stability of these compounds do not increase by changing the R_3 group.

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TOKYO, JAPAN

[CONTRIBUTION NO. 188 FROM RESEARCH CENTER OF THE UNITED STATES RUBBER CO.]

Tertiary Amine Catalysis of the Reaction of Phenyl Isocyanate with Alcohols

JOHN BURKUS

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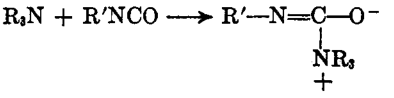
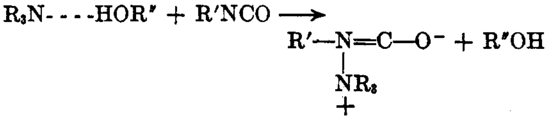
Although the rate of reaction of phenyl isocyanate with an alcohol is directly proportional to the triethylamine concentration in di-*n*-butyl ether solution, this proportionality does not hold in toluene. The relative catalytic activities of twenty-three tertiary amines were determined. These activities varied from 0.075 to 23.9. The steric requirements of the tertiary amine exert an overwhelming influence on its catalytic activity.

The reaction of isocyanates with alcohols is catalyzed by tertiary amines.[1] The possible mechanisms of base catalysis include activation of the isocyanate through the formation of a base-isocyanate complex[2a,b] and the activation of the alcohol through a base-alcohol complex.[3] The base-isocyanate complex may be formed by a direct attack of the isocyanate by the base,



$$R_3N + R'NCO \longrightarrow R'{-}N{=}\underset{\overset{|}{\overset{+}{N}R_3}}{C}{-}O^- \quad (1)$$

and its formation by a base-alcohol complex reaction has also been suggested.[2b]



$$R_3N\text{- - -}HOR' + R'NCO \longrightarrow R'{-}\underset{\overset{|}{\overset{+}{N}R_3}}{N}{=}C{-}O^- + R'OH \quad (2)$$

EXPERIMENTAL

The preparation of toluene, phenyl isocyanate, and 1-butanol and the kinetic method has been described previously.[4]

The tertiary amines, except those described below, were obtained from the commercial sources indicated in Table I. The amines were purified by conventional methods and were used immediately.

The procedure of Clarke, Gillespie, and Weeschaus[5] was used to prepare the following tertiary amines: *N,N,N',N'*-tetramethyl-1,3-propanediamine, *N,N*-dimethyl-*N',N'*-di-

TABLE I

TERTIARY AMINE CATALYTIC ACTIVITIES IN THE REACTION OF PHENYL ISOCYANATE WITH 1-BUTANOL IN TOLUENE AT 39.69°.

Catalytic activity of *N*-methylmorpholine is taken as 1.00. The amines were compared at equal amine equivalents which was about 0.0300*N*. The isocyanate and alcohol concentrations were about 0.100*M*.

Catalyst	Catalytic Activity	pK_a
N-Methylmorpholine[a]	1.00	7.41[b]
N-Ethylmorpholine[a]	0.68	7.70[b]
Ethyl morpholinoacetate	0.21	5.2[c]
Dimorpholinomethane	0.075	7.4[c]
N-(3-Dimethylaminopropyl)morpholine	2.16	
Triethylamine[d]	3.32	10.65[e]
N-Methylpiperidine[a]	6.00	10.08[e]
N,N,N',N'-Tetramethyl-1,3-propanediamine	4.15	9.8
N,N-Dimethyl-*N',N'*-diethyl-1,3-propanediamine	3.10	
N,N,N',N',N''-Pentamethyldiethylenediamine	3.47	9.4[f]
N,N,N',N'-Tetraethylmethanediamine	0.085	10.6[c]
Bis(2-diethylaminoethyl)adipate[g]	1.00	8.6[c]
Bis(2-dimethylaminoethyl)adipate[g]	1.92	8.8[c]
N,N-Dimethylcyclohexylamine[g,h]	6.00	10.1[c]
N,N-Diethylcyclohexylamine[h]	0.70	10.0[c]
N-Methyl-*N*-octylcyclohexylamine[g]	2.00	9.8[c]
N-Methyl-*N*-dodecylcyclohexylamine[g]	1.90	
N-Methyl-*N*-(2-ethylhexyl)cyclohexylamine[g]	0.16	9.6[c]
N-Methyldicyclohexylamine[g]	0.16	
1,4-Diazabicyclo(2.2.2)octane[i]	23.9	5.4[j]
1,2-Dimethylimidazole[i]	13.9	
Quinine[d]	11.3	7.8[c]
Pyridine[d]	0.25	5.29[k]

