Kinetics and Mechanism of the Reaction between Phenyl Isocyanate and Alcohols. Strong Base Catalysis and Deuterium Isotope Effects

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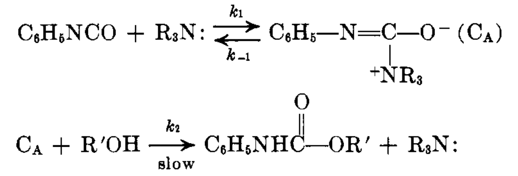
Received April 22, 1963

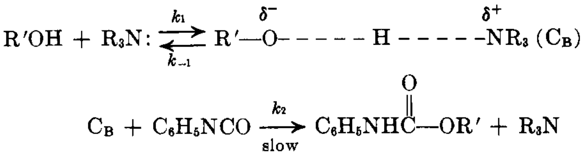
The kinetics of the reactions of phenyl isocyanate with 2-ethylhexanol, methanol, and deuterium methoxide, in the presence of some amine catalysts, have been investigated. A new catalytic species, heptamethylisobiguanide, has been found to possess higher activity than any other amine-type catalyst. Its activity is attributed to its high base strength. The mechanism is explained in terms of an increasing contribution of an amine–isocyanate complex with increasing base strength of the amine. The possibility of proton removal by the amine catalyst appears remote after consideration of deuterium isotope effects.

The most generally accepted mechanism for the amine-catalyzed reaction of aromatic isocyanate with an alcohol is that first offered by Baker and co-workers.[1,2] Designated "mechanism A," it involves a rapid formation of an isocyanate–base complex, followed by attack of the alcohol to form product, urethan. A second mechanism, designated B, has been offered as an alternative by Baker and others.[1,3,4] In mechanism B, the initial interaction occurs between the alcohol and the amine catalyst.[5]



$$C_6H_5NCO + R_3N: \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} C_6H_5\text{—N=}\underset{\substack{|\\ {}^{+}NR_3}}{C}\text{—}O^- \ (C_A)$$

$$C_A + R'OH \underset{\text{slow}}{\xrightarrow{k_2}} C_6H_5NH\overset{\substack{O\\ \|}}{C}\text{—}OR' + R_3N: \qquad (A)$$



$$R'OH + R_3N: \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} R'\text{—}\overset{\delta^-}{O}\text{- - - - - }H\text{ - - - - -}\overset{\delta^+}{N}R_3\ (C_B)$$

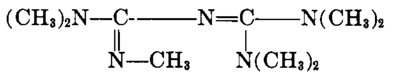
$$C_B + C_6H_5NCO \underset{\text{slow}}{\xrightarrow{k_2}} C_6H_5NH\overset{\substack{O\\ \|}}{C}\text{—}OR' + R_3N \qquad (B)$$

Mechanism A is preferred because of a significant effect presumably brought about by the steric requirements of the catalyst. For example, sterically unhindered but weakly basic amines can show higher catalytic activity than some stronger, hindered amines.[2,4,6] It is reasoned, therefore, that mechanism A is prevailing since mechanism B involves a partial or a complete proton removal by the amine—a step that should be relatively insensitive to steric factors.

In addition to the observed steric factor, it is known that tertiary amines promote the trimerization of isocyanates[7,8] implying an amine–isocyanate complex. Tertiary phosphines, usually more weakly basic but more nucleophilic than amines, are also excellent catalysts for dimerization and trimerization of isocyanates.[9]

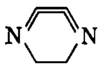
On the other hand, mechanism B finds support from the observations of Baker that hydrogen bonding between the alcohol and the amine catalyst occurs under the conditions employed in his work.[10] Burkus has postulated an amine–alcohol complex to explain some of his results.[4] In addition, it is known that some strongly basic nitrogen compounds are leveled in solvent methanol—implying some proton removal from the solvent.

