BIFUNCTIONAL CATALYSIS BY AMIDES AND UREAS

IN THE REACTION OF AMINES WITH PHENYLISOCYANATE
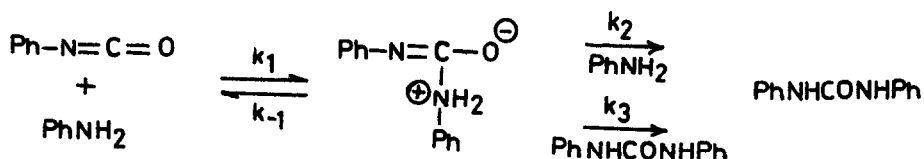
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Bifunctional catalysis has been observed in a variety of reactions and the possible role of such catalysis in enzyme systems has been discussed.[1] Amides other than 2-pyridone, have not been shown to be effective bifunctional catalysts.[2] We now report evidence for bifunctional catalysis by amides and ureas in the reaction between amines and phenylisocyanate.
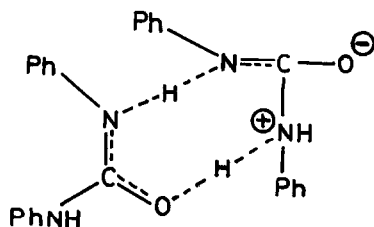
Catalysis by products is a general feature of the reactions of isocyanates.[4] Previous studies of the reactions with alcohols[5] and amines[6] showed complex kinetics and the nature of the catalysis was not elucidated. The choice of acetonitrile as solvent has avoided these complexities for the reaction of phenylisocyanate with aromatic amines. With the isocyanate in excess an accurately first order loss of amine is observed. However, the observed rate constant is linearly related to the initial amine concentration implying that the reaction is really second order in amine.[7] The reaction scheme

$$Ph-N=C=O + PhNH_2 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Ph-N=\overset{\ominus}{C}-O \overset{k_2}{\underset{PhNH_2}{\longrightarrow}} \overset{k_3}{\underset{PhNHCONHPh}{\longrightarrow}} PhNHCONHPh$$

is consistent with the observed kinetics provided $k_2 \simeq k_3$ (i.e. catalytic effect of the product is the same as for the reacting amine), and k_1 and $k_{-1} \gg k_2$ (or k_3). In solvents other than acetonitrile $k_2 \neq k_3$ and complex kinetics are observed. According to the above scheme the rate limiting step is proton transfer in the intermediate. The slow proton transfer is confirmed by a primary isotope effect

$(k_H/k_D = 1.3\text{-}2.0)$ using deuterated amines, and by the fact that catalysis by pyridine derivatives (Table) is consistent with proton transfer[8] but not with nucleophilic catalysis since the 2-substituted pyridines are effective catalysts.

The catalysis by the reacting amines and pyridines represents conventional base catalysis. In order to satisfy the condition $k_2=k_3$ catalysis by the product urea must be effected in a different manner since the urea is a much weaker base, and more sterically hindered than the reacting amine. We suggest that a bifunctional catalysis operates:

The product ureas are not specific catalysts. The Table records catalytic rate constants (k_3) for a range of amides, ureas, and carboxylic acids. Tetraethyl-ammonium iodide, N,N-dimethylacetamide and 2,4-pentanedione were without catalytic activity.

Benzoic acid and 2-pyridone are potent bifunctional catalysts for the muta-rotation of tetramethylglucose whereas benzamide has only a small effect.[3] In the present system they are all of comparable reactivity. The insensitivity of bifunctional catalysis to polar substituent effects has been noted.[9] Our results confirm this for the carboxylic acids, but the diphenylureas, phenylacylureas, acetanilides, and benzamides show an increase in activity on introducing electron donating substituents. The difference between amides and carboxylic acids probably reflects the asymmetrical nature of the transition state for catalysis by an amide since proton transfer is between oxygen and nitrogen atoms and not between two oxygen atoms. The unhindered cyclic acylureas, 2,4-(1H, 3H) quin-azolinedione and 5,5-dimethylhydantoin, are more effective than the phenyl-acylureas.
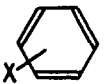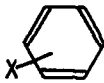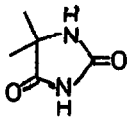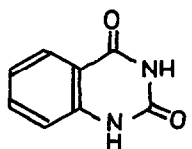
There has been considerable speculation on the question of bifunctional

TABLE

Catalysis of the reaction between aniline and phenylisocyanate in acetonitrile solution at 57°.

$[PhNH_2] = 5.3 \times 10^{-3}M$ $[PhNCO] = 0.183M$

Catalyst	$10^2 k_3 (M^{-1} sec^{-1})$	Catalyst	$10^2 k_3 (M^{-1} sec^{-1})$
NHCONHPh		4-Methoxyacetanilide	2.30
x = 4-MeO	4.1	4-Methylacetanilide	1.56
4-Me	2.8	Acetanilide	0.49
H	2.2	4-Chloroacetanilide	0.16
4-Cl	1.6	Acetamide	33.1
		Phthalimide	17.6
		4-Methoxybenzamide	34.0
NHCONHCOCH$_3$		4-Methylbenzamide	31.8
x = 4-MeO	15.2	Benzamide	29.3
H	13.0	4-Chlorobenzamide	25.6
3,4-diCl	11.3	4-Nitrobenzamide	19.0
N,N -Diphenylthiourea	8.5	2-Pyridone	17.8
Pyridine	24.6	4-Methoxybenzoic acid	41.6
2-Picoline	33.0	Benzoic acid	40.9
3-Picoline	31.8	4-Chlorobenzoic acid	39.0
4-Picoline	47.6	4-Nitrobenzoic acid	40.1
2,6-Lutidine	23.0		50.0
2,4,6-Collidine	25.7		59.8

catalysis in enzymic catalysis.[1] The observation that amides may be effective bifunctional catalysts presents further possibilities. Catalysis would not necessarily require the presence of the free carboxyl groups in aspartic and glutamic acids since catalysis could be effected by suitably placed peptide bonds.

References

1) P.R. Rony, J. Amer. Chem. Soc., 91, 6090 (1969), and references therein.

2) Some catalytic activity has been reported for benzamide[3] in the mutarotation of 2,3,4,6-tetramethyl-D-glucose but other amides are ineffective.[1]

3) C.G. Swain and J.F. Brown, J. Amer. Chem. Soc., 74, 2538 (1952).

4) A. Farkas and G.A. Mills, Advan. Catalysis, 13, 393 (1962).

5) J.W. Baker and J.B. Holdsworth, J. Chem. Soc., 713 (1947); J.W. Baker and J. Gaunt, J. Chem. Soc., 9 (1949).

6) J.W. Baker and D.N. Bailey, 4649, 4663 (1957); R.L. Craven, Amer. Chem. Soc., Div. Paint, Plastics and Printing Ink Chem., paper No 35, Amer. Chem. Soc. meeting, Atlantic City, Sept., 1956.

7) Using naphthylisocyanate we were able to follow the reactions using a large excess of amine. The reactions showed a second order dependence on amine.

8) e.g. J.M. Briody and D.P.N. Satchell, J. Chem. Soc., 3778 (1965).

9) L. do Amaral, K. Koehler, D. Bartenbach, T. Pletcher, and E.H. Cordes, J. Amer. Chem. Soc., 89, 3527 (1967).