[a] From Union Carbide Chemicals Co. [b] H. K. Hall, *J. Phys. Chem.*, **60**, 63 (1956). [c] Determined in this work. [d] From the Distillation Products, Ind. [e] H. K. Hall, *J. Am. Chem. Soc.*, **79**, 5441 (1957). [f] R. Rometsch, A. Marxer, and K. Miescher, *Helv. Chim. Acta*, **34**, 1611 (1951). [g] From the Naugatuck Chemical Co. [h] From the du Pont Co.; [i] From the Houdry Process Corp. [j] pK_b, A. Farkas and K. G. Flynn, *J. Am. Chem. Soc.*, **82**, 642 (1960). [k] H. H. Jaffe and G. O. Doak, *J. Am. Chem. Soc.*, **77**, 4441 (1955).

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ethyl-1,3-propanediamine, N-(3-dimethylaminopropyl)morpholine, and N,N,N′,N′,N″-pentamethyldiethylenetriamine from N,N-dimethyl-1,3-propanediamine, N,N-diethyl-1,3-propanediamine, N-3-aminopropylmorpholine, and diethylenetriamine, respectively. The reactant amines were obtained from the Union Carbide Chemicals Co.

Dimorpholinomethane. Into a 500-ml. round-bottom, three necked flask fitted with an azeotrope trap assembly, thermometer, addition funnel and a stirrer were charged 100 ml. of benzene and 15 g. (0.5 mole) of paraformaldehyde. The flask was heated to reflux and then a solution containing 104 g. (1.29 moles) of morpholine and 100 ml. of benzene was added from the addition funnel over a 1-hr. period. During the addition of the amine solution and for an additional 1.5 hr. a water-benzene azeotrope distilled. The water was separated in the azeotrope trap assembly. The bulk of the benzene and the excess of morpholine were removed by distillation at atmospheric pressure. The residue was fractionated at reduced pressure. An 85-g. (91.4% yield) fraction came over at 113–114°/9 mm. (lit[6]. b.p., 136°/20 mm.).

Anal. Calcd. for $C_9H_{18}N_2O_2$: N, 15.05. Found: N, 15.01.

N,N,N′,N′-Tetraethylmethanediamine. With diethylamine the above procedure gave a 71-g. (90.0% yield) fraction which came over at 162–164° at atmospheric pressure (lit.[7] b.p., 163–167°/760 mm.).

Anal. Calcd. for $C_9H_{22}N_2$: N, 17.71. Found: N, 17.22.

Ethyl morpholinoacetate. A reaction mixture consisting of 300 ml. of morpholine, 200 ml. of benzene and 122.5 g. (1 mole) of ethyl chloroacetate was refluxed for 2 hr. The reaction mixture was cooled and the morpholine hydrochloride was separated by filtration. The bulk of the excess of morpholine and benzene were distilled at atmospheric pressure. The residue was fractionated twice at reduced pressure. A 136-g. (78.6% yield) fraction distilled at 108°/8 mm. (lit[8]. b.p., 117°/12 mm.).

Anal. Calcd. for $C_8H_{15}NO_3$: N, 8.20. Found: N, 8.25.

RESULTS

Effect of base concentration. 1. *Triethylamine.* The reaction of phenyl isocyanate with 1-butanol in toluene was catalyzed at several triethylamine concentrations. The results are shown in Fig. 1. The calculated second-order rate constant is not a linear function of the base concentration. This is contrary to that observed previously in di-n-butyl ether.[2b]

2. *1,4-Diazabicyclo [2,2,2]octane.* The base, 1,4-diazabicyclo[2,2,2] octane, is a powerful catalyst for the reaction of isocyanates with alcohols. Used in low concentrations the rates are still comparable to the rates obtained at much higher triethylamine concentrations. In reactions covering the range of rates observed in the triethylamine catalyzed reactions, the rate of reaction was directly proportional to the base concentration.