In our work it has been found that the strongly basic heptamethylisobiguanide[11] (I) possessed over ten times the activity of the nucleophilic 1,4-diaza[2.2.2]bicyclooctane (II).



$$(CH_3)_2N\text{—}\underset{\substack{\|\\ N\text{—}CH_3}}{C}\text{———N=}\underset{\substack{|\\ N(CH_3)_2}}{C}\text{——}N(CH_3)_2$$

I



II

Consequently, it was of interest to determine if the effect of I could be explained in terms of mechanism A or mechanism B.

Experimental

Materials.—Phenyl isocyanate (Eastman) was distilled, and the fraction boiling at 30–31° (0.45 mm.) was used. Benzene (Fisher) was refluxed over CaH_2. A more extensive drying of the solvent was necessary when heptamethylisobiguanide was used. The solvent (benzene) was refluxed with phenyl isocyanate for 4 hr. after treatment with CaH_2. Reflux was continued for another few hours after the addition of a few drops of heptamethylisobiguanide. Benzene was distilled from the mixture and the fraction boiling at 79° was used. The fraction of 2-ethylhexanol (Eastman) used was distilled at 129–130° (80 mm.). Methanol was refluxed overnight with magnesium turnings and after distillation was kept under nitrogen. Deuterium methoxide (purity >98% by n.m.r.) was used as received from Merck and Co., Ltd.

The sample of 1,4-diaza[2.2.2]bicyclooctane (Houdry Process and Chemical Co.) was sublimed at 0.05 mm. Heptamethylisobiguanide (American Cyanamid) was distilled twice, and fractions boiling at 112–115° (0.55 mm.) and 70–72° (0.15 mm.) were used, respectively. N,N,N′,N′-Tetramethyl-1,3-butanediamine was distilled at 30–33° (0.45 mm.). 1,1,3,3-Tetramethylguanidine (TMG) and pentamethylguanidine were used as received from American Cyanamid Co. The purity of the liquid amine catalysts, determined by gas–liquid chromatography, was always >98%. The purity of the solid catalysts were determined by nonaqueous titrimetry using the method of Streuli.[12] Only those materials having purities ≥98% were used.

Preparation of Carbamoyl Derivatives.—A typical preparation of the carbamoyl derivative of a guanidine and an isobiguanide is

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[1] J. W. Baker and J. Gaunt, *J. Chem. Soc.*, 9, 19, 27 (1949).

[2] J. W. Baker and J. B. Holdsworth, *ibid.*, 713 (1947).

[3] J. V. Smith and E. C. Friedrich, *J. Am. Chem. Soc.*, **81**, 161 (1959).

[4] J. Burkus, *J. Org. Chem.*, **26**, 779 (1961).

[5] The structure of C_B is not known but is represented in this manner only to imply amine–alcohol interaction.

[6] A. Farkas and K. G. Flynn, *J. Am. Chem. Soc.*, **82**, 642 (1960).

[7] D. A. Chadwick and T. C. Allen, U. S. Patent 2,733,254 (1961).

[8] J. M. Lyons and R. H. Thompson, *J. Chem. Soc.*, 1971 (1950).

[9] R. G. Arnold, J. A. Nelson, and J. J. Verbane, *Chem. Rev.*, **57**, 47, (1957).

[10] J. W. Baker, M. M. Davies, and J. Gaunt, *J. Chem. Soc.*, 24 (1949).

[11] Dr. L. T. Capell of Chemical Abstract Service, our nomenclature consultant, has found the name "isobiguanide" acceptable and has approved our numbering system for this structure.

[12] C. A. Streuli, *Anal. Chem.*, **31**, 1652 (1959).

given in the next paragraph. The preparations of the starting isobiguanides are described elsewhere.[13]

2-(Phenylcarbamoyl)-1,1,3,3-tetramethylguanidine.—Phenyl isocyanate, 17.9 g. (0.15 mole), dissolved in anhydrous ether was added dropwise to a solution of 17.3 g. (0.15 mole) of 1,1,3,3-tetramethylguanidine in 100 ml. of ether at room temperature. The temperature rose to 40° and was cooled to room temperature while stirring for 2 hr. During this time a solid separated. The white solid was vacuum-filtered and dried *in vacuo* giving a material with m.p. 106.5–108°. The yield was 65%.

