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(16) A small uncertainty in the value of k_H results from the extrapolation of plots of k_{obsd} to zero buffer concentration, because of the possible contribution of partially rate-determining amine expulsion (k_{2H}; see text) to some of these extrapolated rate constants used in the determination of k_H. Based on the values for the individual rate constants cited in the text, the experimental value of k_H differs from k_{1H} for fully rate-determining water attack by no more than 20%. This uncertainty is insufficient to account for the observed deviation of k_H from the Brønsted plot for general acid catalysis of the attack step.
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Elimination–Addition Mechanisms of Acyl Group Transfer: The Hydrolysis and Synthesis of Carbamates

Huda Al-Rawi and Andrew Williams*

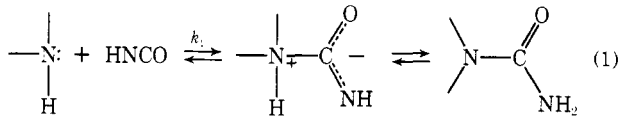
Contribution from the University Chemical Laboratories, Canterbury, Kent, England. *Received September 21, 1976*

Abstract: The equilibrium constants for formation of aryl carbamates from isocyanic acid and a series of phenols have been measured. The Bronsted β_N value for the reaction of phenolate anion with isocyanic acid and the selectivity of the equilibrium constant for formation of carbamate anion $ArO^- + HNCO \rightleftarrows ArOC(NH)O^-$ are consistent with a transition state half-way between reactants and product. The Bronsted selectivity for the latter equilibrium indicates that the carbamide group $[-CO(NH)^-]$ is significantly more electropositive than a proton in electrophilic attack on aryl oxide ions. The formation and decomposition of carbamoyl phosphate, an important metabolite, does not involve intramolecular proton transfer concerted with C–O bond fission.

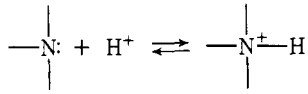
Introduction

It was recently shown[1,2] that attack of strong amines on isocyanic acid (eq 1) possesses a relatively low Bronsted selectivity (β_N) with respect to changing ammonium ion structure. Decomposition of the zwitterionic intermediate becomes rate limiting at low amine basicity, giving rise to a higher β_N value derived from a composite rate constant. Low selectivities have also been observed for attack of nucleophiles on a number of heterocumulenes.[3,4] The β_N obtained from the Bronsted type relationship essentially measures the selectivity of a reaction vs. the ionization of the conjugate acid of the nucleophile and therefore does not provide strong evidence for the structure of the transition state of the reaction. Comparison of reactivity change with change in equilibrium constant for the reaction yields more meaningful β_N quantities, and this type of result is available for many acyl transfer reactions[5] and recently for reaction of alcoholate anions with carbon dioxide.[4] This type of selectivity is somewhat difficult to obtain because of the scarcity of good data on equilibrium constants, so it is not surprising that the ionization equilibria are used as general standards.

The equilibrium constant for formation of the zwitterion (eq 1) from amine and isocyanic acid is unfavorable[2] whereas the



(1)



(2)

low value for β_N (vs. the pK_a of the ammonium ion) suggests an early transition state apparently violating the Hammond postulate.[6] "Anti-Hammond" behavior could arise from three sources: (1) the β_N may not be a good measure of the position of the transition state because the ionization of the conjugate acid of the nucleophile is not a good comparison with the equilibrium, (2) the Hammond postulate refers to potential energies whereas reactivities and equilibria are free energies and possess an entropy component which may not be negligible or cancel, (3) some subtle effect such as that discussed by Pross[7] may be operating.

This work seeks to obtain the effect of structure variation on the equilibrium constant and individual rate constants for the reaction of phenolate anions with isocyanic acid.

Experimental Section

Materials. Phenyl carbamate was purchased from Aldrich and other aryl carbamates were prepared by the following procedure. Phenol (0.2 mol) was dissolved in carbon tetrachloride (100 mL) and dry, powdered sodium cyanate (13 g) was added. The mixture was stirred while a solution of trichloroacetic acid (33 g) in carbon tetrachloride (80 mL) was added. Stirring was continued at 55 °C for 3 h, water added, and the organic layer separated. The carbon tetrachloride solution was dried with Na_2SO_4, evaporated, and the residue recrystallized from a suitable solvent (Table I). This procedure worked well

Table I. The Hydrolysis of Carbamate Derivatives[b]

Ester	Mp, °C	k_{OH}, M^{-1} s^{-1}	pK_a[a]	λ, nm	k_1, M^{-1} s^{-1}
		Phenyl ester			
1. Unsubstituted[i]		220	9.95	270	210
2. 4-Chloro[l,r]	159–161 (142)[j]	940	9.38	280	160
3. 4-Methoxy	129–130 (127–129)[j]	81	10.2	290	260
4. 4-Methyl[m,r]	158–159	120	10.19	375	250
5. 4-Nitro[m,r]	119–120[k]	2×10^5	7.14	350	6.7
6. 3-Nitro[m,r]	131–132	3.2×10^4	8.35	400	48
7. 3-Chloro[n,r]	130–132 (135–137)[j]	2.6×10^3	9.02	350	58
8. 4-Formyl[u]			7.60	320	3.8
9. 4-Acetyl[m,r]	151–152	3.8×10^4	8.05	325	7.5
10. 3-Ethoxycarbonyl[m,r]	119–120	2.7×10^3	8.90[t]	300	49
11. 4-Ethoxycarbonyl[m,r]	132–133	2.0×10^4	8.50	260	19
		Other derivatives			
12. $-OPO_3^{2-}$		1.9[f,g]	12.32		1.5×10^3
13. $-OPO_3H^-$		1.6×10^5[f,g]	7.21		9.8
14. $-OC_2H_5$		2×10^{-5}[e]	16.0[4]		
15. $-NHNO_2$		1.9×10^5[c]	6.6[d]		
16. -ImidazoliumH$^+$		7.6×10^7[h]	7.17[2]		71
17. -*N*-Methylimidazolium$^+$		9.3×10^7[h]	7.20[2]		135
18. $-N_3$	96–97[q]	1.1×10^5	4.70[1]	230	17
19. $-SC_6H_5$	96–97[p]	2.3×10^5	6.53[s]	290	
20. H_2O			−1.7		7.9×10^{-2}[8]
21. OH^-			16.4[4]		9.8×10^2[8]

