chemical study is the following. (a) In the case of internal olefins of the type $R_1CH{=}CHR_2$ for which R_1 is not very different from R_2, it seems that steric factors are more pronounced in the initiation step leading to the first metallocarbene, rather than in the propagation step. Initiation seems to require a cis olefin or an α olefin. Propagation is less sterically demanding.

(b) Concerning *cis*-2-pentene, productive metathesis and cis–trans isomerization are the results of four different types of coordination of *cis*-2-pentene on the same metallocarbene. It seems that these four types of coordination and/or reaction have about the same rate.

(c) The stereoselectivities observed with cis and trans olefin can be explained on the basis of steric repulsion between the R groups of the olefin and the bulky ligands coordinated to tungsten, or stability of various configurations of metallocyclobutanes.

Most of the conclusions drawn here are related to internal olefins for which the R groups are not significantly different. In fact various recent works by Calderon,[16] Katz,[22] and Casey[23] seem to indicate that in the case of α olefins some types of coordination (head to tail) leading to "regenerative" metathesis are much more favored than others (head to head) leading to "productive" metathesis. These results are not surprising if we consider that steric effects of alkylidene groups are in this case very different and can play a role (a) on the nature of the first metallocarbene formed during the initiation steps; (b) on the course of the chain mechanism itself where some catalytic cycles can be much more favored than others.

References and Notes

(1) N. Calderon, E. A. Ofstead, J. P. Ward, W. A. Judy, and K. W. Scott, *J. Am. Chem. Soc.*, **90**, 4133 (1968).
(2) W. B. Hughes, *Chem. Commun.*, 431 (1969).
(3) J. L. Wang, H. R. Menapace, and M. Brown, *J. Catal.*, **26**, 455 (1972).
(4) J. M. Basset, G. Coudurier, R. Mutin, and H. Praliaud, *J. Catal.*, **34**, 152 (1974).
(5) J. M. Basset, G. Coudurier, R. Mutin, H. Praliaud, and Y. Trambouze, *J. Catal.*, **34**, 196 (1974).
(6) R. J. Angelici and M. D. Malone, *Inorg. Chem.*, **6**, 9 (1967).
(7) J. Wang and H. R. Menapace, *J. Org. Chem.*, **33**, 3794 (1968).
(8) J. L. Herisson and Y. Chauvin, *Makromol. Chem.*, **141**, 161 (1970).
(9) T. J. Katz and J. Mc. Ginnis, *J. Am. Chem. Soc.*, **97**, 1592 (1975).
(10) R. H. Grubbs, P. L. Burk, and D. D. Carr, *J. Am. Chem. Soc.*, **97**, 3265 (1975).
(11) T. J. Katz and R. Rothchild, *J. Am. Chem. Soc.*, **98**, 2519 (1976).
(12) R. H. Grubbs, D. D. Carr, C. Hoppin, and P. L. Burk, *J. Am. Chem. Soc.*, **98**, 3478 (1976).
(13) C. P. Casey and T. J. Burkhardt, *J. Am. Chem. Soc.*, **96**, 7808 (1974).
(14) R. R. Schrock, *J. Am. Chem. Soc.*, **97**, 6577 (1975).
(15) L. J. Guggenberger and R. R. Schrock, *J. Am. Chem. Soc.*, **97**, 6578 (1975).
(16) W. J. Kelly and N. Calderon, *J. Macromol. Sci., Chem.*, **9**, 911 (1975).
(17) J. M. Basset, J. L. Bilhou, R. Mutin, and A. Theolier, *J. Am. Chem. Soc.*, **97**, 7376 (1975).
(18) G. Pampus, "Catalyse par Coordination", Guyot, Ed., 1974, p 172.
(19) P. Chevalier, D. Sinou, G. Descotes, R. Mutin, and J. M. Basset, *J. Organomet. Chem.*, **113**, 1 (1976).
(20) M. Leconte and J. M. Basset, to be submitted. When heating $W(CO)_4Br_2$ in presence of *cis*-2-pentene, the ratio trans/cis C_4 at low conversion is equal to 0.50 ± 0.05 whereas a value of 0.69 is obtained with $W(CO)_4Cl_2$.
(21) Thus, the term "cis–trans isomerization" should be substituted by the term "cis–trans interconversion" throughout the manuscript.
(22) J. Mc. Ginnis, T. J. Katz, and S. Hurwitz, *J. Am. Chem. Soc.*, **98**, 605 (1976).
(23) C. P. Casey, H. E. Tuinstra, and M. C. Saeman, *J. Am. Chem. Soc.*, **98**, 608 (1976).
(24) A. Agaplos and E. Mc Nelis, *J. Organomet. Chem.*, **99**, C47 (1975).
(25) M. T. Mocella, R. Rovner, and E. L. Muetterties, *J. Am. Chem. Soc.*, **98**, 4689 (1976).

Changing Views on the Mechanism of Base Catalysis in Nucleophilic Aromatic Substitution. Kinetics of Reactions of Nitroaryl Ethers with Piperidine and with *n*-Butylamine in Aqueous Dioxane

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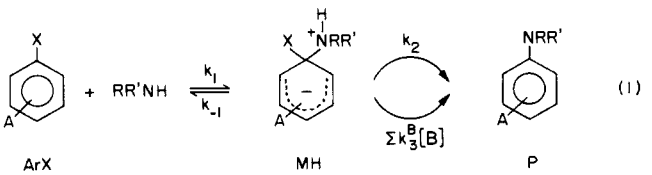
Abstract: The reactions of piperidine with 2-cyano-4-nitrophenyl phenyl ether in 10% aqueous dioxane, and of *n*-butylamine with 1-methoxy-4,7-dinitronaphthalene in 60% aqueous dioxane, are subject to general base catalysis; the reaction of *n*-butylamine with 2,4-dinitroanisole in the same solvent is probably also general base catalyzed. The reactions of piperidine with 2,4-dinitroanisole and with 1-methoxy-4,7-dinitronaphthalene in 60% aqueous dioxane are subject to specific base catalysis; the reactions of *n*-butylamine with 2-cyano-4-nitrophenyl phenyl ether and with 2,4-dinitrophenyl phenyl ether in 10% and in 60% aqueous dioxane are not subject to base catalysis. General base catalysis is shown to be a consequence of rate-limiting deprotonation of the zwitterionic intermediate complex, specific base catalysis a consequence of rapid equilibrium deprotonation of the zwitterion followed by spontaneous (noncatalyzed) leaving group expulsion. This is at variance with the hitherto generally accepted SB–GA mechanism. It is shown that the rate-limiting proton transfer mechanism is a general one in protic solvents while the SB–GA mechanism is only a significant pathway in aprotic media.

The broad mechanistic features of activated nucleophilic aromatic substitutions by amines are well established, mainly due to the work of Bunnett in the 1950s and 1960s.[1,2] The mechanism is commonly represented by eq 1.

Until recently the detailed mechanism of the base-catalyzed product-forming step(s) (k_3^B; B usually lyate ion and RR′NH) also seemed established.[1,3] It consisted of a rapid equilibrium deprotonation of MH, followed by rate-limiting, *general-acid-catalyzed* leaving group expulsion (SB–GA for specific base–general acid).