Anal. Calcd. for $C_{12}H_{18}N_4O$: C, 61.53; H, 7.69; N, 23.93. Found: C, 61.23; H, 7.90; N, 23.95.

2,4-Bis(phenylcarbamoyl)-1,1,3,3-tetramethylisobiguanide.—A solution of 23.8 g. (0.2 mole) of phenyl isocyanate dissolved in 60 ml. of dry benzene was slowly added to 15.7 g. (0.1 mole) of 1,1,3,3-tetramethylisobiguanide in 70 ml. of benzene while stirring at room temperature. During addition the temperature rose to 60°. The contents were allowed to return to room temperature while stirring for 2 hr. The solvent was evaporated and the resulting solid was recrystallized from petroleum ether (b.p. 30–60°), and the yield was 70%.

Anal. Calcd. for $C_{20}H_{24}N_7O_2$: C, 60.76; H, 6.33; N, 24.13. Found: C, 60.58; H, 6.90; N, 23.83.

2,4-Bis(phenylcarbamoyl)-1,1,2,3,3-pentamethylisobiguanide.—Starting from 1,1,2,3,3-pentamethylisobiguanide and after recrystallization from petroleum ether (b.p. 30–60°), the melting point of the product was 94–97°, and the yield was 70%.

Anal. Calcd. for $C_{21}H_{27}N_7O_2$: C, 61.61; H, 6.60; N, 23.96. Found: C, 62.03; H, 6.52; N, 23.68.

4-(Phenylcarbamoyl)-1,1,2,2,3,3-hexamethylisobiguanide.—Starting from 1,1,2,2,3,3-hexamethylisobiguanide, the white crystals were recrystallized from hot heptane giving a product melting at 124–126°. The yield was 95%.

Anal. Calcd. for $C_{15}H_{24}N_7O$: C, 59.21; H, 7.89; N, 27.63. Found: C, 59.55; H, 7.78; N, 27.12.

Procedure. Isocyanate–Alcohol Reaction.—Stock benzene solutions of phenyl isocyanate and 2-ethylhexanol, both 0.4 *M*, and 0.04 *M* stock solutions of catalysts were prepared by weighing out the proper amount and diluting to the mark in volumetric flasks. The 0.4 *M* methanol and deuterium methoxide stock solutions were prepared in benzene in a drybox.

The catalyst was pipeted into a reaction mixture of phenyl isocyanate and the alcohol in dry benzene and immersed in a constant temperature bath of 26.8 ± 0.01°. At appropriate time intervals a sample was withdrawn with a syringe and injected into a sodium chloride cell of 0.68-mm. thickness. The disappearance of the isocyanate peak[14] was measured using a Beckman IR-4 spectrophotometer at 2260–2270 cm.$^{-1}$. The pen speed was decreased to one-half speed while tracing the isocyanate band.

In a typical run the starting concentrations of the reaction mixture were 0.08 *M* in phenyl isocyanate, 0.08 *M* in 2-ethylhexanol, and 0.0016 *M* in the catalyst. Zero time was taken immediately after the addition of the catalyst. Seven to nine readings were taken during each run over an interval of 5–7 hr. A calibration curve was prepared by measuring the absorbance *vs.* phenyl isocyanate concentration in benzene; the solution was found to obey Beer's law throughout the desired concentration range. The rate constants were calculated by using the second-order rate equation for reactants present in equimolar amounts. Runs were always followed to at least 80% reaction. In all cases good agreement with pseudo second-order kinetics was observed throughout the reaction span. A typical example of the experimental results is given in Table I.