Effect of base structure. The catalytic activity of twenty-three tertiary amines of varying structure was determined for the reaction of phenyl isocyanate with 1-butanol. These are listed in Table I. Quinine and 1,4-diazabicyclo[2,2,2] octane, both containing bridgehead nitrogen atoms, exhibited the highest catalytic activities. The methylamines always showed higher activities than the corresponding ethylamines. The substituted cyclohexylamines, although of about equal basicities, showed a wide range of catalytic activities. N,N-Diethylcyclohexylamine exhibited an abnormally low activity.

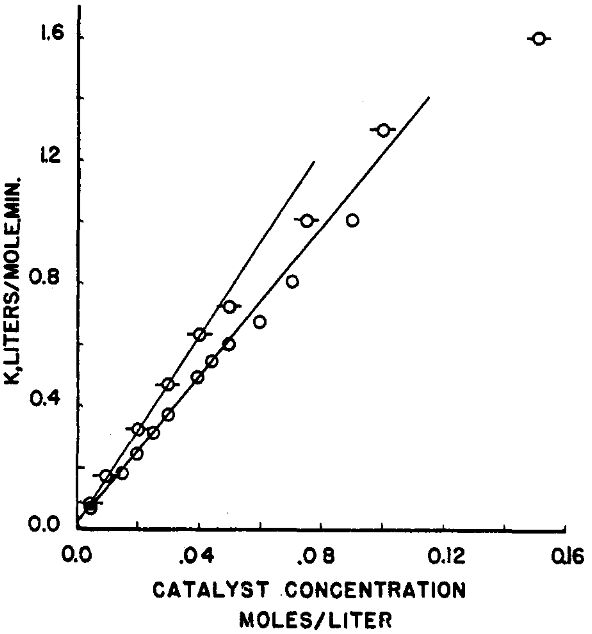

Fig. 1. Effect of triethylamine concentration on the calculated second-order rate constant for the reaction of phenyl isocyanate with 1-butanol in toluene at 39.67°. -○- Phenyl isocyanate concn. = 1-butanol concn. = 0.0510 M. ○ Phenyl isocyanate concn. = 1-butanol concn. = 0.1050M

N,N,N′,N′-Tetraethylmethanediamine and dimorpholinomethane did not catalyze the reaction appreciably.

DISCUSSION

The linearity in di-n-butyl ether and the nonlinearity in toluene of the second-order rates as a function of triethylamine concentration may be resolved if the role of the solvent is considered. In di-n-butyl ether the solvent-alcohol interaction is such that no monomeric alcohol is present.[9,10] The addition of base does not effect the molecular species of alcohol present and it produces only a small base-alcohol interaction and the stability of the complex is small.[11] Thus, in di-n-butyl ether the base interacts mainly with the isocyanate. The weak base-alcohol complex may also attack the isocyanate to form the base-isocyanate complex (Equation 2). The base-isocyanate complex concentration is then proportional to the base concentration and the linearity between the rate and base concentration is anticipated.

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[11] L. Sobczyk, Roczniki Chem. 31, 349 (1957).

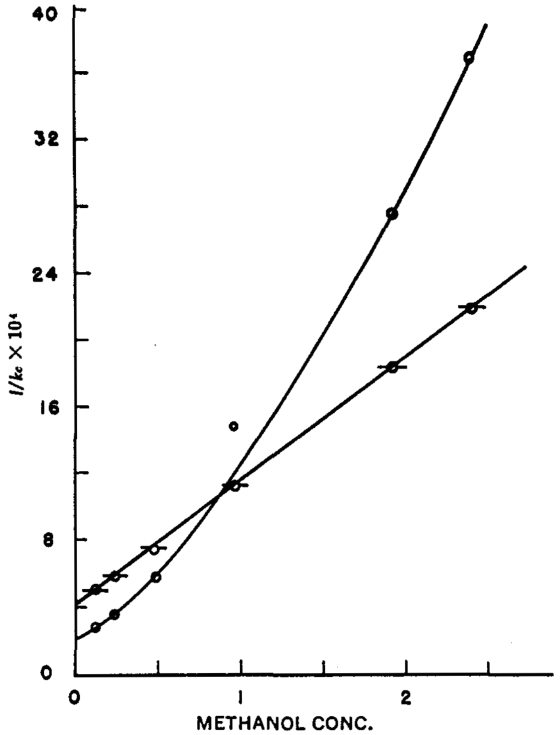

Fig. 2. Baker's $1/k_c$ as a function of alcohol concentration. ○ Our treatment of Baker's data[12] for the triethylamine (0.010*M*) catalyzed reaction of phenyl isocyanate (0.24*M*) with various methanol concentrations in benzene at 20°. -○- Our treatment of Baker's data[12] for the triethylamine (0.010*M*) catalyzed reaction of phenyl isocyanate (0.24*M*) with various methanol concentrations in di-*n*-butyl ether at 20°. The ordinate for this curve is one quarter of that shown