(1)

In 1974[4a] we started to question the generality of the SB–GA mechanism and suggested that, under certain cir-

Table I. Reactions in 10% Dioxane–90% Water (*v*/*v*) at 29.4 °C. Dependence on Hydroxide Ion Concentration[a]

$[NaOH]_{st}$, M	$[OH^-]_{eff}$, M	$[RR'NH]_{eff}$, M	10^5k_ψ, s^{-1}	Yield, %	10^5k_A*, s^{-1}	10^4k_A, $M^{-1}\,s^{-1}$	10^5k_{OH}*, s^{-1}	10^3k_{OH}, $M^{-1}\,s^{-1}$
A. Reaction of Piperidine with 2-Cyano-4-nitrophenyl Phenyl Ether, $[RR'NH]_{st}$ = 0.1 M								
b	0.0001	0.10	1.67	100	1.67	1.67		
0.025	0.029	0.096	6.51	84	5.47	5.72	1.04	0.36
0.050	0.052	0.098	8.08	77	6.22	6.37	2.86	0.55
0.075	0.077	0.098	9.17	74	6.78	6.90	2.39	0.31
0.10	0.101	0.099	10.0	70	7.03	7.09	2.97	0.29
0.15	0.151	0.099	11.7	65	7.61	7.68	4.10	0.27
0.20	0.20	0.10	12.9	59	7.60	7.60	5.30	0.26
B. Reaction of *n*-Butylamine with 2-Cyano-4-nitrophenyl Phenyl Ether, $[RR'NH]_{st}$ = 0.075 M								
Nil	0.004	0.071	0.15	98	0.147	0.207		
0.025	0.025	0.075	0.694	25.7	0.178	0.238	0.516	0.21
0.050	0.050	0.075	1.09	19.8	0.217	0.289	0.877	0.18
0.075	0.075	0.075	1.43	14.8	0.212	0.283	1.22	0.16
0.010	0.10	0.075	1.79	13.6	0.243	0.324	1.55	0.15
0.15	0.15	0.075	2.36	11.3	0.267	0.356	2.09	0.14
0.20	0.20	0.075	2.84	10.4	0.296	0.394	2.54	0.13
C. Reaction of *n*-Butylamine with 2,4-Dinitrophenyl Phenyl Ether, $[RR'NH]_{st}$ = 0.075 M								
0.025	0.025	0.075	10.5	100	10.5	14.0		
0.050	0.050	0.075	12.1	93.5	11.3	15.1		
0.075	0.075	0.075	12.4	88.0	11.0	14.6	1.4	0.19
0.10	0.10	0.075	13.1	83.4	11.0	14.6	2.1	0.21
0.15	0.15	0.075	15.5	72.9	11.3	15.1	4.2	0.28
0.20	0.20	0.075	17.3	68.2	11.8	15.7	5.5	0.27

[a] Total electrolyte concentration maintained at 1.0 M by addition of NaCl; $[substrate]_0 = 4 \times 10^{-5}$ M. [b] 1 M piperidine hydrochloride added instead.

cumstances, deprotonation of MH may be rate limiting; this view was reenforced by subsequent studies.[4b,4c]

In this paper we go one step further and show that all current available evidence indicates that the SB–GA mechanism is not a significant pathway in protic solvents. Instead, the prevailing mechanism consists of a rate-limiting deprotonation of MH when leaving group expulsion is relatively fast (e.g., X = PhO), or of a rapid equilibrium deprotonation of MH followed by a rate-limiting, *non*catalyzed leaving group expulsion when the leaving group is a very poor one (e.g., X = CH_3O under certain conditions).

Results

The kinetics, usually as a function of both the NaOH and amine concentration, of the reactions summarized in Tables I–IV have been investigated. Tables I and II summarize data concerning catalysis by OH^-, and also data on the reactions of OH^- with the various substrates. Tables III and IV summarize data on the catalysis by the respective amines. The various symbols used in the tables are defined in the Experimental Section; we shall mainly focus our attention on k_A, the second-order rate constant of the reaction of the aromatic substrate with the amine. All determinations were done at 29.4 °C, under pseudo-first-order conditions and at constant ionic strength with NaCl as compensating electrolyte.

2-Cyano-4-nitrophenyl Phenyl Ether with Piperidine. This reaction was investigated in 10% dioxane. It is strongly catalyzed by OH^- (Table IA); a plot (not shown) of k_A vs. $[OH^-]$ is curvilinear and very similar to the one for the reaction of 2,4-dinitrophenyl phenyl ether with piperidine under the same conditions.[5] The reaction is also catalyzed by piperidine (Table IIIB) with k_A increasing somewhat less than linearly with piperidine concentration, again quite analogous to the same reaction with 2,4-dinitrophenyl phenyl ether.[5]

2-Cyano-4-nitrophenyl Phenyl Ether with *n*-Butylamine. This reaction was investigated in both 10 and 60% dioxane. There is a slight acceleration by OH^- in 10% dioxane; the rate approximately doubled upon the addition of 0.2 M NaOH (Table IB) but increased by less than 50% in 60% dioxane (Table IIC). Increasing the amine concentration has a small effect in 10% dioxane (Table IIIC) but no effect at all in 60% dioxane (Table IVE).

2,4-Dinitrophenyl Phenyl Ether with *n*-Butylamine. Some data showing that the reaction is not accelerated by the addition of NaOH in 10% dioxane are summarized in Table IC. Shortly after we started measurements in this system we learned that it had already been investigated, both in 10% and in 60% dioxane, over a wide range of NaOH and *n*-butylamine concentrations.[6]

1-Methoxy-4,7-dinitronaphthalene with Piperidine. This reaction is strongly catalyzed by OH^- in 60% dioxane (Table IIB), with a curvilinear plot (not shown) of k_A vs. $[OH^-]$. On the other hand *no* catalysis by piperidine could be detected (Table IVC), indicating that we deal with the rather rare case[1] of *specific* instead of *general* base catalysis.

1-Methoxy-4,7-dinitronaphthalene with *n*-Butylamine. In 60% dioxane the rate is rather strongly dependent on the amine concentration (Table IVD); a plot is shown in Figure 1. The reaction is also strongly catalyzed by OH^- but no meaningful data could be obtained. This is because one needs to measure this catalysis at butylamine concentrations which are considerably below the leveling off range of Figure 1; at these low butylamine concentrations hydrolysis of the ether competes so strongly with the amine reaction that k_A cannot be determined with any meaningful precision. Nevertheless, measurements at different amine/amine hydrochloride ratios show that the reaction is accelerated ~30% by an increase in OH^- concentration from $\sim 2 \times 10^{-7}$ M to $\sim 2 \times 10^{-6}$ M (Table IVD; note that at amine concentrations above the leveling off, changing the buffer ratio has no effect on the rate.)

2,4-Dinitroanisole with Piperidine. In 60% dioxane the reaction is strongly catalyzed by NaOH (Table IIA) but not by piperidine (Table IVA), i.e., the reaction is subject to specific base catalysis, like the reaction of piperidine with 1-methoxy-4,7-dinitronaphthalene in the same solvent. Initially this result surprised us because we had found earlier that in 10%

Table II. Reactions in 60% Dioxane–40% Water (v/v) at 29.4 °C. Dependence on Hydroxide Ion Concentration[a]

[NaOH],[b] M	$10^5 k_\psi$, s^{-1}	Yield, %	$10^5 k_A$*, s^{-1}	$10^4 k_A$, $M^{-1} s^{-1}$	$10^5 k_{OH}$*, s^{-1}	$10^3 k_{OH}$, $M^{-1} s^{-1}$
A. Reaction of Piperidine with 2,4-Dinitroanisole,[c] [RR'NH] = 4.96×10^{-2} M						
Nil	0.47	81.5	0.38	0.77		
0.0049	2.45	61.1	1.49	3.00	0.96	1.96
0.049	14.2	41.7	5.92	11.9	8.26	1.63
0.075	20.9	39.6	8.27	16.7	12.6	1.68
0.098	23.7	34.3	8.12	16.4	15.6	1.60
0.124	29.1	32.0	9.31	18.8	19.8	1.59
0.150	33.8	28.6	9.65	19.4	24.1	1.60
0.175	36.4	28.0	10.2	20.6	26.2	1.50
0.197	41.9	26.3	11.1	22.2	30.8	1.56
B. Reaction of Piperidine with 1-Methoxy-4,7-dinitronaphthalene,[d] [RR'NH] = 5.00×10^{-2} M						
0.0098	1.50	66.0	0.99	1.98	0.51	0.52
0.0266	2.59	65.0	1.68	3.37	0.91	0.34
0.0532	4.36	57.0	2.49	4.97	1.87	0.35
0.0749	5.96	54.1	3.23	6.46	2.73	0.36
0.0985	7.67	47.6	3.65	7.30	4.02	0.41
0.120	8.33	49.5	4.12	8.24	4.21	0.35
0.140	10.7	41.6	4.46	8.92	6.26	0.45
0.167	10.7	42.8	4.58	9.16	6.12	0.37
0.197	11.5	43.0	4.96	9.92	6.58	0.33
C. Reaction of *n*-Butylamine with 2-Cyano-4-nitrophenyl Phenyl Ether,[e] [RR'NH] = 7.5×10^{-2} M						
0.025	0.448	32.9	0.147	0.196	0.301	0.120
0.050	0.735	21.5	0.158	0.211	0.577	0.115
0.075	0.978	17.0	0.166	0.221	0.812	0.108
0.10	1.18	14.0	0.166	0.221	1.02	0.102
0.15	1.63	11.2	0.183	0.244	1.45	0.097
0.20	2.08	9.9	0.205	0.273	1.87	0.094
0.025[f]	0.760	50.0	0.380	0.190	0.380	0.152
0.050[f]	1.02	39.1	0.400	0.200	0.624	0.124
0.075[f]	1.29	34.0	0.439	0.219	0.851	0.114
0.10[f]	1.67	25.9	0.432	0.216	1.23	0.123
0.15[f]	2.14	21.2	0.454	0.227	1.69	0.113
0.20[f]	2.22	20.3	0.452	0.226	1.77	0.089