Polymerization of Phenyl Isocyanate.—The polymerization of phenyl isocyanate was measured using the same technique described before. Reactions were followed until 40–50% of the isocyanate concentration had disappeared. Relative rates were determined by comparing the initial slopes obtained from a plot of phenyl isocyanate concentration *vs.* time.

In a typical run the starting concentrations were 0.08 *M* in phenyl isocyanate and 0.0016 *M* in the catalyst.

Results and Discussion

General Base Catalysis. Isocyanate–Alcohol Reaction.—The reaction of phenyl isocyanate with 2-ethylhexanol was used as a model to determine catalytic activities. The catalytic activity parameter k_c, was determined from the relationship

$$k_c = \frac{k_2 - k_0}{[C]}$$

where [C] is the catalyst concentration, while k_2 and k_0 are the observed rate constants for the catalyzed and uncatalyzed reactions, respectively. In order to provide a more consistent picture, the k_c values of a number of other base catalysts were determined. Included in this series are the carbamoyl derivatives of some other isobiguanides, prepared from reaction of phenyl isocyanate with the appropriate isobiguanide.

TABLE I

REACTION BETWEEN PhNCO (0.08 *M*) AND 2-ETHYLHEXANOL (0.08 *M*) IN BENZENE USING 0.0016 *M* TMG·PhNCO

Time, hr.	Absorbance	Concn., moles/l.	k_2, l./mole-hr.
0.0		0.080	
0.151	0.542	.075	(5.65)
0.820	.454	.062	4.65
1.69	.372	.050	4.43
3.03	.291	.038	4.55
3.93	.260	.034	4.35
4.66	.239	.031	4.32
5.46	.213	.027	4.52
6.40	.198	.025	4.32

In Table II are tabulated the k_c values of the catalysts examined in this work. Whenever possible the pK_a values also are given. A plot of the catalyst pK_a values *vs.* their log k_c values in Fig. 1 shows the expected relationship between base strength and catalyst activity[15] for most of the catalysts employed. In agreement with the findings of previous work,[6] the comparative activity of 1,4-diaza[2.2.2]bicyclooctane (TED) is higher than its base strength would warrant. In direct contrast the activity of pentamethylguanidine (PMG) is much lower than its base strength would predict.

TABLE II

CATALYTIC ACTIVITIES IN THE REACTION OF PHENYL ISOCYANATE (0.08 *M*) WITH 2-ETHYLHEXANOL (0.08 *M*) IN BENZENE AT 26.8°[a]

Catalyst	k_2, l./mole-hr.	k_c	pK_a
Heptamethylisobiguanide (HpMIBG)	105. ± 3.	65,800	17.1
1,4-Diaza[2.2.2]bicyclooctane (TED[b])	8.89 ± 0.09	5,450	8.7
Pentamethylguanidine (PMG)	4.41 ± 0.17	2,660	15.6
2-(Phenylcarbamoyl)-1,1,3,3-tetramethylguanidine (TMG·PhNCO)	4.50 ± 0.05	2,720	10.4
N,N,N′,N′-Tetramethyl-1,3-butanediamine (TMBDA)	3.09 ± 0.07	1,830	10.1
4-(Phenylcarbamoyl)-1,1,2,2,3,3-hexamethylisobiguanide (HxMIBG·PhNCO)	2.38 ± 0.08	1,390	10.0
2,4-Bis(phenylcarbamoyl)-1,1,3,3-tetramethylisobiguanide (TMIBG·PhNCO)	1.03 ± 0.05	545	...
2,4-Bis(phenylcarbamoyl)-1,1,2,3,3-pentamethylisobiguanide (PMIBG·PhNCO)	0.65 ± 0.03	310	6.54

[a] $k_c = k_2 - k_0/[C]$; $k_0 = 0.16 \pm 0.04$ l./mole-hr. [b] Triethylenediamine.

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[13] I. Hechenbleikner and D. W. Kaiser, U. S. Patent 2,768,205.