[a] For the conjugate acid of the leaving group; taken largely from J. Regenstein and W. P. Jencks, "Handbook of Biochemistry", 2nd ed, H. A. Sober, Ed., Chemical Rubber Co., Cleveland, 1970. [b] Except where stated conditions are: 25 °C, ionic strength made up to 1 M with KCl. [c] B. Boopsingh and J. M. Briody, *J. Chem. Soc., Perkin Trans. 2,* 1487 (1972); data are extrapolated to 25 °C from parameters at higher temperatures and utilize the pK_a of nitrourea (3.47). [d] This pK_a is calculated from data in J. N. Bronsted and H. C. Duus, *Z. Phys. Chem.,* **108,** 185 (1924) and J. N. Bronsted and C. V. King, *J. Am. Chem. Soc.,* **49,** 193 (1927). [e] Unspecified ionic strength; calculated from data of Dittert and Higuchi.[25] [f] Ionic strength 0.6 M. [g] 37 °C; calculated from data in C. M. Allen and M. E. Jones, *Biochemistry,* **3,** 1238 (1964) and M. E. Jones and F. Lipmann, *Proc. Natl. Acad. Sci. U.S.A.,* **46,** 1194 (1960). [h] Calculated from the hydroxide dependent rate constant (at low pH) from the pH profile for the hydrolysis of *N*-carbamoylimidazole.[2] [i] Recrystallized from benzene–petroleum ether from the commercial product. [j] J. H. Barnes, M. V. A. Chapman, P. A. McCrea, P. G. Marshall, and P. A. Walsh, *J. Pharm. Pharmacol.,* **13,** 39 (1961). [k] Dittert and Higuchi[25] quote 110–140 °C and a value 161 °C is reported in German Patent 318 803, Feb 13, 1920 [*Chem. Zentralbl.,* **91,** 15 (1920)]. [l] Recrystallized from ethyl acetate. [m] Recrystallized from methanol. [n] Recrystallized from benzene. [p] T. Wagner-Jauregg, H. Vonderbank, and H. Witzel, *Chem. Ber.,* **81,** 417 (1948), find mp 96–97 °C. [q] Allen and Jones (footnote *g*) find mp 96–98 °C. [r] Analyses for these compounds are as follows:

Compound	Found, % C	H	N	Formula	Requires, % C	H	N
4-Chloro	48.5	3.3	8.0	$C_7H_6ClNO_3$	49.0	3.5	8.2
4-Methyl	63.7	6.3	9.4	$C_8H_8NO_3$	63.6	6.0	9.3
4-Nitro	45.8	3.6	15.1	$C_7H_6N_2O_4$	46.2	3.3	15.4
3-Chloro	48.6	3.5	8.2	$C_7H_6ClNO_3$	49.0	3.5	8.2
3-Nitro	46.0	3.4	15.3	$C_7H_6N_2O_4$	46.2	3.3	15.4
4-Acetyl	60.1	5.3	7.6	$C_9H_9NO_3$	60.3	5.1	7.8
3-Ethoxycarbonyl	57.6	5.2	6.8	$C_{10}H_{11}NO_4$	57.4	5.3	6.7
4-Ethoxycarbonyl	57.6	5.1	6.6	$C_{10}H_{11}NO_4$	57.4	5.3	6.7

[s] M. M. Kreevoy, E. T. Harper, R. E. Duvall, H. S. Wilgers, and L. T. Ditsch, *J. Am. Chem. Soc.,* **82,** 4899 (1960); M. M. Kreevoy, B. E. Eichinger, E. E. Story, E. A. Katz, and J. H. Sallstedt, *J. Org. Chem.,* **29,** 1641 (1964). [t] Determined by titration using radiometer pH equipment. [u] We were unable to synthesize samples of this compound by the methods described in the materials section.

for the least acidic phenols; the preparation of 4-nitro- and 3-nitrophenyl carbamates required the use of chloroform as a reaction solvent.

Carbamoyl azide was prepared by adjusting the pH of a solution of potassium cyanate (8.1 g), sodium azide (6.5 g), and water (50 mL) using HCl to 5.0. The azide product precipitated, and the solution was extracted with ether (3 × 100 mL). The ether was dried with Na_2SO_4 and evaporated, and the residue was recrystallized from ether (Table I).

Substituted phenyl *N*-methylcarbamates were prepared by adding dropwise, with stirring, a solution of methyl isocyanate (10 mmol) in dichloromethane (10 mL) to the phenol (10 mmol) dissolved with triethylamine (10 mmol) in dichloromethane (20 mL). The solution was kept for 3 to 4 h and extracted with 2 M HCl, and the organic layer (dried over $MgSO_4$ and filtered) was evaporated. The product was recrystallized from the solvent indicated in Table II. The procedure was slightly different for the 2,4- and 2,6-dinitrophenyl esters in that the product crystallized directly from the reaction mixture, and no extraction was necessary.

Carbamates of 3- and 4-ethoxy- and 4-acetylphenols were prepared by dissolving 1 mmol of phenol in 1 mmol of chlorosulfonyl isocyanate and hydrolyzing the product with water.

S-Phenyl thiocarbamate was prepared by adding acetic acid (1 mL) over a period of 5 min to a stirred suspension of thiophenol (1 g) and potassium cyanate (0.8 g) in water (10 mL). After about 15 min, a precipitate formed which was filtered and recrystallized (Table I).

Structures of the substrates were confirmed by use of infrared spectra determined with Unicam SP 200 or Perkin-Elmer Model 237 instruments using Nujol mulls. NMR spectra and mass spectra were also utilized. The former were obtained with a Perkin-Elmer R 10 machine or with the help of Dr. D. O. Smith using a Jeol PP 100 Mc/s instrument equipped with Fourier transform apparatus. The latter were recorded by Dr. R. B. Turner using an A.E.I. MS 902 high-resolution mass spectrograph. Elemental analyses were carried out

Table II. Hydrolysis of *N*-Methylcarbamate Esters[a]

Ester	Mp, °C	Lit. mp, °C	k_{OH}, M^{-1} s^{-1} [a]	pK_a^{ROH} [b]	λ, nm
		Phenyl esters			
1. Unsubstituted[h]	84–85	85–86[d]	3.4[l]	9.95	287
2. 4-Nitro[e,j]	145–146	160.5–162[d]	3600[m]	7.14	400
3. 3-Nitro[e]	129–130	130–131[d]	110	8.35	270
4. 4-Chloro[e]	116–117	115–116[d]	8.1	9.38	250
5. 2-Nitro[f]	88–89	87–88[d]	5200	7.23	430
6. 2-Chloro[f]	90–91	80.5–81[d]	64	8.48	290
7. 3-Chloro[f]	80–81	95–96[d]	17	9.02	240
8. 4-Methyl[f]	95–96		0.58	10.19	240
9. 4-Formyl[f,j]	126–128		610	7.66	262
10. 4-Methoxy[f,j]	95–96		0.40	10.20	307
11. 4-Acetyl[g,j]	107–108		180	8.05	260
12. 2,4-Dinitro[i,j]	97–99	130–131[d]	7.7×10^6	4.11	400
13. 2,6-Dinitro[i,j]	114–115		2.4×10^5	5.23	430
14. 2-Chloro-4-nitro[e,j]	135–136		2.0×10^5	5.45	290
15. 4-Chloro-2-nitro[e]	148–149		6.0×10^4	6.46	430
		Other			
16. Ethyl ester			5.7×10^{-6} (24)	16.0[n]	
17. Methyl isocyanate (pH(D) 6.00)					