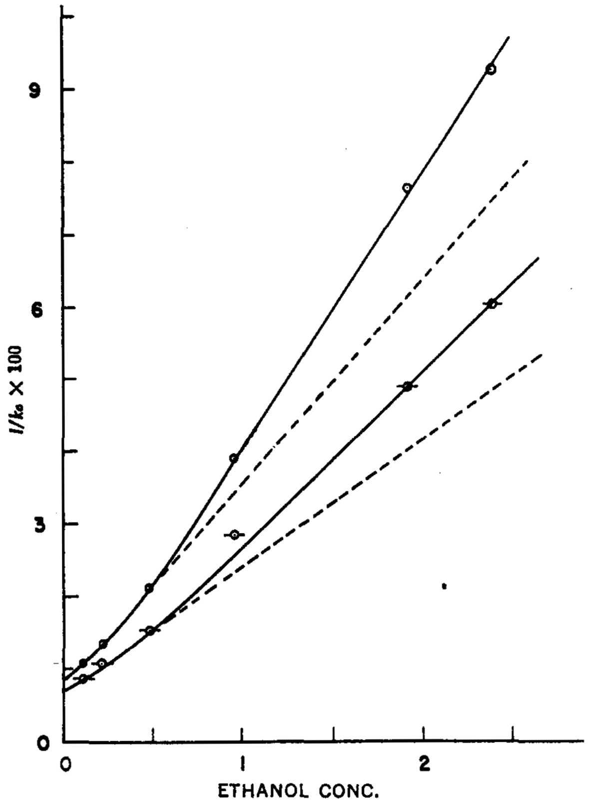

Fig. 3. Baker's $1/k_c$ as a function of alcohol concentration. Our treatment of Baker's data[12] for the triethylamine (0.010*M*) catalyzed reaction of phenyl isocyanate (0.24*M*) with various ethanol concentrations in benzene at: ○ 20°; -○- 30°

In toluene, however, the base-alcohol interaction is very appreciable and the stability of the complex is much greater than that in di-*n*-butyl ether.[11] Contrary to di-*n*-butyl ether solutions, the molecular species of alcohol present in toluene is a function of base concentration.[9,10] Thus, the strong base-alcohol interaction precludes appreciable reaction with the isocyanate (Equation 2) and it alters the molecular species of alcohol present. At low base concentrations the base-alcohol complex occurs mainly by reaction with the alcohol polymolecules and very slightly with the monomeric species. At higher base concentrations the base-alcohol complex occurs at the expense of the monomeric alcohol molecules. It follows that in toluene the nonlinearity between rate and base concentration is not unexpected.

The discussion of the preceding paragraph would predict that Baker's $1/k_c$[12] would not be a linear function of alcohol concentration in benzene. Our treatment of Baker's data[12] according to the method of Baker is shown in Figs. 2 and 3. The nonlinearity as predicted by the above discussion is evident.

The above discussion also predicts that in benzene at very high alcohol concentrations the strong base-alcohol interaction should result in a typical uncatalyzed reaction—*i.e.*, the rate of reaction should increase with increasing alcohol concentration. The data of Farkas and Flynn[13] illustrate this point.

The lower basicity and higher nucleophilicity of 1,4-diazabicyclo[2,2,2]octane[14] favor the formation of the base-isocyanate complex and minimize the base-alcohol interaction. At low base concentrations a direct proportionality between base concentration and the base-isocyanate complex concentration is a possibility. If this were so, then a direct proportionality between base concentration and rate would be observed. A linear relationship has been observed. Thus at 0.00270*N* and 0.0262*N* base concentrations the observed rates were 0.232 l./mole^{-1}/min.$^{-1}$ and 2.21 l./mole^{-1}/min.$^{-1}$, respectively. The phenyl isocyanate and 1-butanol concentrations in toluene were about 0.100*M* and the temperature was 39.69°. The rates in this series were greater than those observed in the triethyl-

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amine series where nonlinearity between rate and base concentration was observed.