[14] M. E. Bailey, V. Kirss, and R. G. Spaunburgh, *Ind. Eng. Chem.*, **48** 794 (1956).

[15] R. P. Bell, "Acid–Base Catalysis," Oxford University Press, Amen House, London E. C. 4, 1941, p. 82.

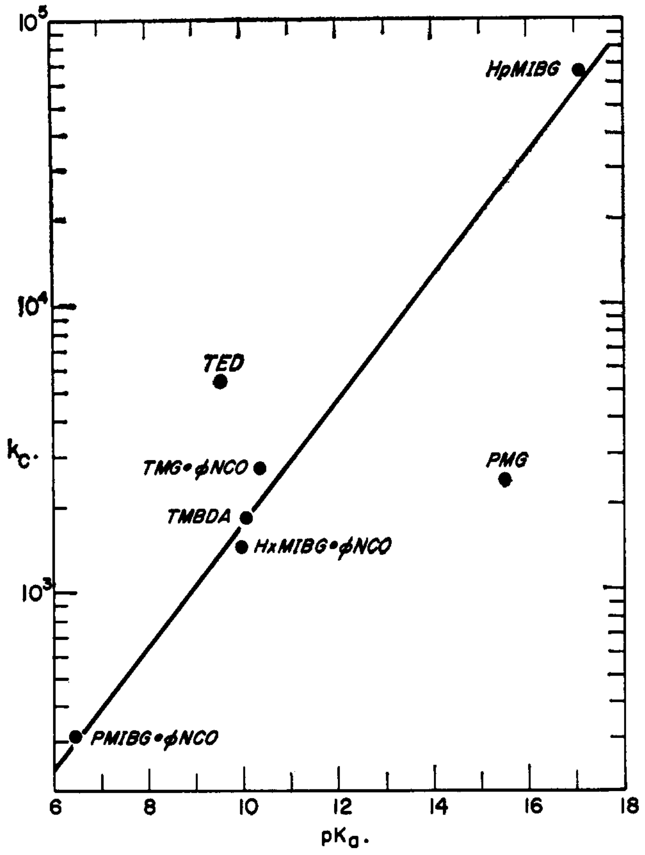
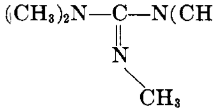


Fig. 1.—Relationship between log k_c and pK_a for various amine catalysts.

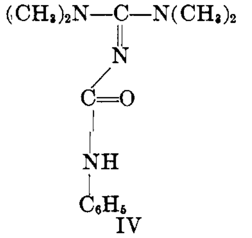
In general the catalytic rate constants (k_c) are directly related to the base strengths of the catalysts. The exceptionally high activity of heptamethylisobiguanide can best be explained in terms of high base strength together with minimum steric hindrance. The high efficiency of 1,4-diaza[2.2.2]bicyclooctane, a weak base relative to those used in this work, has been explained previously on the basis of its high nucleophilicity,[6] similar to quinuclidine.[16]

The low activity of pentamethylguanidine (III) is surprising when compared with the carbanilide of 1,1,3,-3-tetramethylguanidine (IV). Both materials appear



$(CH_3)_2N{-}\underset{\underset{\underset{CH_3}{\diagdown}}{N}}{\underset{\|}{C}}{-}N(CH_3)_2$

III
pK_a = 15.6



$(CH_3)_2N{-}\underset{\underset{\underset{\underset{\underset{C_6H_5}{|}}{NH}}{|}}{C{=}O}}{\underset{\|}{C}}{-}N(CH_3)_2$

IV
pK_a = 10.4

to be essentially sterically equivalent and yet IV, a weak base, exhibits approximately the same activity as III. It is possible that the methyl group on III produces a critical change in catalytic activity, but this explanation is not entirely satisfactory.