$k_{H_2O} = 1.47 \times 10^{-3}$ s^{-1}, $k_{D_2O} = 1.01 \times 10^{-3}$ s^{-1}, $k_{H_2O}/k_{D_2O} = 1.45$

[a] 25 °C, ionic strength made up to 1 M with KCl. [b] pK_a of the conjugate acid of the leaving group taken from the compilation quoted in footnote *a* of Table I. [c] Wavelength for kinetic study. [d] M. J. Kolbezen, R. L. Metcalf, and T. R. Fukuto, *Agric. Food Chem.*, **2**, 864 (1954). [e] Recrystallized from methanol/water. [f] Recrystallized from *n*-hexane. [g] Recrystallized from acetone. [h] Recrystallized from benzene/petroleum ether. [i] Recrystallized from ethanol/water. [j] These esters gave the following analyses:

	Found, %				Requires, %		
Ester	C	H	N	Formula	C	H	N
4-Nitro	48.7	4.1	14.3	$C_8H_8N_2O_4$	49.0	4.1	14.3
4-Formyl	60.4	5.1	7.8	$C_9H_9NO_3$	60.3	5.1	7.8
2,4-Dinitro	39.7	3.0	16.9	$C_8H_7N_3O_6$	39.8	2.9	17.4
4-Acetyl	62.3	5.8	7.2	$C_{10}H_{11}NO_3$	62.2	5.7	7.3
4-Methoxy	59.5	6.0	7.8	$C_9H_{11}NO_3$	59.7	6.1	7.7
2,6-Dinitro	39.8	2.9	17.3	$C_8H_7N_3O_6$	39.8	2.9	17.4
2-Chloro-4-nitro	41.6	3.0	12.1	$C_8H_7ClN_2O_4$	41.7	3.1	12.2
4-Chloro-2-nitro	41.6	2.9	12.2	$C_8H_7ClN_2O_4$	41.7	3.1	12.2

[l] Dittert and Higuchi find 1.2×10^2 M^{-1} min^{-1}.[25] [m] Dittert and Higuchi find 3.5×10^4 M^{-1} min^{-1}.[25] [n] P. Ballinger and F. A. Long, *J. Am. Chem. Soc.*, **82**, 795 (1960).

by Mr. G. Powell using a Hewlett-Packard Model 185 CHN analyzer in this laboratory.

Buffers and other materials were of analytical reagent grade or were recrystallized or redistilled before use. Water, doubly distilled from glass, was used throughout the work. D_2O (99.8%) was from Prochem Ltd.

Methods. The hydrolysis of the carbamates was followed spectrophotometrically using the appropriate wavelength (Tables I and II). A stock solution of the ester (usually λ 50) in ethanol was added on the tip of a glass rod (flattened at one end) to buffer (2.5 mL) in a silica cell in the thermostated cell compartment of the spectrophotometer (Beckmann DBG or Unicam SP 800 both equipped with Servoscribe recorders). The zero time was accurately determined by activating the recorder at the instant of addition of ester. The pH of the solution in the cell was measured before and after reaction using a Pye Dynacap pH meter calibrated with E.I.L. buffer powders accurate to ±0.01 unit. Pseudo-first-order rate constants were measured from the plots of $(OD_t - OD_\infty)$ vs. time using two-cycle semilogarithmic paper. The appropriate wavelength for study was determined in separate experiments using repetitive wavelength scanning of the hydrolytic reactions.

Reaction of phenols with isocyanic acid was carried out with buffers at a pH sufficiently high to reduce the rate of hydrolysis of the isocyanic acid present as ion at 1 M concentration. Equilibrium was not attained between synthetic carbamate and the reactants because the hydrolysis of the cyanate causes a slow increase in pH and also depletes the cyanate concentration level. An aliquot of the phenol in ethanol (usually λ 50) was added to buffer (2.5 mL) in the thermostated cell compartment of a spectrophotometer and containing potassium cyanate (1 M) and 0.1 M *N*-ethylmorpholine adjusted to a pH between 7 and 8. The absorption at the appropriate wavelength (Table I) was monitored on the external recorder and decreased steadily due to the formation of aryl carbamate and the depletion of free phenol. As time progresses the absorption starts to rise, and this is judged to be caused by an increase in pH (pH was monitored at intervals) resulting from cyanate hydrolysis effecting the decomposition of the carbamate. The rate of increase in pH in the ultraviolet cell was slower in the pH range 7–8 than in the 6–7 range (2,6-lutidine buffer) because cyanate decomposition is proportional to acidity in this region.[1,8]

The hydrolysis of the synthetic carbamates indicated that the extinction coefficient at the wavelength employed for kinetics is negligible for the ester as compared with the resulting phenols. We assume the same is true for those reactions where the synthetic carbamate is not available; this is a reasonable assumption because other esters of these phenols show negligible absorption at these wavelengths compared with the free phenol. The rate constant for carbamate formation is obtained by dividing the initial rate of decrease in optical density by the absorbance at zero time.

In order to test that carbamates were being formed in the synthetic reaction of cyanate with phenols, we studied the hydrolysis of the material from reaction with 4-nitrophenol. 4-Nitrophenol (13.9 mg) was dissolved in a solution of potassium cyanate (1 M, 0.1 M 2,6-lutidine buffer, 10 mL) and brought to pH 6 in a pH stat. After holding at pH 6 for 10 min, an aliquot of the solution (λ 50) was added to phosphate buffer at pH 6.0 (1 M ionic strength, 25 °C) and the rate constant for release of absorbance at 400 nm measured.

The hydrolysis of methyl isocyanate was carried out in the thermostated cell of a Radiometer pH-stat assembly and followed by the addition of 0.01 M HCl. The pH(D) of the solution was maintained at 6.00.