A catalytic mechanism consistent with the experimental data discussed above involves a base-isocyanate complex formed by the direct attack of the isocyanate by the free base. The experimental data does not support a catalytic mechanism which involves the base-alcohol complex in the formation of the base-isocyanate complex.

The sensitivity of the catalytic activity to the steric requirements of the base does not support a mechanism involving activation through a base-alcohol interaction whereby the reacting species is an alkoxide anion. Such a mechanism would be insensitive to the steric requirements of the base because of the small spatial needs of the hydrogen entity. The independence of the basicity of an amine to the steric requirements of the base[15] supports this conclusion. Further, the mechanism can not account for the high catalytic activities of 1,4-diazabicyclo[2,2,2]octane, 1,2-dimethylimidazole and quinine. The very low activities of *N,N,N′,N′*-tetraethylmethane-diamine and dimorpholinomethane are also in conflict with the mechanism.

The large effect that the steric requirements of the base have on the catalytic activities is consistent with a catalytic mechanism involving direct attack of the isocyanate by the free base to form the reactive base-isocyanate complex. The dependence of the catalytic activity on the nucleophilicity of the base rather than base strength is consistent with such a catalytic mechanism.

Acknowledgment. The author wishes to express deep appreciation to Professor H. Kwart for many valuable discussions. The able technical assistance of John E. Wells is gratefully acknowledged.

WAYNE, N. J.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY, TOKYO INSTITUTE OF TECHNOLOGY]

Dehydration Reactions of Hydroxamic Acids. A New Method for the Preparation of Isocyanates

TERUAKI MUKAIYAMA AND HIROYUKI NOHIRA

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Dehydration reactions of an aliphatic aldoxime and several hydroxamic acids with organic reagents have been studied. The reaction of hydroxamic acids with phenyl isocyanate in the presence of triethylamine led to the formation of ureas through the intermediate phenylcarbamyl hydroxamates. Isocyanates were not isolated in this process but they were successfully isolated from hydroxamic acids by use of ketene dimer. The pyrolysis at 350–400° of acetoacetyl hydroxamates, initially formed, gave the corresponding isocyanates in fairly good yields along with acetone and carbon dioxide.

Dehydration reactions of primary nitroparaffins into nitrile oxides by means of organic reagents such as phenyl isocyanate, carbodiimide, or acetylenic ether in the presence of a catalytic amount of an aliphatic tertiary amine have been described in preceding papers.[1,2] The reactions can be explained by assuming initial formation of addition compounds of *aci*-nitroalkanes and the above-mentioned reagents, which in turn decompose into nitrile oxides. Further study[2,3] on the dehydrations of aldoximes with carbodiimide, acetylenic ether, ketene acetal, vinyl ether, vinyl acetate, acrylonitrile, and benzil also suggests that the initially formed adducts are the necessary intermediates for the reaction.

In the present study, the dehydration of an aliphatic aldoxime with phenyl isocyanate was tried first. Benzaldoxime is known to react with phenyl isocyanate to form *O*-phenylcarbamylbenzaldoxime and this adduct decomposes[4] into nitrile, aniline, carbon dioxide, and sym-diphenyl urea by heating. It is now established that an aliphatic aldoxime, heptanaldoxime, also reacts with phenyl isocyanate in the presence of triethylamine to give *sym*-diphenylurea, carbon dioxide, and heptanenitrile in high yields.

$$C_6H_{13}CH{=}NOH + 2C_6H_5NCO \longrightarrow C_6H_{13}CN + CO_2 + CO(NHC_6H_5)_2$$

Analogous to the explanation used for nitroparaffins, the reaction is thought to produce the intermediate $C_6H_{13}CH{=}NOCONHC_6H_5$ (I), which is successively deprotonated by amine to yield the nitrile and phenylcarbamic acid (or aniline + carbon dioxide).

This type of reaction was next extended to hydroxamic acids, compounds which resemble *aci*-nitroalkanes and aldoximes in possessing the structural possibility of dehydration (Lossen re-

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