Polymerization of Phenyl Isocyanate.—It is well known that tertiary amines catalyze the trimerization of aromatic isocyanates. Since polymerization or trimerization does not involve an alcohol substrate, the initial interaction must occur between the base catalyst and the isocyanate. Thus, a measure of the effect of catalysts upon the polymerization of phenyl isocyanate would allow conclusions without the complicating presence of an alcohol.

The absolute rates of polymerization were not determined for each catalyst, but the relative order of catalytic activity was determined by measuring the per cent isocyanate reacted over a set time span. Table III compares polymerization and urethan catalytic activities with catalyst base strength. Again, it is seen that base strength of the amine catalyst is related to polymerization rate.

Table III

Catalysis of Polymerization of Phenyl Isocyanate[a] and Urethane Formation with 2-Ethylhexanol in Benzene

Catalyst[b]	Polymerization, catalytic activity[c]	pK_a	Urethane formation, catalytic activity[c]
1,4-Diaza[2.2.2.]bicyclooctane	4	8.7	2
2-(N-Phenylcarbamoyl)-1,1,3,3-tetramethylguanidine	3	10.4	3
Pentamethylguanidine	2	15.6	4
Heptamethylisobiguanide	1	17.1	1

[a] C_6H_5NCO = 0.08 M. [b] Catalyst = 0.0016 M. [c] The lower number designates the most active catalyst.

Deuterium Isotope Effect.—The reactions of phenyl isocyanate with methanol and methanol-*d* were investigated. The kinetic isotope effect k_i was determined from the relationship

$$k_i = \frac{k_c^H}{k_c^D} = \frac{\dfrac{k_2^H - k_0^H}{[C]}}{\dfrac{k_2^D - k_0^D}{[C]}}$$

where the superscripts H and D refer respectively to the reaction of the isocyanate with the normal and the deuterated alcohol. The subscripts retain the meanings given previously. Qualitatively, it can be seen from Table IV that the isotope effect increases as the base strength of the catalyst increases. Figure 2 shows more graphically the good agreement between the isotope effect and catalyst base strength.

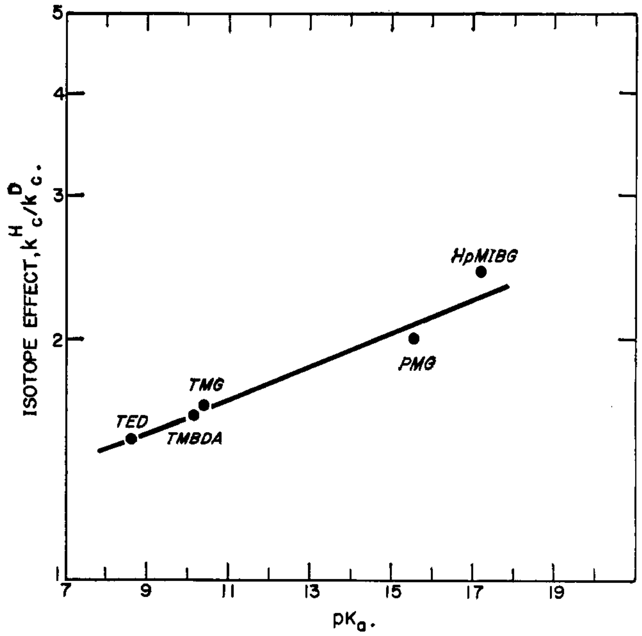


Fig. 2.—Relationship between isotope effect and catalyst base strength.

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(16) H. C. Brown and N. R. Eldred, *J. Am. Chem. Soc.*, **71**, 445 (1949).