[a] Total electrolyte concentration maintained at 0.2 M by addition of NaCl as required. [b] [NaOH] $\simeq$ $[OH^-]_{eff}$ in this solvent. [c] $[Substrate]_0 = 6.4 \times 10^{-4}$ M. [d] $[Substrate]_0 = 2\text{–}4 \times 10^{-4}$ M. [e] $[Substrate]_0 = 4 \times 10^{-5}$ M. [f] [RR'NH] = 0.2 M.

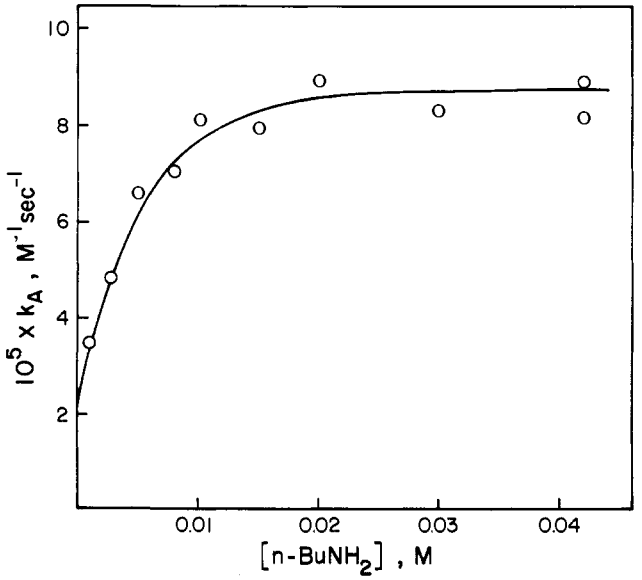


Figure 1. Reaction of *n*-butylamine with 1-methoxy-4,7-dinitronaphthalene in 60% dioxane–40% water (v/v) at 29.4 °C. Data from Table IVD.

dioxane there *is* piperidine catalysis.[7] Thus we checked our original findings[7] by doing some additional experiments (Table IIIA). The present experiments were carried out at a lower ratio [RR'NH]:[$RR'NH_2^+$] (lower pH) than previously[7] in order to increase the relative importance of piperidine catalysis by reducing the OH^- concentration and thereby suppressing part of the OH^- catalysis. The results of Table IIIA confirm that piperidine catalyzes the reaction in 10% dioxane.

2,4-Dinitroanisole with *n*-Butylamine. In 60% dioxane the reaction is slightly accelerated by increasing amine concentration (Table IVB). A plot (not shown) of k_A vs. amine concentration is curvilinear. Problems of competition with hydrolysis, similar to the ones with 1-methoxy-4,7-dinitronaphthalene, prevented us from investigating OH^- catalysis.

Reactions of Hydroxide Ion with the Various Substrates. Our data allowed the calculation of k_{OH} for the reaction of hydroxide ion with the various substrates to form the corresponding phenols or naphthol (Tables I and II). Some scatter is evident in most cases, as has commonly been observed in similar studies:[5,8,9] In some cases the reason for the scatter may be low yields of the phenolic product (high yield of aminolysis product), which makes a determination of k_{OH} inherently inaccurate; in other cases it may be due to some hydrolysis of the aminolysis product which can slightly distort the true yields, and perhaps to some other unidentified factors. Nevertheless, the data are a useful by-product of our determinations and provide at least approximate values for these rate constants. We will not discuss them further.

Discussion

We have analyzed our data according to the steady state

Table III. Reactions in 10% Dioxane–90% Water (v/v) at 29.4 °C. Dependence on Amine Concentration

$[RR'NH]_{st}$, M	$[RR'NH_2^+ Cl^-]_{st}$, M	$[RR'NH]_{eff}$, M	$10^5 k_\psi$,[a] s^{-1}	$10^4 k_A$, $M^{-1} s^{-1}$
A. Reaction of Piperidine with 2,4-Dinitroanisole[b,c,d]				
0.020	0.020	0.0187	0.149	0.80
0.040	0.040	0.0387	0.361	0.93
0.068	0.068	0.0667	0.691	1.04
0.20	0.20	0.199	3.31	1.65
B. Reaction of Piperidine with 2-Cyano-4-nitrophenyl Phenyl Ether[e,f,g]				
0.025	0.05	0.024	0.25	1.04
0.05	0.10	0.049	0.78	1.58
0.075	0.15	0.074	1.47	1.97
0.10	0.20	0.10	2.26	2.28
0.20	0.40	0.20	7.12	3.56
0.25	0.50	0.25	10.4	4.16
C. Reaction of *n*-Butylamine with 2-Cyano-4-nitrophenyl Phenyl Ether[e,f,h]				
0.01	0.02	0.01	0.019	0.190
0.025	0.05	0.025	0.045	0.179
0.05	0.10	0.05	0.104	0.207
0.10	0.20	0.10	0.210	0.210
0.15	0.30	0.15	0.339	0.226
0.20	0.40	0.20	0.459	0.229
0.25	0.50	0.25	0.628	0.251
0.25	0.75	0.25	0.607	0.243
0.25	1.00	0.25	0.618	0.247
0.30	0.60	0.30	0.777	0.259
0.40	0.80	0.40	1.10	0.275

[a] Yield 100% in all runs, hence $k_\psi = k_A$*. [b] $[Substrate]_0 = 2.7 \times 10^{-4}$ M. [c] Total electrolyte concentration maintained at 0.2 M by addition of NaCl. [d] $[OH^-]_{eff} \approx 10^{-3}$ M. [e] $[Substrate]_0 = 4 \times 10^{-5}$ M. [f] Total electrolyte concentration maintained at 1.0 M by addition of NaCl. [g] $[OH^-]_{eff} \approx 5 \times 10^{-4}$ M. [h] $[OH^-]_{eff} \approx 1.2 \times 10^{-4}$ M.

equation

$$\frac{\text{rate}}{[ArX][RR'NH]} = k_A = \frac{k_1(k_2 + k_3^A[RR'NH] + k_3^{OH}[OH^-])}{k_{-1} + k_2 + k_3^A[RR'NH] + k_3^{OH}[OH^-]} \quad (2)$$

where k_1, k_{-1}, and k_2 are as defined in eq 1, and k_3^A and k_3^{OH} refer to the base-catalyzed transformation of MH to P (eq 1) with the amine ($k_3^B \equiv k_3^A$) and the hydroxide ion ($k_3^B \equiv k_3^{OH}$), respectively, acting as the bases. Using standard procedures described elsewhere[5,7,8] we have calculated k_1 and the various ratios summarized in Table V, which also includes data from the literature.

Authentic Base Catalysis or "Small Acceleration"? With the exception of the reaction of *n*-butylamine with 2,4-dinitrophenyl phenyl ether we found that all reactions studied are accelerated by either OH^-, the amine, or by both. In some cases this catalysis is very strong and manifests itself by a several-fold increase in k_A, leaving no doubt that it represents authentic base catalysis of the product-forming step(s) in the mechanism of eq 1.[1] Hydroxide ion catalysis in all reactions involving piperidine as nucleophile falls into this category.

When catalysis is weak, the distinction between authentic base catalysis and the "mild accelerations of unclear origin" discussed by Bunnett and Garst[10] poses some problems. A useful criterion in distinguishing between the two interpretations is the concentration range of the catalyst in which catalysis is observed.

