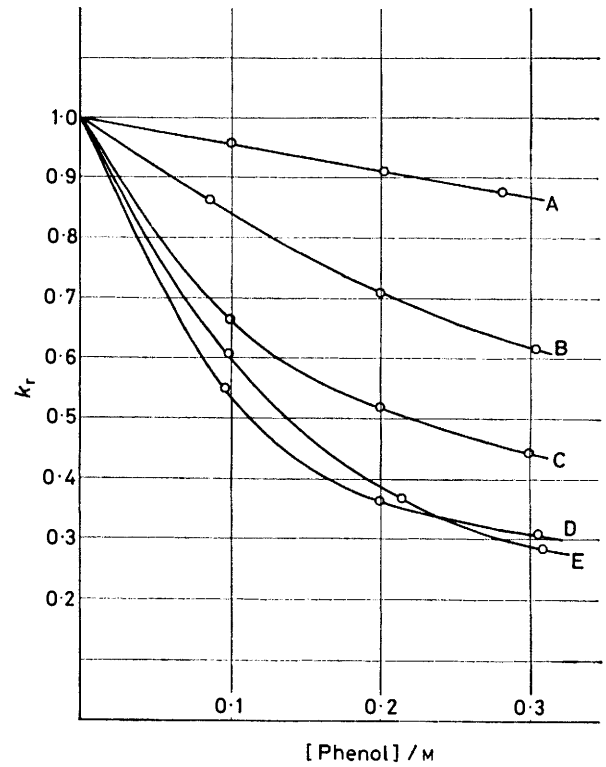


FIGURE 5 Kinetic effect of phenol in A, *NN*-dimethylformamide; B, acetone; C, acetonitrile; D, nitrobenzene; E, nitromethane for DABCO–2IEB

compound, the basic solvent protects the amine against the inhibitory power of the protic compound. Such a role cannot be played by a neutral or less basic solvent such as nitromethane. Hence the order of increasing basicity is nitromethane, nitrobenzene, acetonitrile, acetone, and DMF. Moreover the above order agrees with the association constants of phenol with the three last solvents (Table 6). Also several authors have shown nitro compounds form weakly hydrogen bonded complexes with phenols.[5]

It is possible to relate the kinetic scale of deactivation with the scale for electron pair donor solvents (EPD) given by Gutman.[9] In this scale, each solvent is characterized by a donor number (DN) [equation (3)] defined as the negative value of the enthalpy of interaction between

an EPD and $SbCl_5$ in high dilution in 1,2-dichloroethane (Table 7). Figure 4 illustrates the variation of k_r with

$$EPD + SbCl_5 \longrightarrow EPD,SbCl_5 - \Delta H(EPD,SbCl_5) = DN \quad (3)$$

the concentration of phenol in the five chosen solvents for DABCO–2CEB. Except for DABCO–2CEB in acetone, the importance of the basicity of the solvent appears once more.

TABLE 6

Association constants of phenol with various solvents

Solvent	K/l mol^{-1}	T/°C	Medium	Reference
Acetonitrile	5.0	25	CCl_4	6
	5.7	25	C_2Cl_6	7
Acetone	13.5	25	CCl_4	6
DMF	70	25	CCl_4	8

TABLE 7

Donor number for various solvents [9]

Solvent	DN
Nitromethane	2.7
Nitrobenzene	4.4
Acetonitrile	14.1
Acetone	17.0
DMF	26.6

With regard to DABCO–2CEB in acetone, neither the protective effect of acetone towards amine *versus* the inhibitory effect of phenol, nor the catalytic effect of phenol on 2CEB can explain the pronounced maximum above the curve for acetone (Figure 4). In this case, the intervention of the purely physical influence of acetone–phenol complexes formed should be taken into account. The same result was reported by Barrier who observed polar complexes formed between ethyl ether and *o*-chlorophenol by viscosimetric and dielectrometric measures.[10] He uses this to explain the large increase in the rate of reaction between triethylamine and methyl iodide in this medium. The polar character of these complexes is very noticeable and moreover these compounds show some polarizability due to the aromatic ring. The large increase in the rate could be attributed at least in part to the purely physical effect of those complexes.

Conclusions.—Binary mixtures involving protic compounds are very complex media. The protic compound may influence the reaction rate through various effects, some of which are interdependent. Nevertheless we are able to interpret, though only qualitatively, the behaviour of the binary mixtures on the basis of two factors. The physical influences, resulting from polarity and polarizability of the various species present in the medium, always have a catalytic effect on the reaction rate. The specific influences arise from the formation of complexes between the protic compound and the various species in the medium. If the protic compound forms hydrogen bonded complexes with the amine, its nucleophilicity becomes weaker. The diminution is proportional to the acidity of the protic compound and thus we observe a specific inhibitory effect. By association with the halide, the protic compound will have a specific catalytic effect which increases as the halogen becomes more electronegative or smaller in size. Moreover the protic compound may also combine with the solvent. That association leads to the formation of polar complexes which have physical effects on the reaction rate and leads to a diminution of the inhibitory and catalytic specific effects. If the main solvent is not very basic, the addition of protic compound has a very great inhibitory effect, proportional to its acidity, on the reaction with an iodide and a lesser inhibitory effect on the reaction with a chloride. If the main solvent is very basic, the protic compound gives polar complexes and the inhibitory and catalytic effects become weak. All these effects are always in competition and the result is a function of the chemical nature of the reactants.

EXPERIMENTAL

The reactants and solvents used were purified and the data obtained as previously described.[1]

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