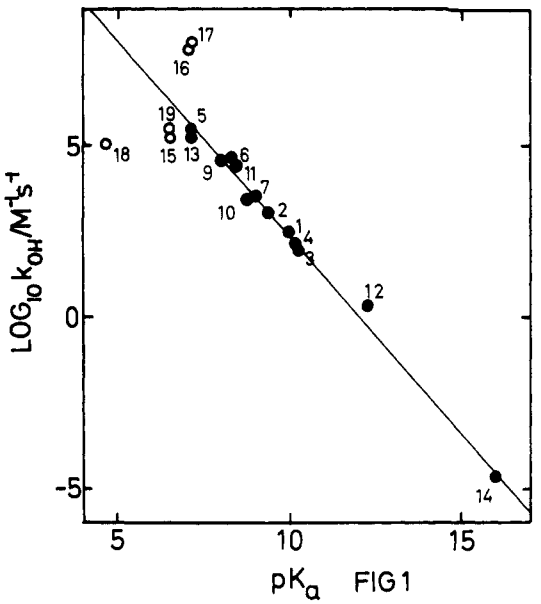


Figure 1. Plot of log k_{OH} vs. the pK_a of the conjugate acid of the leaving group for carbamate hydrolysis. The numbering scheme and conditions are as quoted in Table I; the line has a slope −1.15 and is drawn to correlate only the phenyl carbamates. Filled circles represent oxyanion leaving groups.

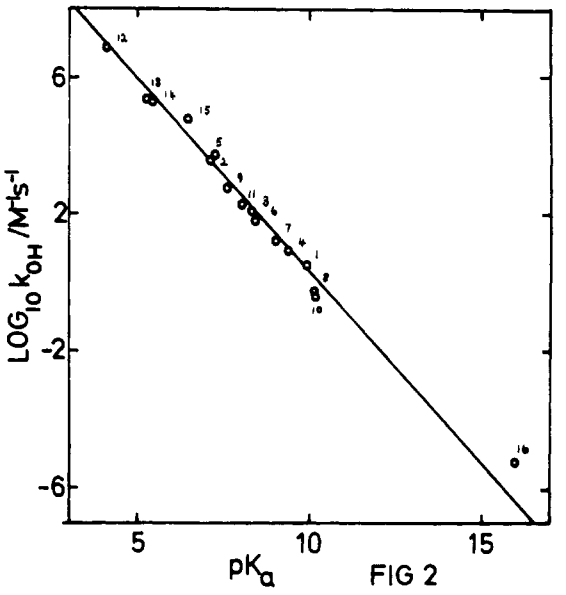


Figure 2. Plot of log k_{OH} vs. pK_a of the conjugate acid of the departing group for the hydrolysis of *N*-methylcarbamates. The numbering scheme and conditions are as reported in Table II; the line has a slope −1.1.

Results

The carbamate derivatives (Tables I and II) hydrolyzed in buffer with pseudo-first-order rate constants. Selected derivatives were shown to hydrolyze independently of buffer concentration or type, and the pseudo-first-order rate constants were proportional to hydroxide ion concentration. Second-order rate constants (k_{OH}) were calculated by dividing through by hydroxide ion concentration, and these are illustrated in Figures 1 and 2 as Bronsted type plots vs. the pK_a of the conjugate acid of the leaving group. In the case of the 4-nitrophenyl carbamates, the extinction coefficient (at 400 nm) of 4-nitrophenol at the pH in question and the observed final absorption indicated complete hydrolysis.

Reaction of nucleophiles with isocyanic acid yields an ambiguous rate law involving the pairs: nucleophile/isocyanic acid or nucleophileH^+/cyanate ion; there is ample evidence[1,2] to show that the isocyanic acid is the reactive species, and our calculations assume this to be the case. The rate law for the phenol reaction with the cyanate ion (under the conditions of our experiments the major species were cyanate and free phenol) is converted to phenolate/isocyanic acid using the pK_a of the phenol and that of isocyanic acid (3.29)[1] under the conditions of the experiments. Over the limited pH range employed, the rate of carbamate formation from a constant phenolate and cyanate ion concentration is invariant in accord with the rate law. In the synthesis of 4-nitrophenyl carbamate, the rate constants varied by only 6% from pH 6.4 to 7.5. The rate constant from the zero-order rate is not the same as that for approach to equilibrium, but the latter may not be measured owing to hydrolysis problems already discussed in the Experimental Section. That aryl carbamates are formed in the reaction of phenols with cyanate is clearly shown by the similar rate constants for hydrolysis of the synthetic 4-nitrophenyl carbamate (2.1×10^{-3} s^{-1}) at pH 6.02 and the material prepared in situ (2.2×10^{-3} s^{-1}) in phosphate buffers. The Bronsted type plot of log k_1 vs. the pK_a of the attacking phenol is illustrated in Figure 3.

The equilibrium constant for formation of substituted phenyl carbamates may be obtained from the rate constants for forward and reverse reactions (k_{OH} and k_1); these parameters are

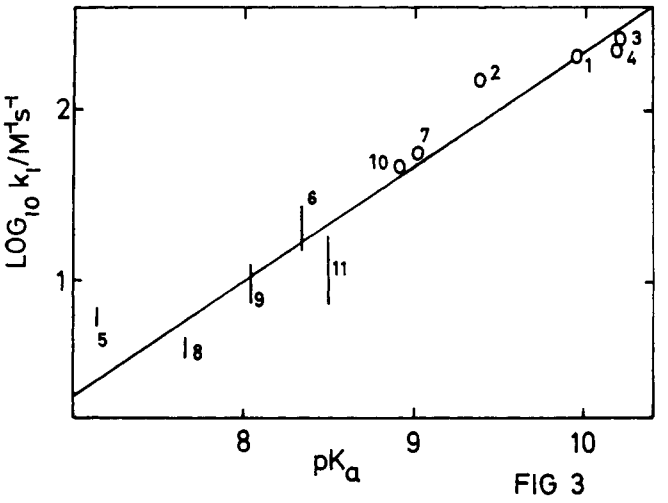


Figure 3. Bronsted type correlation of log k_1 and the pK_a of the phenol for reaction of phenolate ion with isocyanic acid; see Table I for details. Line has the slope +0.66; the vertical lines represent errors where they are large enough to show up on the logarithmic plot.

included in Table I with equilibrium constants for other carbamate reactions. It is impossible at this stage to estimate the equilibrium constants for the *N*-methylcarbamates owing to the hydrolytic lability of methyl isocyanate which may not be depressed by ionization as for the parent isocyanic acid.