One extreme is represented by the reaction of *n*-butylamine with 2-cyano-4-nitrophenyl phenyl ether. In 10% dioxane k_A doubles between the lowest and highest NaOH concentration (Table IB). But because the effect occurs at high base concentrations it is not really impressive. If it were assumed to represent authentic base catalysis and the data were analyzed according to eq 2 one would obtain $k_3^{OH}/k_2 = 27.4$, which is about two orders of magnitude smaller than comparable k_3^{OH}/k_2 ratios in authentically base catalyzed reactions. The k_3^{OH}/k_2 ratio in 60% dioxane and the k_3^A/k_2 ratios for amine analysis (Table V, values put in parentheses) also come out very small. Thus we do not think that any of these effects represent authentic base catalysis.

The other extreme is represented by the reaction of *n*-butylamine with 2,4-dinitroanisole. Here k_A increases only about 50% between the lowest and highest amine concentration, but the effect occurs at low concentrations (<0.01 M, Table IVB). In our view, this could possibly be authentic catalysis; with this interpretation the smallness of the effect on k_A would be a consequence of a relatively large k_2/k_{-1} ratio which means that the k_1 step is already almost entirely rate determining even in the absence of a catalyst. In fact, if one analyzes the data according to eq 2, one obtains $k_2/k_{-1} = 1.6$. The fairly high value of k_3^A/k_2 (169) which results from the same analysis would be consistent with authentic base catalysis. Nevertheless, in view of the smallness of the effect on k_A these conclusions should be regarded as tentative.

The situation is much more clear cut in the reaction of *n*-butylamine with 1-methoxy-4,7-dinitronaphthalene. Here the increase in k_A not only occurs at low amine concentrations but it amounts to a 2.5-fold acceleration between the lowest and highest concentration (Table IVD). Analysis according to eq 2 affords $k_2/k_{-1} = 0.32$ and $k_3^A/k_2 = 946$. In this case we are confident that the effect represents authentic base catalysis; *we note that this is the first such example with a primary amine in a protic solvent.*

A still different situation prevails with respect to piperidine catalysis in the reaction of piperidine with 2,4-dinitroanisole in 10% dioxane. From the very strong OH^- catalysis[5,7] we know that the reaction is genuinely base catalyzed. On the other hand the increase in k_A is only about twofold between 0.02 and 0.2 M piperidine (Table IIIA), which is a considerably smaller acceleration than in the reactions of piperidine with 2-cyano-4-nitrophenyl phenyl ether (~fourfold, Table IIIB) or with 2,4-dinitrophenyl phenyl ether (~sixfold).[5] This is reflected in the k_3^A/k_3^{OH} ratio, which is at least 10 times smaller than in the above-mentioned reactions. A possible interpretation of these findings will be offered in the section entitled "Methoxide as Leaving Group".

Mechanism of Base Catalysis. Five different mechanisms of base catalysis have been proposed over the years and have enjoyed various degrees of acceptance. The three principal ones can be discussed with reference to Scheme I with

$$k_{3p} = k_{3p}^{OH}[OH^-] + k_{3p}^A[RR'NH] \quad (3)$$

$$k_{-3p} = k_{-3p}^{OH} + k_{-3p}^A[RR'NH_2^+] \quad (4)$$

$$k_4 = k_4^{OH} + k_4^A[RR'NH_2^+] \quad (5)$$

k_{3p}^{OH} and k_{3p}^A refer to the deprotonation of MH by OH^- and by the amine, respectively; k_{-3p}^{OH} and k_{-3p}^A refer to the protonation of M^- by the solvent and by $RR'NH_2^+$, respectively; k_4^{OH} refers to uncatalyzed or solvent-assisted leaving group expulsion whereas k_4^A allows for the possibility of general-acid-catalyzed leaving group departure by the protonated amine.[11]

Treating both MH and M^- as steady state intermediates affords

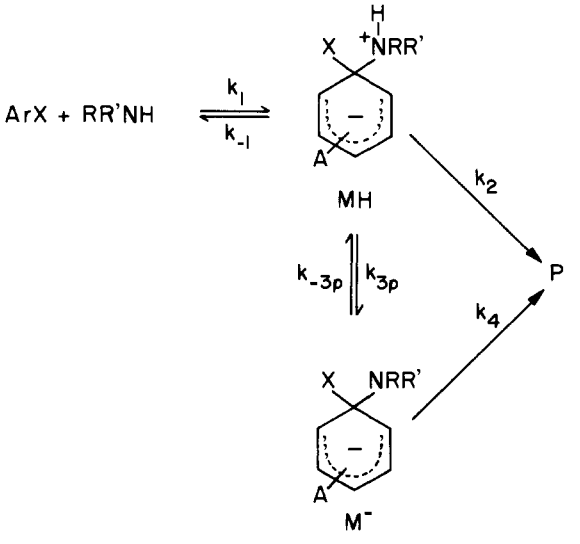
$$k_A = \frac{k_1k_2(k_{-3p} + k_4) + k_1k_{3p}k_4}{(k_{-1} + k_2)(k_{-3p} + k_4) + k_{3p}k_4} \quad (6)$$

Table IV. Reactions in 60% Dioxane–40% Water (v/v) at 29.4 °C. Dependence on Amine Concentration[a]

[RR′NH], M	[RR′NH$_2$$^+Cl^-$], M	10^6k_ψ, s^{-1}	Yield, %	10^6k_A*, s^{-1}	10^5k_A, M^{-1} s^{-1}
	A. Reaction of Piperidine with 2,4-Dinitroanisole[b,c]				
0.01	0.01	0.055	88.5	0.048	0.48
0.05	0.05	0.25	88.0	0.22	0.44
0.10	0.10	0.49	90.4	0.44	0.44
0.20	0.20	1.10	88.7	0.98	0.49
	B. Reaction of *n*-Butylamine with 2,4-Dinitroanisole[d,e,f]				
0.0005	0.0005	0.108	98	0.106	21.2
0.001	0.001	0.241	98	0.236	23.6
0.0025	0.0025	0.612	96	0.585	23.5
0.003	0.003	0.845	98	0.827	27.6
0.004	0.004	1.20	97	1.17	29.3
0.005	0.005	1.48	98	1.45	29.1
0.010	0.010	3.33	98	3.26	32.6
0.040	0.004[i]	13.5	97	13.1	32.8
	C. Reaction of Piperidine with 1-Methoxy-4,7-dinitronaphthalene[c,g]				
0.020	0.020	0.0196	35.4	0.0070	0.035
0.050	0.050	0.0480	36.3	0.017	0.034
0.20	0.20	0.103	56.0	0.058	0.032
	D. Reaction of *n*-Butylamine with 1-Methoxy-4,7-dinitronaphthalene[f,h]				
0.001	0.001	0.0345	100	0.0345	3.45
0.0025	0.0025	0.121	100	0.121	4.84
0.005	0.005	0.303	100	0.303	6.06
0.005	0.0005[i]	0.396	100	0.396	7.92
0.008	0.008	0.563	100	0.563	7.03
0.010	0.010	0.825	100	0.825	8.25
0.015	0.015	1.18	100	1.18	7.94
0.030	0.030	2.50	100	2.50	8.34
0.030	0.003[i]	2.51	100	2.51	8.35
0.040	0.040	3.32	100	3.32	8.15
0.040	0.004[i]	3.58	100	3.58	8.95
	E. Reaction of *n*-Butylamine with 2-Cyano-4-nitrophenyl Phenyl Ether[j]				
0.075		1.23	100	1.23	1.65
0.10		1.67	100	1.67	1.67
0.15		2.51	100	2.51	1.67
0.20		3.35	100	3.35	1.67
0.25		4.07	100	4.07	1.63
0.30		4.89	100	4.89	1.63

[a] Total electrolyte concentration maintained at 0.2 M by addition of NaCl. [b] [Substrate]$_0$ = 6 × 10^{-4} M. [c] [OH$^-$]$_{eff}$ ≈ 4 × 10^{-7} M. [d] [Substrate]$_0$ = 6 × 10^{-5} M. [e] Temperature 25 °C. [f] [OH$^-$]$_{eff}$ ≈ 2 × 10^{-7} M. [g] [Substrate]$_0$ = 2–4 × 10^{-4} M. [h] [Substrate]$_0$ = 0.6–1.6 × 10^{-4} M. [i] [OH$^-$]$_{eff}$ ≈ 2 × 10^{-6} M. [j] [Substrate]$_0$ = 4 × 10^{-5} M, no RR′NH$_2$Cl added.