TABLE IV

ISOTOPE EFFECT IN BENZENE[a]

Catalyst	k_0^H/k_0^D	pK_a
1,4-Diaza[2.2.2]bicyclooctane (TED)	1.48 ± 0.04	8.7
N,N,N′,N′-Tetramethyl-1,3-butanediamine (TMBDA)	1.72 ± 0.02	10.1
2-(N-Phenylcarbamoyl)-1,1,3,3-tetramethylguanidine (TMG·PhNCO)	1.79 ± 0.02	10.4
Pentamethylguanidine (PMG)	1.97 ± 0.07	15.6
Heptamethylisobiguanide (HpMIBG)	2.5 ± 0.2	17.1

[a] k_0^H = 0.22 l./mole-hr.; k_0^D = 0.11 l./mole-hr.; C_6H_5NCO = CH_3OH = CH_3OD = 0.08 *M;* catalyst = 0.0016 *M*.

Before discussing the evidence obtained from this work, it is necessary to point out that the steric argument advanced by most workers is not enough to distinguish between the two postulated mechanisms. From consideration of the transition states of both mechanisms, it is obvious that steric factors could be important in either of them.

To help substantiate this hypothesis, it is only necessary to compare, as in Table IV, the base strengths of some of the amines with their relative efficiencies in promoting both the trimerization of phenyl isocyanate and its urethan formation with 2-ethylhexanol.

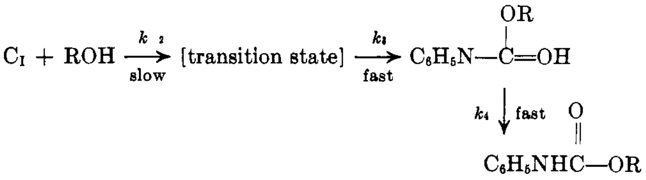
It is clear from these data that the formation of the amine–isocyanate complex necessary to effect polymerization is not noticeably sensitive to a steric element but is directly related to catalyst base strength. Since it is generally agreed that an amine–alcohol interaction should also be sterically insensitive, the apparent steric effect observed in urethan formation must arise through a "crowded" transition state, *regardless* of the identity of the complex that precedes it. That a similar transition state "crowding" does not arise in the polymerization of phenyl isocyanate might be explained by postulating an attack of the complex upon an unassociated isocyanate molecule, whereas its interaction in urethan formation may be with bulkier associated alcohol molecules.

As mechanism A is written, it is apparent that most of the O–H bond breaking occurs during the rate-determining step with the possibility of some bond breaking occurring in further steps. On the other hand, in mechanism B, bond breaking can occur in the fast equilibrium prior to formation of the transition state. An *a priori* theory concerning the mechanism would predict that mechanism B would produce an isotope effect *decreasing* with increasing base strength. That is, the amount of O–H breaking that could occur in the sensitive, rate-determining step would be decreased by any O–H breaking due to alcohol–base interactions. Stronger bases should produce relatively more O–H breaking in the alcohol–base complex than weaker bases.

Since our results definitely show that the isotope effect k_H/k_D and trimerization catalytic activity *increase* with increasing base strength, the most reasonable conclusion is that mechanism A is being followed. The isocyanate–base complex formed by the stronger bases produces relatively more O–H breaking in the transition state than do the weaker bases. The absolute size of the isotope effect leads to the conclusion that additional O–H breaking occurs after the rate-determining step.[17]

In agreement with the findings of Baker and coworkers, the following is offered as the most reasonable representation of the mechanism of the isocyanate–alcohol reaction.

$$C_6H_5NCO + R_3N\colon \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{complex } (C_I)$$



$$C_I + ROH \xrightarrow[\text{slow}]{k_2} [\text{transition state}] \xrightarrow[\text{fast}]{k_3} C_6H_5N{-}\overset{\displaystyle OR}{\overset{|}{C}}{=}OH \;\xrightarrow[\text{fast}]{k_4}\; C_6H_5NH\overset{\displaystyle O}{\overset{\|}{C}}{-}OR$$

Acknowledgment.—The p*K*a measurements were carried out by Dr. C. A. Streuli and Mr. T. Meade. Assistance in carrying out the infrared measurements was given by Dr. R. Hannan.

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[17] F. H. Westheimer, *Chem. Rev.*, **61**, 265 (1961).