$$HNCO + {}^-OAr + H_2O \rightleftharpoons NH_2CO_2Ar + OH^- \quad (3)$$

$$[NH_2CO_2Ar][OH^-]/[HNCO][{}^-OAr] = k_1/k_{OH} = K_1 \quad (4)$$

$$[NH_2CO_2Ar]/[HNCO][HOAr] = k_1K_a^{ArOH}/(k_{OH}K_w) = K_2 \quad (5)$$

Discussion

There is abundant evidence to indicate that the hydrolysis of aryl carbamates involves an isocyanate intermediate (eq 6).[9] The synthesis of carbamate from isocyanic acid must, by the principle of microscopic reversibility, follow the same mechanistic pathway as its decomposition.

$$NH_2CO_2Ar \underset{-0.5}{\overset{-1.15}{\rightleftharpoons}} {}^{-}NHCO_2Ar \underset{-0.65}{\overset{-1.81}{\rightleftharpoons}} HNCO + {}^{-}OAr \quad (6)$$

Although we can only at present estimate the ionization constants for aryl carbamates to an order of magnitude, the effect of changing the phenyl substituent on this value may be quite accurately determined. The Bronsted exponent for the effect of changing the phenyl group in substituted phenyl *N*-(4-nitrophenyl)carbamates is 0.5:[10]

$$NO_2C_6H_4NHCO_2Ar \rightleftharpoons NO_2C_6H_4\bar{N}CO_2Ar + H^+ \quad (7)$$

$$\log K_a = -0.5pK_a^{ArOH} + \text{constant} \quad (8)$$

this exponent refers to the ionization of the corresponding phenol as standard. Molday and Kallen[11] studied the hydroxide ion catalyzed proton exchange of *N*-methylamides:

$$CH_3NHCOX \rightleftharpoons CH_3\bar{N}COX + H^+ \quad (9)$$

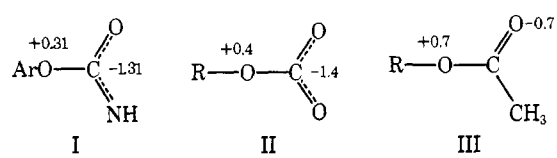
the base-catalyzed rate constant may be related to the ionization constant by the equation $k_{exch} = k/(1 + 10^{-(pK_{acc}-pK_{don})})$ and the resulting pK_a obeys a good Taft correlation. Since ρ^* and ρ are defined on the same scale, we may use the conversion factor (1/2.23) to obtain the corresponding β; the conversion factor is derived from the Hammett ρ value for the ionization of phenols.[12a] The observed ρ^* value corresponds to a β of -0.5 to -0.6. These β values refer to ionization of an NH group bearing either aliphatic or aromatic substituents, and since they are approximately identical, we judge that β for the ionization of the parent carbamates is close to -0.5. Recently Bergon and Calmon[12b] measured the alkaline hydrolysis rate constants for aryl and alkyl *N*-acetylcarbamates and found a sensitivity of the pK_a of the NH group toward the pK_a of the leaving group to be 0.3. In this system there is a delocalization of charge over system i, thus the substituents would have less effect than in the present carbamates where the charge is more localized.

$$CH_3\overset{\frown}{CO}\text{-}\bar{N}\text{-}\overset{\frown}{CO}CH_3$$

i

The rate constants for carbamate formation (k_1) and decomposition (k_{OH}) allow an overall equilibrium constant to be determined for eq 6, and the variation of this equilibrium constant with phenol has a $\beta = -\beta_N + \beta_{LG} = -0.66 - 1.15 = -1.81$. The equilibrium constant for the decomposition of the conjugate anion of the carbamate (to give isocyanate) has a Bronsted sensitivity $\beta = -1.81 - (-0.5) = -1.31$ compared with the pK_a of the leaving phenol.

The β value for the loss of unit negative charge upon protonation of the phenolate ion is by definition unity; this means that, since the β value for synthesis of carbamate anion from phenoxide ion and isocyanic acid is -1.31, electron-donating substituents stabilize the aryl carbamate anion relative to free phenols by the amount that would be expected if there were an effective positive charge of 0.31 on the ether oxygen. In spite of the negative charge on the amido group, there is sufficient electron delocalization into it to render it more strongly electron withdrawing relative to hydrogen. A similar observation was made by Sauers, Jencks, and Groh[4] for the reaction of carbon dioxide with alkoxide ions. The slightly lower charge on the ether oxygen (I) compared with that in II is possibly due to the lower electron-withdrawing power of the amide anion compared with the carboxylate probably resulting from the more electropositive nitrogen in the former. These results are of the correct order compared with transfer of the more electron-withdrawing acetyl group (III) which induces an effective charge of +0.7 on the ether oxygen.[5,13,14]



I II III

Since we know the β values for all the equilibria in the synthetic scheme for carbamates (eq 6), we may estimate the transition-state structure for attack of aryl oxide on isocyanic acid *relative to reactants and products*. The Bronsted selectivity of k_1 is +0.66 (see Figure 3), thus there is $-1 + 0.66/1.31 = -0.5$ more negative charge on the ether oxygen in the transition state than in the product relative to a unit difference of charge on this oxygen between reactants and product. The corresponding value for attack of alkoxide ion on carbon dioxide ($-1 + 0.33/1.4 = -0.76$) is more negative than the oxygen in the isocyanic acid case, suggesting a later transition state for the latter. This is contrary to the conclusion of Sauers, Jencks, and Groh[4] who indicate that the development of charge on the oxygen in the decomposition of conjugate base is similar for both cases. This indication is based on the comparison of β_{LG} for the alkaline hydrolysis of alkyl and aryl *N*-phenylcarbamates (-1.15) and the decomposition of alkyl carbonates (-1.1); the former parameter, however, is composed of an equilibrium and a decomposition step both with separate β values. Comparison of the reactivity of alkoxide ions with carbon dioxide[15] and aryl oxide ions with isocyanic acid indicates that, if the Bronsted type line holds for all oxide ions in each case, then a hypothetical oxide with $pK_a^{ROH} = 10$ has a tenfold greater reactivity toward carbon dioxide than isocyanic acid. This could be a lower limit as it is known that Bronsted plots for oxyanion attack on acyl compounds show depression of rate constants for alkoxide ions from the line for aryl oxide ions.[16] The rather small difference in reactivity is in the correct direction according to the Hammond postulate[6] for the transition state for the isocyanate reaction to be later than for the carbon dioxide one. Of course the difference in reactivity will depend on the pK_a of the nucleophile because of the selectivity difference.