Scheme I



The Proton Transfer Mechanism. When leaving group departure is much faster than protonation of M$^-$, i.e., $k_4 \gg k_{-3p}$, deprotonation of MH (k_{3p}) becomes rate limiting. This is evident from inspection of Scheme I; it also follows from eq 6 which simplifies to

$$k_A = \frac{k_1k_2 + k_1k_{3p}}{k_{-1} + k_2 + k_{3p}} = \frac{k_1(k_2 + k_{3p}^A[RR'NH] + k_{3p}^{OH}[OH^-])}{k_{-1} + k_2 + k_{3p}^A[RR'NH] + k_{3p}^{OH}[OH^-]} \quad (7)$$

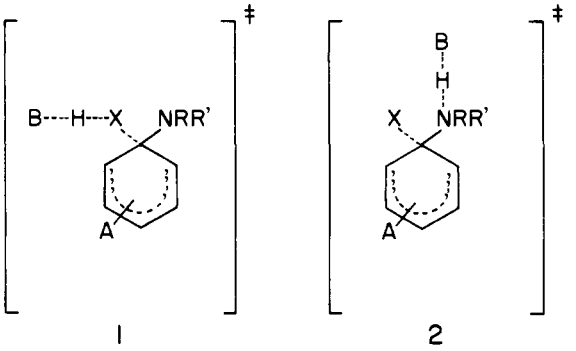
Comparing eq 7 with eq 2 shows that for this mechanism

$$k_3^A \equiv k_{3p}^A;\ k_3^{OH} \equiv k_{3p}^{OH} \quad (8)$$

i.e., the rate constants k_3^A and k_3^{OH} of eq 1 and 2 refer simply to the rate constants of the deprotonation of MH.

This mechanism was the first to be proposed (Bunnett and Randall).[12] Since it requires not only $k_4 > (\gg) k_{-3p}$ but also $k_{-1} > (\gg) k_{3p}$ (if $k_{-1} \ll k_{3p}$, the k_1 step becomes rate determining and no base catalysis can be observed), i.e., C–X and C–N bond breaking to be faster than proton transfer, this mechanism became unpopular in the early 1960s, mainly on the basis of Eigen's findings that proton transfers between "normal" acids and bases are very fast.[13] It was replaced by the SB-GA mechanism.

The SB–GA Mechanism. In this mechanism the proton transfer equilibrium is rapidly established whereas leaving group departure is relatively slow and rate limiting, i.e., $k_4 \ll k_{-3p}$. Furthermore, the k_4 step represents general-acid-catalyzed leaving group departure (transition state **1**), i.e., the term $k_4^A[RR'NH_2^+]$ in eq 5 is large.



1 2

For this mechanism eq 6 simplifies to

$$k_A = \frac{k_1k_2 + k_1K_{3p}k_4}{k_{-1} + k_2 + K_{3p}k_4} \quad (9)$$

with

$$K_{3p} = \frac{k_{3p}}{k_{-3p}} = \frac{k_{3p}^{OH}[OH^-]}{k_{-3p}^{OH}} = K_{3p}^{OH}[OH^-]$$
$$= \frac{k_{3p}^{A}[RR'NH]}{k_{-3p}^{A}[RR'NH_2^+]} = K_{3p}^{A}\frac{[RR'NH]}{[RR'NH_2^+]} \quad (10)$$

A more familiar form of eq 9 is eq 11[1,9]

$$k_A = \frac{k_1(k_2 + K_{3p}^{A}k_4^{A}[RR'NH] + K_{3p}^{OH}k_4^{OH}[OH^-])}{k_{-1} + k_2 + K_{3p}^{A}k_4^{A}[RR'NH] + K_{3p}^{OH}k_4^{OH}[OH^-]} \quad (11)$$

which is obtained from eq 9 by alternatively substituting K_{3p} with the appropriate expression from eq 10. Comparison of eq 11 with eq 2 shows that here

$$k_3^A \equiv K_{3p}^{A}k_4^{A};\ k_3^{OH} \equiv K_{3p}^{OH}k_4^{OH} \quad (12)$$

The SB-GA mechanism was also initially proposed by Bunnett;[14] it has been accepted by a majority of workers in the field,[1,3] particularly after Orvik and Bunnett's[15] study of the reaction of 1-ethoxy-2,4-dinitronaphthalene with *n*-butylamine and *tert*-butylamine in Me_2SO. These authors showed that the reaction occurs in two stages, the first being the formation of the anionic σ complex (M^-), the second being the butylammonium ion catalyzed ethoxide ion expulsion from M^-.

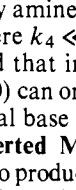
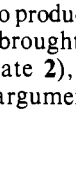
The SB Mechanism (Specific Base). A variation of the SB-GA mechanism is one where leaving group departure is *not* acid catalyzed, i.e., $k_4^A = 0$ (or k_4^A very small) and eq 9 simplifies to

$$k_A = \frac{k_1(k_2 + K_{3p}^{OH}k_4^{OH}[OH^-])}{k_{-1} + k_2 + K_{3p}^{OH}k_4^{OH}[OH^-]} \quad (13)$$

The equivalent of our Scheme I with $k_4^A = 0$ has occasionally appeared in the literature, mainly in discussions of small accelerations by amines in nonprotic solvents;[16,17] however, the situation where $k_4 \ll k_{-3p}$ has not usually been discussed. It is to be noted that in protic solvents this mechanism ($k_4 \ll k_{-3p}$; $k_4^A = 0$) can only account for the observation of specific, not for general base catalysis.

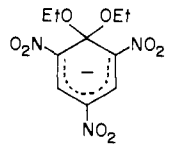
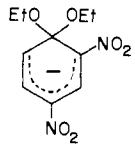
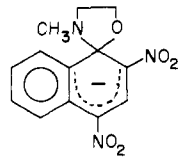
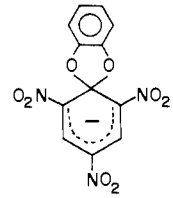
The Concerted Mechanism. In this mechanism MH is transformed to products by concerted breaking of the N–H and C–X bonds, brought about by the attack of the base on H (transition state **2**), similar to an E2 elimination reaction. Compelling arguments against it have been advanced,[15,18]

Table V. Summary of Results

Substrate	Amine	% dioxane	10^4k_1, M^{-1} s^{-1}	k_2/k_{-1}	k_3A/k_{-1}, M^{-1}	k_3OH/k_{-1}, M^{-1}	k_3A/k_2, M^4	k_3OH/k_2, M^{-1}	k_3A/k_3OH	(k_4A/k_4OH) "hypothetical"	Ref
	Piperidine	10	311	0.069	7.86	121	114	1750	0.065	~65	5
	Piperidine	60	350	0.012	0.73	12.2	61	1014	0.060	~10^5	8
	n-$BuNH_2$	10	15.0	>>1							This work, 6
	n-$BuNH_2$	60	40.0	>>1							6
	MBA[b]	10	64.0	0.005	0.96	17.2	192	3440	0.056	~1700	7
	Morpholine	10	33.3	0.0015	0.13	11.9	86.5	7900	0.011	~5500	*c*
	Piperidine	10	8.2	0.035	3.22	63	92	1800	0.051	~51	This work
	n-$BuNH_2$	10	0.2	>>1 (0.64)	(2.1)[d]	(17.5)[d]	(3.28)[d]	(27.4)[d]			This work
	n-$BuNH_2$	60	0.2	>>1 (2.7)	0	(100)[d]	0	(37)[d]			This work
	Piperidine	10	37.7	<0.001	0.12	25.7	>120	>25 700	0.0047		5, 7, This work
	Piperidine	60	29.9	0.0016	0	13.2	0	8250	0		This work
	n-$BuNH_2$	60	3.26	(1.6)[d]	(270)[d]	Large	(169)[d]	Very large			This work
	Piperidine	60	13.8	0.00025	0	11.9	0	47 500	0		This work
	n-$BuNH_2$	60	0.87	0.32	300	Large	946	$\sim10^4$–10^5	~0.01–0.1	~5×10^4 to 5×10^5	This work

[a] Calculated from eq 15; see text. [b] *N*-Methylbenzylamine. [c] C. F. Bernasconi and P. Schmid, *J. Org. Chem.*, **32**, 2953 (1967). [d] Calculated assuming that *n*-butylamine catalysis represents authentic base catalysis; see Discussion.

Table VI. Rate Constant Ratios ("k_4^A/k_4^{OH}") for Acid-Catalyzed over Noncatalyzed Alkoxide Ion Expulsion from Meisenheimer Complexes

Catalyst (pK_a)[a]	 3 ($pK_a^{ROH} \sim 16$)[a,b]	 4 ($pK_a^{ROH} \sim 16$)[a,b]	 5 ($pK_a^{ROH} \sim 14.5$)[a,b]	 6 ($pK_a^{ROH} \sim 10$)[a,b]
$PipH^+$ (11.1)	<1 (H_2O)[c] 80 (60% dioxane–40% H_2O)[c]	~2.4 (60% EtOH–40% H_2O)[c]		
n-$BuNH_3^+$ (10.6)	80 (60% dioxane–40% H_2O)[c]		~2.2 (H_2O)[d]	
CH_3COOH (4.7)	37 (60% EtOH–40% H_2O)[e]		7.3 (H_2O)[e]	Undetectable (50% Me_2SO–50% H_2O)[f]

[a] pK_a in water. [b] pK_a^{ROH} refers to leaving group, e.g., EtOH. [c] Reference 26. [d] Reference 25. [e] Reference 4c. [f] Reference 24.

making it unnecessary to consider it further even though it has been readvocated recently.[19]

Cyclic Mechanisms. For reactions in nonpolar solvents transition states assigning a bifunctional role to the base catalyst have been proposed.[20] Since in this paper we deal with protic solvents only, these will not be discussed further.

In the following we show that base catalysis is due to the proton transfer or the SB mechanism in all cases of the present study as well as in previously studied systems.

The Case against the SB–GA Mechanism When X = Phenoxy. We have shown recently that deprotonation of the zwitterionic intermediate (corresponding to MH) can be rate limiting in the formation of anionic spiro-Meisenheimer complexes (corresponding to M^-),[4] as a consequence of a high k_{-1} value. This led to our first suggestion that general base catalysis in nucleophilic aromatic substitutions may be a manifestation of the proton transfer mechanism rather than the SB–GA mechanism.[4] The following new evidence strongly supports this view for all reactions summarized in Table V where phenoxy is the leaving group.

1. k_3^A/k_3^{OH} Ratios. If the SB–GA mechanism were to prevail, k_3^A and k_3^{OH} would be defined as in eq 12 and the k_3^A/k_3^{OH} ratios given by

$$\frac{k_3^A}{k_3^{OH}} = \frac{K_{3p}^A k_4^A}{K_{3p}^{OH} k_4^{OH}} \tag{14}$$

After rearranging and substituting K_W/K_a^A for K_{3p}^A/K_{3p}^{OH} where K_a^A is the acid dissociation constant of $RR'NH_2^+$ and K_W the ionic product of water, one obtains

$$\frac{k_4^A}{k_4^{OH}} = \frac{k_3^A K_a^A}{k_3^{OH} K_W} \tag{15}$$

We have used our experimental k_3^A/k_3^{OH} ratios, in conjunction with K_a^A/K_W,[21] to calculate hypothetical k_4^A/k_4^{OH} ratios according to eq 15; they are summarized in Table V.

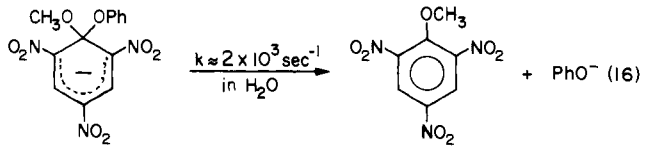
In the reactions with phenoxy as leaving group these hypothetical k_4^A/k_4^{OH} ratios vary from ~51 to ~5500 in 10% dioxane, depending on the amine; in 60% dioxane $k_4^A/k_4^{OH} \sim 10^5$ for the reaction of piperidine with 2,4-dinitrophenyl phenyl ether. These large numbers imply that $RR'NH_2^+$ is a very effective catalyst. This is, however, in direct conflict with growing evidence that, in protic solvents, general acid catalysis of alkoxide ion expulsion from Meisenheimer complexes is *weak*, or occurs only with acids considerably more acidic than $RR'NH_2^+$. In order to illustrate this point we have summarized some typical data on general acid catalysis of alkoxide ion departure from Meisenheimer complexes in Table VI.[4c,24-26] The data are presented as ratios of the rate constant for general acid catalysis over the rate constant for the noncatalyzed reaction; this corresponds to k_4^A/k_4^{OH} in our symbolism for the SB–GA mechanism and permits comparison with the hypothetical k_4^A/k_4^{OH} ratios of Table V.

It is evident that for catalysts of comparable acidity the ratios in Table VI are several orders of magnitude smaller than those in Table V. For example, catalysis by piperidinium ion of ethoxide expulsion from **3** is hardly detectable in aqueous solution (Table VI) but the SB–GA mechanism would require k_4^A/k_4^{OH} to be ~65 for the reaction of piperidine with 2,4-dinitrophenyl phenyl ether (Table V); in 60% dioxane the k_4^A/k_4^{OH} ratio is 80 for ethoxide ion expulsion from **3** (Table VI), but the SB–GA mechanism requires this ratio to be $\sim 10^5$ for the reaction of piperidine with 2,4-dinitrophenyl phenyl ether (Table V).

The situation is actually much worse than these comparisons suggest, because acid catalysis for the weakly basic phenoxide ion is expected to be much weaker than for the strongly basic ethoxide ion, as is borne out by the absence of detectable catalysis by acetic acid for **6** (Table VI). In fact, for the piperidine reactions in 10% dioxane, catalysis by the piperidinium ion would not be expected on theoretical grounds,[27,28] because no driving force for such catalysis is apparent since not even the proton transfer from $pipH^+$ ($pK \approx 11$) to the completely detached PhO^- ($pK \approx 10$) is thermodynamically favorable, let alone in the transition state **1** ("libido rule" [27]). To put it into even more drastic terms: as a consequence of the principle of microscopic reversibility, the reverse reaction of the SB–GA mechanism would require formation of the less reactive phenol by the thermodynamically unfavorable reaction of PhO^- + $PipH^+ \rightarrow$ PhOH + Pip, followed by piperidine-catalyzed (concerted) nucleophilic attack by phenol.

For the reactions involving *N*-methylbenzylamine or morpholine in 10% dioxane and the reactions of piperidine in 60% dioxane the situation is not quite as dramatic because the reaction $PhO^- + RR'NH_2^+ \rightarrow$ PhOH + RR'NH is now thermodynamically somewhat favored, by 1.6 pK units for the morpholine reaction, by ~2–3 pK units[21,29] in the piperidine reaction in 60% dioxane. Still, this provides not enough driving force to compensate for the expense in entropy of incorporating an additional molecule into the transition state (see absence of CH_3COOH catalysis for **6** in Table VI); at most one could expect very small k_4^A/k_4^{OH} ratios, many orders of magnitude smaller than those in Table V.

2. k_4/k_{-3p} Ratios. The SB–GA mechanism requires that $k_4/k_{-3p} \ll 1$. However, it is easily shown that with phenoxy as leaving group one must have $k_4/k_{-3p} \gg 1$ instead. An estimate of k_4 can be based on reaction 16.[30] Assuming that the effect of removing one *o*-nitro group from **7** accelerates reaction 16 as much (~4×10^4 fold) as it accelerates reaction 17,



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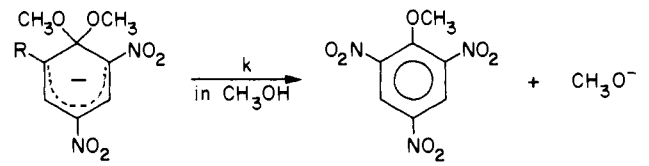
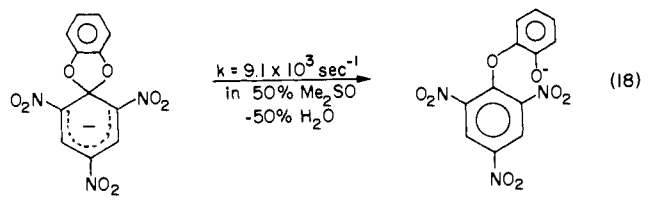
one estimates $k_4 \approx 8 \times 10^7\ s^{-1}$ for a 2,4-dinitrophenyl derivative.