We are not yet in a position to determine β for the equilibrium between nucleophiles and other heterocumulenes and may not therefore discuss the nature of the transition state for nucleophilic attack relative to ground and product states. Table III illustrates a collection of β_N values (vs. pK_a of attacking nucleophile) for a series of heterocumulene reactions. The main conclusions from these data are that β_N lies below 0.5 with the sole exception of the present study. This is so despite a fairly wide range of reactivity values and favorable and unfavorable equilibrium constants; this is not inconsistent with Hammond's postulate.[6] The equilibrium constant for zwitterion formation from 4-anisidine and isocyanic acid (some 10^{-7})[2] is extremely unfavorable, yet the β_N ($\sim$0.3)[1] suggests an early transition state. However, a considerable proportion of the unfavorable free energy must be due to entropies of translational and rotational motion lost in bringing the two reactants together, and these are not accomodated in the Hammond approach. Moreover, reactivity is of necessity a free-energy quantity possessing its own entropy of activation component.

Equilibrium Constants for Carbamate Formation. It is difficult to measure the dissociation constants of aryl carbamates since these species decompose rapidly under the conditions of the normal techniques[17] and isotope exchange methods are not capable of measuring the high rates. Estimation of pK_a's from linear free-energy relationships starting with reasonable models is a valid method for our purposes since these values are not required to a high degree of accuracy. We are not able to use the simple σ_I for phenoxy[18] to estimate the pK_a for phenyl

Table III. Reaction of Nucleophiles with Heterocumulenes

Nucleophile	Hetero-cumulene	k, M^{-1} s^{-1} [g]	β_N	K, M^{-1} [h]
RNH_2	CO_2	5900[c]	0.26[a,e]	1[i]
RNH_2	HNCO	840[c]	0.3[c-e]	footnote k
RNH_2	CS_2	0.25[j]		500[j]
RO^-	CO_2		0.3[f]	1.5×10^8[f]
RNH_2	COS	59[b]	0.26[b]	
RNH_2	C_2H_5NCS	4.2×10^{-2}[c]	0.28[c]	
RNH_2	C_2H_5NCO	840[d]	0.3[d]	
$C_6H_5O^-$[l]	HNCO	210	0.66	0.076

[a] Reference 3a. [b] M. M. Sharma[3c] finds $\log k_{am.COS} = \log k_{am.CO_2} - 2$. [c] Reference 1. [d] G. R. Stark [*Biochemistry*, **4**, 1030 (1965)] finds that HNCO and ethyl isocyanate have equal reactivity to amines. [e] Reference 3b. [f] Reference 4. [g] This value refers to experimental data for ethylamine and in some cases values estimated for this amine from Bronsted type plots. [h] $K = K_a^{NH}(K_1/K_w) = [^-NHCOX]/[HNCO][X]$ as in eq 11. [i] Derived from data in M. Caplow, *J. Am. Chem. Soc.*, **90**, 6797 (1968), assuming the pK_a of $C_2H_5{}^+NH_2CO_2{}^-$ is approximately 5 [see S. L. Johnson and D. L. Morrison, *J. Am. Chem. Soc.*, **94**, 1323 (1972)]. [j] Calculated from data in S. J. Joris, K. I. Aspila, and C. L. Chakrabarti, *Anal. Chem.*, **41**, 1441 (1969). [k] If the Bronsted β for K for the reaction of amines with isocyanic acid is unity then K for ethylamine is $2.8 \times 10^{-2} M^{-1}$ starting with $K = 8.1 \times 10^{-8}$ M^{-1} for 4-anisidine.[2] [l] This work.

Table IV

System	pK_a
$CH_3COCH_2COCH_3 \rightleftarrows CH_3COC^-HCOCH_3 + H^+$	9.3[21]
$CH_3COCH_2COOC_6H_4$-4-$NO_2 \rightleftarrows$ $CH_3COC^-HCOOC_6H_4$-4-$NO_2 + H^+$	8.5[20]
$C_2H_5OCOCH_2COCH_3 \rightleftarrows C_2H_5OCOC^-HCOCH_3 + H^+$	10.5[21]
$C_2H_5OCOCH_2COOC_6H_4$-4-$NO_2 \rightleftarrows$ $C_2H_5OCOC^-HCOOC_6H_4$-4-$NO_2 + H^+$	10.4[20]

N-methylcarbamate from the values for CH_3NHCOX derivatives (eq 9)[11] because σ_I is defined from the equilibrium (eq 10) involving no mesomeric transfer effect:

$$Ar\text{-}O\text{-}CH_2CO_2H \rightleftarrows Ar\text{-}O\text{-}CH_2CO_2^- + H^+ \quad (10)$$

There is little data to judge the magnitude of this effect but perusal of the literature indicates that in at least two cases 4-nitrophenoxy has approximately the same effect on the ionization of CH as has CH_3- when the electronic effect is transmitted through a carbonyl group. Since the ionizations illustrated in Table IV are close structural analogues in the isoelectronic sense of the carbamate system, we judge the pK_a of the RNHCOOAr species to be close to that of $RNHCOCH_3$; the latter pK_a values are readily available[11,19] and we take the pK_a's of phenyl carbamate and N-methylcarbamate to be 15.1 and 17.1, respectively, the pK_a's for acetamide[19] and N-methylacetamide,[11] respectively. The substituent effect (methyl vs. 4-nitrophenoxy) could be small for the models in Table IV because of charge delocalization over two carbonyl groups and this must be borne in mind as a source of uncertainty in our estimates of pK_a values and hence of rate constants. The equilibrium constant for formation of the conjugate anion of phenyl carbamate from phenolate anion and isocyanic acid may be derived from the overall equilibrium constant for formation of carbamate by use of the ionization constant for the carbamate (K_a^{NH}) and the autoprotolysis constant for water:

$$K_a^{NH}K_1/K_w = [^-NHCOOPh]/[HNCO][PhO^-] \quad (11)$$

This value ($K_a^{NH}K_1/K_w$) is rounded to 10^{-1} M^{-1} due to the uncertainty in the estimate for K_a^{NH} for phenyl carbamate.

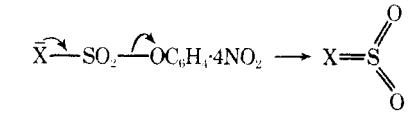
Table V

Phenyl carbamate	pK_a^{NH}	k_2, s^{-1}
1. Unsubstituted carbamate	15.1[a]	2800
2. N-Methylcarbamate	17.7[a]	17000
3. N-Phenylcarbamate	14.66[b]	250
4. N-4-Nitrophenylcarbamate[10]	12.5	1.54
5. N-Acetylcarbamate[12b]	10.65	0.00832

[a] See text. [b] The ionization constant for phenyl N-phenylcarbamate may be estimated via the application of linear free-energy relationships. The acidity of aromatic anilides $ArNHR \rightleftarrows ArN^-R + H^+$ has a β of 0.6 vs. the pK_a of the corresponding anilinium species,[24] and we believe this reaction to be a good model for the effect of substituents in the N-phenyl group of the carbamate. Taking the pK_a for phenyl N-(4-nitrophenyl)carbamate to be 12.50,[10] we may then calculate the required pK_a.

The equilibrium is slightly unfavorable and could easily be consistent with a transition state 50% along the reaction path. Most of the unfavorable nature of the process must come from entropy factors so that, in terms of potential energy, the formation of the addition complex might be quite a favorable process.

A knowledge of the equilibrium constants allows us to estimate the values for all the rate constants in the kinetic scheme. The rate constant for the decomposition of the conjugate base of the carbamate (k_2, see Table V) enables us to study the effect of internal nucleophilicity[9a,21] for a given leaving group and from an anion whose structure is relatively smoothly altered. There is too little data to obtain a meaningful free-energy relationship but qualitatively the trend to be expected, namely, an increase of k_2 with increasing basicity of the carbamate anion (RN^-CO-) is observed. Figure 4 illustrates this trend for k_2 for a series of esters $RNHCO\text{-}OC_6H_5$ as a function of pK_a^{NH} and a Bronsted type β of approximately unity is observed. Changing the heteroatom bearing the charge to oxygen ($^-O\text{-}CO\text{-}OC_6H_5$) gives a k_2 value estimated from data reported by Sauers, Jencks, and Groh[4] some 1000-fold greater than expected from the correlation in Figure 4; presumably this reflects heterocumulene stability as well as the pK_a^{NH} as factors influencing internal nucleophilicity. A similar selectivity has been discussed by Davy and co-workers for the elimination of 4-nitrophenolate anion from the system 12[23]



(12)

where a decrease in k_2 follows a decrease in basicity. These results are in accord with the reasonable hypothesis that factors contributing to donation of electrons to a proton are similar to those for donation of the same electrons to form a heterocumulene and for expelling the leaving group.

The large difference in rate between carbamates and N-methylcarbamates (roughly 100-fold) observed by Dittert and Higuchi[25] and by us (Tables I and II) is essentially a concentration effect due to the different acidities of the two carbamates (Table V); despite the high reactivity for decomposition of the conjugate anion from the N-methylcarbamate the pK_a difference is sufficient to force the carbamates to hydrolyze in base more quickly.

Concertedness. The absence of buffer catalysis in either the formation of carbamates or their decomposition suggests a stepwise process. This is consistent with the mechanism predicted from a consideration of the free-energy surface for the reaction of eq 6; Figure 5 illustrates this surface and the numbers at the four corners are the negative logarithms of the equilibrium constants (and are thus proportional to free energies) relative to the reactants isocyanic acid, phenolate

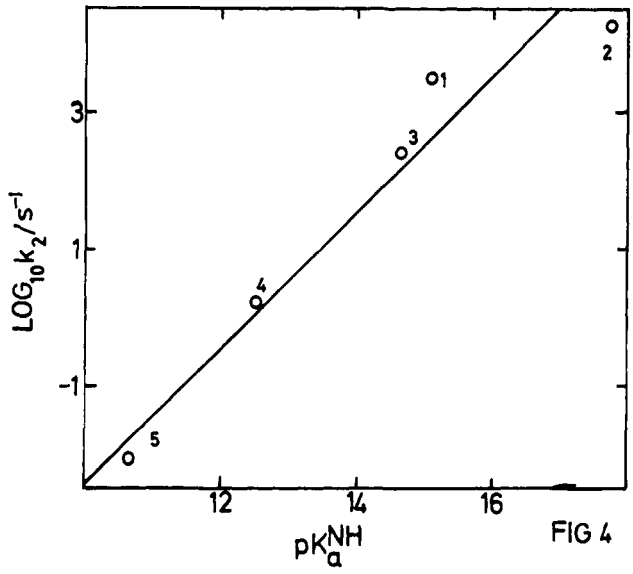


Figure 4. Bronsted type correlation for the decomposition of the anion $R^-NCO\text{-}OC_6H_5$ vs. the pK_a^{NH} of the conjugate acid. The line has an arbitrary slope of 0.85 and the numbers refer to the species listed in Table V.

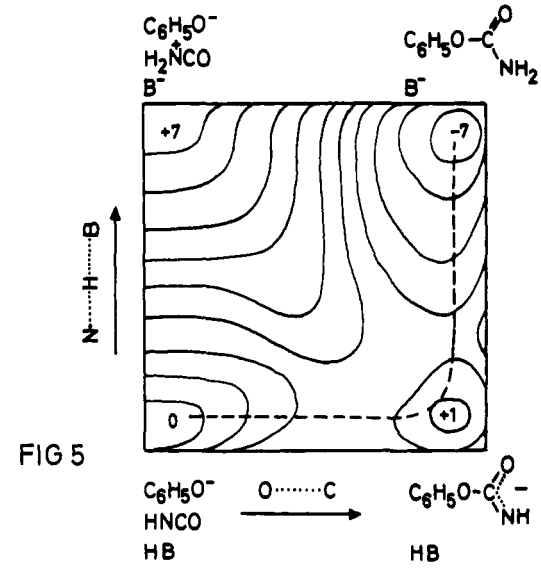
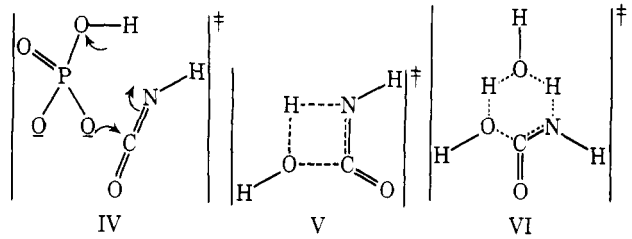


Figure 5. Three-dimensional free-energy diagram for the reaction of phenolate anion with isocyanic acid in the presence of an acid with pK_a = 7. The pK_a of HNCO is almost certainly less than zero and the number in the top left corner, the negative logarithm of the equilibrium constant for formation from reactants (bottom left), is thus a lower limit. The outer numbers are derived from equilibrium constants cited in the text; the contour lines are notional. The horizontal coordinate refers to C–O bond formation and the vertical to the proton transfer; the dashed line represents the reaction coordinate.

anion, and acid (pK_a = 7) in the bottom left corner. The very unsymmetrical nature of this surface forces the reaction coordinate to follow a stepwise process along the bottom and right-hand coordinates. For attack of oxide groups, the proton switch mechanism postulated for amine attack[2] is no longer relevant, and the high pK_a^{NH} of the carbamate relative to that of water ensures that proton transfer to the conjugate anion from acids does not compete with that from water.