8a (R = NO_2) : k = 10^{-3} sec^{-1} [31]

8b (R = H) : k = 42 sec^{-1} [32] (17)

Another method of estimating k_4 is based on comparing reactions 18[24] and 19.[33] The rate is 10^5 times faster for the



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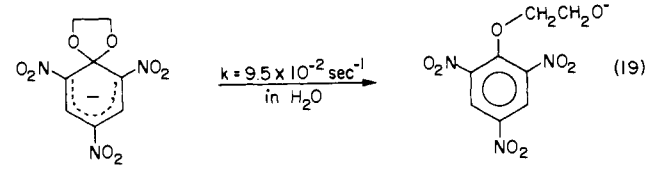

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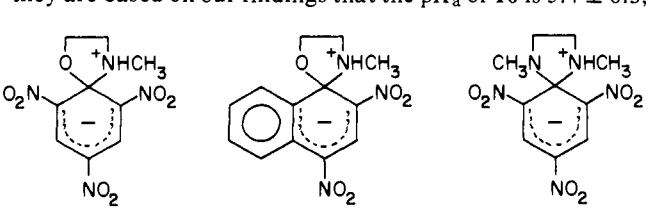
phenoxy type leaving group compared to the alkoxy type leaving group. Considering that reaction 18 is likely to be even faster in water, and that reaction 19 would be even slower for an alkoxy type leaving group whose pK_a is that of methanol, one estimates that phenoxy is a $\sim 10^6$ times better leaving group than methoxy. Taking reaction 17 with **8b** as the standard, one thus estimates k_4 with phenoxy as leaving group to be $\approx 4.2 \times 10^7\ s^{-1}$; thus both methods lead to about the same prediction.

It is clear that k_{-3p} can never even approach a value of 10^7 or 10^8. This is because MH is much more acidic than $RR'NH_2^+$ making the protonation of M^- a thermodynamically unfavorable proton transfer reaction under all reaction conditions. Estimates of the pK_a of MH are shown in Table VII; they are based on our findings that the pK_a of **10** is 5.4 ± 0.3,



10 11 12

that of **11** is 6.1 ± 0.3 in aqueous solution,[4c] and considering the pK_a of $RR'NH_2^+$, the effect of having fewer activating nitro groups and solvent effects. These pK_a estimates permit one to estimate the k_{-3p}^A and k_{-3p}^{OH} values given in Table VII. In a typical case, for example, the reaction of piperidine with 2,4-dinitrophenyl phenyl ether in 10% dioxane, one then obtains $k_{-3p} = k_{-3p}^{OH} + k_{-3p}^A[RR'NH_2^+] \approx 500 + 2 \times 10^4 [RR'NH_2^+] \ll 10^7$.

Kinetic ^{18}O Isotope Effect. The only piece of evidence which seems to contradict the notion of a rate-limiting proton transfer is Hart and Bourn's[34] report of a kinetic ^{18}O isotope effect in the reaction of piperidine with 2,4-dinitrophenyl phenyl ether in 60% dioxane. They report $k_A^{16}/k_A^{18} = 1.0109 \pm 0.0014$, 1.0070 ± 0.0007, and 1.0024 ± 0.0017 at $[OH^-] = 0.005$, 0.033, and 0.149 M, respectively. The decreasing trend in the isotope effect values with increasing base concentration was linked to the observation that at low base concentration the base-catalyzed step ($k_3^B[B]$, eq 1) is rate limiting whereas at high base concentration nucleophilic attack (k_1, eq 1) becomes rate limiting. The authors concluded that C–O bond breaking must occur in the base-catalyzed step, which is consistent with the SB-GA or the concerted mechanism for base catalysis.

It should be noted that this conclusion rests upon the assumption that the measured isotope effect is a primary rather than a secondary one. This is a questionable assumption in view of the fact that the isotope effect is much smaller than expected for a primary effect where C–O bond breaking is rate limiting, but is of the order of magnitude of typical secondary effects. For example, in the hydrazinolysis of methyl formate (^{18}O-methoxyl), $k^{16}/k^{18} = 1.0621 \pm 0.0008$ (primary effect) under conditions where methoxide ion expulsion from the tetrahedral intermediate is rate limiting, whereas $k^{16}/k^{18} = 1.0048 \pm 0.0006$ (secondary effect) when formation of the tetrahedral complex is rate limiting.[35] Other examples of secondary effects refer to the alkaline hydrolysis ($k^{16}/k^{18} = 1.0091 \pm 0.0004$) and the general-base-catalyzed hydrolysis ($k^{16}/k^{18} = 1.0115 \pm 0.0002$) of the same substrate.[35]

Upon reinvestigation of the ^{18}O isotope effect on the reaction of piperidine with 2,4-dinitrophenyl phenyl ether in our own laboratory,[36] we were able to confirm the order of magnitude of k_A^{16}/k_A^{18} reported by Hart and Bourns for low base concentrations, but in our experiments the scatter in the data was of the same order of magnitude as the differences between the values of isotope effects at low and high base concentrations reported by Hart and Bourns.

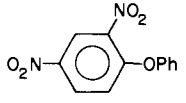
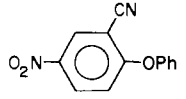
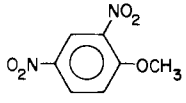
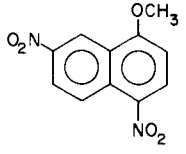
We conclude that, because of the smallness of the isotope effect and in view of the evidence, presented in this paper, in favor of a rate-limiting proton transfer mechanism, the isotope effect is a secondary one.

Dissection of Rate Coefficients of Elementary Steps (X = PhO^-). Having established the mechanism we can now estimate the values for k_{-1}, k_2, k_3^A, and k_3^{OH}. In 10% dioxane we need to make only one assumption, namely, that deprotonation of MH by OH^- is diffusion controlled or nearly so, with $k_{3p}^{OH} \approx 4 \times 10^9\ M^{-1}\ s^{-1}$ as for the deprotonation of **10**[4c] and **12**.[4a] Since $k_3^{OH} \equiv k_{3p}^{OH}$, k_{-1}, k_2, and $k_3^A \equiv k_{3p}^A$ are then obtained from the various ratios of Table V; they are summarized in Table VII.

With regard to the k_{-1} values we note that they are remarkably close to what we have predicted on the basis of model reactions (for example, formation of **12**[4a]), further testifying to the correctness of our mechanistic conclusions. Comparison of the k_{-1} values of the reactions of 2,4-dinitrophenyl phenyl ether with piperidine, *N*-methylbenzylamine, and morpholine shows a weak dependence on amine basicity. The comparison between piperidine and morpholine is the most meaningful because these two amines have essentially identical steric requirements; by applying the Bronsted relationship to k_{-1} one obtains $\log (k_{-1}^{Mor}/k_{-1}^{Pip}) = \alpha \log (K_a^{MorH^+}/K_a^{PipH^+})$ with $\alpha = 0.37$.