The linear free-energy relationship between phenolate anion reactivity and pK_a of the phenol gives a measure of reactivity of oxide ions not subject to catalysis in the rate-limiting step; this relationship may therefore be used to study the reaction of oxide ions with isocyanic acid where catalysis could occur. The reactivity of phosphate dianion (HPO_4^{2-}) with isocyanic acid to yield carbamoyl phosphate, an important metabolite, is close to that expected for an oxide ion of similar pK_a (Figure 6). Acceleration by facilitated proton transfer as for example in IV does not therefore contribute much to the reaction and by the principle of microscopic reversibility does not influence the decomposition of the carbamoyl phosphate; perusal of Figure 1 confirms the latter conclusion where no abnormal rate constant is seen for the decomposition. Phosphate trianion and



IV V VI

hydroxide ion parameters lie below the regression line for nucleophilic attack (Figure 6) in agreement with observations on the reactivity of the species with other acyl compounds.[16]

The involvement of carbamoyl phosphate in the biosynthesis of carbamoyl aspartate as the first step in pyrimidine metabolism could be via nucleophilic attack at the carbonyl group of the complexed species in the active site. An alternative mechanism is the decomposition of the carbamoyl phosphate via its conjugate anion (NH^-) to give isocyanic acid, followed by nucleophilic attack on the heterocumulene by the amino group of the aspartic acid;[26] the isocyanic acid may or may not

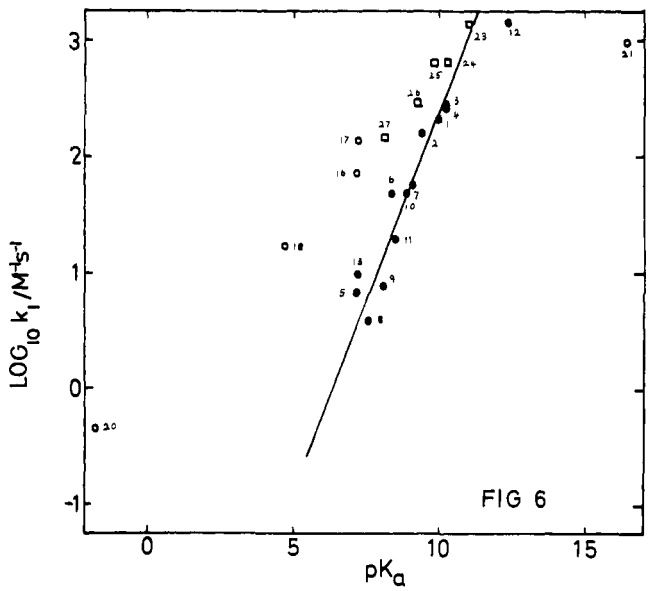


Figure 6. Bronsted type correlation of log k_1 and the pK_a of the conjugate acid of the nucleophile which adds to isocyanic acid. Details are given in Table I and the line is the correlation for phenolate anions (β_N = +0.66). The squares represent values of k_1 for attack of primary amines (taken from a previous paper)[1] and obeying a more shallow Bronsted law: 23, methylamine; 24, β-alanine; 25, glycine; 26, methyl β-alaninate; 27, triglycine. The filled circles represent attack of oxyanions.

diffuse into the bulk solvent before reaction with the nucleophile. Stark and his co-workers show that the rate constant for transfer of the carbamoyl group in the fully saturated active site of the enzyme subunit aspartyl transcarbamoylase is 9×10^4 min^{-1} [27] at pH 7.8 and this becomes 5×10^2 s^{-1} when allowing for three active sites.[28] Perusal of Table V shows that even for the poor phenolate leaving group the decomposition of the carbamate conjugate anion is certainly fast enough to support the mechanism involving isocyanic acid. Let us assume

that a base of $pK_a = 7$ affects the ionization of the carbamoyl group in the active site and the pK_a of the latter to be 15 then the pseudo-first-order rate constant for decomposition is $(10^{-15}/10^{-7})k_2\ s^{-1}$. The value of k_2 for the oxide leaving group with $pK_a = 7$ is determined from the k_2 for the phenolate group and the Bronsted β_{LG} to be $1.3 \times 10^8\ s^{-1}$ and the overall first-order rate constant is therefore $1.3\ s^{-1}$. Since the equilibrium concentration of the conjugate base of the carbamate and the protonated base is likely to be highly dependent on the microscopic medium which could be vastly different in the active site from the bulk solvent, then this value for the calculated rate constant is not sufficient to exclude the isocyanic acid pathway. Arguments against the elimination–addition mechanism such as sensitivity to acyl substituent[27,29] may be countered by postulating the existence of a high steric requirement.

Moreover, the formation of a ketene from acetyl phosphate is a possibility.[30] If isocyanic acid is an intermediate in the aspartyl transcarbamoylase reaction, then it must react in the active site with the nucleophile at a speed greater than it can diffuse into the bulk solution because phosphate in solution is not exchanged into the carbamoyl phosphate[31] nor is free cyanate incorporated into the product.[32a] We point out here the parallelism between the reaction of cyanate and phosphate and the proposed reaction in carbamoyl phosphate synthetase, namely, reaction of carbon dioxide with phosphate.[32b] The chemistry of these reactions (heterocumulenes with phosphate) ought to be closely similar.

The water rate constant (Figure 6) lies well above the regression line involving the oxygen nucleophiles and this could be due to an alternative mechanism such as the symmetry allowed paths (V, VI). Some form of concerted mechanism as in V or VI might be expected since the stepwise process would involve $NH_2{}^+CO,OH^-$ and $NHCO^-(OH_3)^+$ states both of which are expected to be extremely unstable. These mechanisms are similar to the proton switch process postulated to account for the abnormal water term in amine attack on isocyanic acid.[2] In the latter case, however, it was proposed that nucleophilic attack is not concerted with proton transfer. Concerted mechanisms of type V are well known in 1,2 cycloadditions of isocyanates,[33] and the existence of these cyclic products would indicate the feasibility of such a four-centered transition state. The relatively low deuterium oxide solvent isotope effect for the hydrolysis of methyl isocyanate (Table II) is consistent with a concerted mechanism where the proton-transfer component has a late or early transition state. It could be argued, however, that attack of neutral oxygen on the isocyanic acid should follow the amine regression line of Figure 6 rather than the oxyanion line and the closeness of the water point (assuming $pK_a = -1.7$) to the amine line would suggest a normal stepwise mechanism.

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