The k_2 values permit some insight into the mechanism of the k_2 step. Using arguments based on the at the time fash-

Table VII. Dissection of Rate Coefficients of Elementary Steps

Substrate	Amine (pK_aA)[a]	% dioxane	pK_w[a]	pK_aMH[b]	$k_{3p}OH$,[c] M^{-1} s^{-1}	$k_{3p}A$,[d] M^{-1} s^{-1}	k_2,[e] s^{-1}	k_{-1},[f] s^{-1}	$k_{-3p}OH$,[g] s^{-1}	$k_{-3p}A$, [h] M^{-1} s^{-1}	$k_4 = k_4OH$,[i] s^{-1}
	Piperidine (11.1)	10	14	~7.0	4×10^9	2.6×10^8	2.3×10^6	3.3×10^7	~400	$\sim 2 \times 10^4$	$\sim 10^8$
	Piperidine (~10.4)	60	~16.5	~8.5	$\sim 4 \times 10^8$	$\sim 2.4 \times 10^7$	$\sim 3.9 \times 10^5$	$\sim 3.3 \times 10^7$	~4	3×10^5	$\sim 2 \times 10^7$[j]
	MBA (9.6)	10	14	~5.5	4×10^9	2.2×10^6	$\sim 1.2 \times 10^6$	2.3×10^8	~13	$\sim 1.7 \times 10^4$	$\sim 10^8$
	Morpholine (8.4)	10	14	~4.3	4×10^9	4.4×10^7	5.1×10^5	3.4×10^8	~0.8	$\sim 3.5 \times 10^3$	$\sim 10^8$
	Piperidine (11.1)	10	14	~7.3	4×10^9	2.0×10^8	2.2×10^6	6.3×10^7	~200	$\sim 8 \times 10^4$	$\sim 10^8$
	Piperidine (11.1)	10	14	~7.0	4×10^9	$\sim 2.6 \times 10^8$[k]	$\leq 1.5 \times 10^5$	*l*	~400	$\sim 2 \times 10^4$	$10^2 - 10^3$
	Piperidine (~10.4)	60	~16.5	~8.5	$\sim 4 \times 10^8$	$\sim 2.6 \times 10^7$[m]	5×10^4	$\sim 3 \times 10^7$	~4	3×10^5	20 – 200
	n-$BuNH_2$ (~9.8)	60	~16.5	~7.9	$\sim 4 \times 10^8$	$\sim 2.6 \times 10^7$[m]	($\sim 1.5 \times 10^5$)	($\sim 10^5$)	~1	$\sim 3 \times 10^5$	$\geq 3 \times 10^4$
	Piperidine (~10.4)	60	~16.5	~8.0	$\sim 2 \times 10^9$	$\sim 1.3 \times 10^8$[m]	$\sim 4.2 \times 10^4$	1.7×10^8	~6	$\sim 5 \times 10^5$	$\leq 10^3$
	n-$BuNH_2$ (~9.8)	60	~16.5	~7.4	$\sim 2 \times 10^9$	$\sim 1.3 \times 10^8$[m]	$\sim 1.4 \times 10^5$	4.3×10^5	~1.6	$\sim 5 \times 10^5$	$\geq 5 \times 10^4$

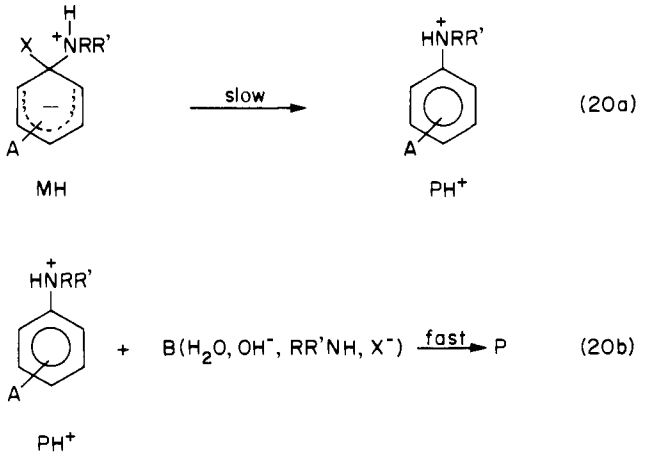
[a] In 10% dioxane assumed to be as in water; in 60% dioxane, see ref 21. [b] Estimated to be ~7 in 10% dioxane, based on model systems **10** and **11**; see text. For other amines assumed to change linearly with change in pK_a of amine. In 60% dioxane assumed to increase by 1.5 units over value in 10% dioxane, based on the solvent effect on the pK_a of glycine zwitterion: H. S. Harned and C. M. Birdsall, *J. Am. Chem. Soc.*, 65, 1117 (1943). For 2-cyano-4-nitrophenyl ether, assumed to be 0.3 units higher, due to smaller electron-withdrawing effect of cyano group. For 1-methoxy-2,4-dinitronaphthalene assumed to be 0.5 units lower than for 2,4-dinitroanisole in 60% dioxane, due to absence of intramolecular hydrogen bond. [c] Assumed to be 4×10^9 M^{-1} s^{-1} in 10% dioxane, based on $k_{3p}OH$ for **10**[a,c] and **12**;[a] in 60% dioxane assumed to be reduced tenfold where there is an *o*-nitro group, due to intramolecular hydrogen bonding. For 1-methoxy-4,7-dinitronaphthalene assumed to be reduced twofold, due to the effect of a twofold larger viscosity on a diffusion controlled reaction. [d] Calculated from k_3A/k_3OH unless otherwise indicated. [e] Calculated from k_3OH/k_2 or k_3A/k_2 unless otherwise indicated. [f] Calculated from k_3OH/k_{-1} or k_3A/k_{-1} unless otherwise indicated. [g] $k_{-3p}OH = k_{3p}OHK_W/K_aMH$. [h] $k_{-3p}A = k_{3p}Ak_aA/K_aMH$. [i] For X = phenoxy, estimate in 10% dioxane based on model reactions such as 16–19, see text; for reaction of piperidine with 2,4-dinitroanisole, estimate based on reaction 17 with 8b, see text; for reactions of *n*-butylamine estimate based on requirement $k_4/k_{-3p} >> 1$; for reaction of piperidine with 1-methoxy-4,7-dinitronaphthalene estimate based on requirement $k_4/k_{-3p} << 1$. [j] Solvent effect assumed to be the same as for reaction with 2,4-dinitroanisole. [k] Assumed to be the same as in reaction with 2,4-dinitrophenyl phenyl ether in 10% dioxane. [l] Cannot be obtained from k_3OH/k_{-1} because here $k_3OH \neq k_{3p}OH$; see text. [m] Assumed that $k_{3p}A/k_{3p}OH$ is the same as in reaction of piperidine with 2,4-dinitroanisole.

ionable SB-GA mechanism for base catalysis we showed that the k_2 pathway cannot involve rate-limiting deprotonation of MH by water followed by rapid leaving group departure, nor can it involve rapid equilibrium deprotonation of MH followed by rate-limiting H^+-catalyzed leaving group departure.[1,37] These conclusions still hold but they need to be justified differently.

If deprotonation of MH by the solvent were rate limiting k_2 would have to increase proportionally with the acid dissociation constant of MH. The fact is that all k_2 values are essentially the same (there is even a slight tendency for k_2 to *decrease* with increasing acidity of MH) even though there is a 500-fold increase in acidity between the least acidic and the most acidic MH. Furthermore, to account for the k_2 values in the order of 10^6, the pK_a of MH would have to be ~4, which is only the case in the morpholine reaction.

Essentially the same arguments apply in excluding a mechanism where rapid equilibrium deprotonation of MH is followed by rate-limiting, H^+-catalyzed phenoxide departure. Even if this last step were diffusion controlled ($\sim 10^{10}$ M^{-1} s^{-1}), k_2 could not be higher than 10^3 in the piperidine reaction ($k_2 = K_a^{MH} \times 10^{10}$). And again, k_2 should increase proportionally with the acidity of MH if this mechanism were to prevail.

A mechanism which *is* consistent with our k_2 values would be one where phenoxide departure is rate limiting, followed by rapid proton loss as shown in eq 20.



(20a)

(20b)

Another possibility is that leaving group departure is concerted with deprotonation by water. This would avoid the creation of the highly acidic species PH^+ which is a high-energy intermediate in basic solution (pK_a of $PH^+ \sim -1$ with piperidine[38]); it would also make the lone electron pair on nitrogen partially available as additional driving force for the reaction.

A third possibility which we have favored in previous discussions[1,37] is that the proton assists leaving group departure *intra*molecularly. Apart from an entropy advantage, this mechanism might be favored over the concerted mechanism because proton transfer to the incipient leaving group anion may be thermodynamically more favorable than the proton transfer to water. Whether this is true would depend on the basicity of the leaving group in the transition state, i.e., on how much progress C–O bond breaking has made in the transition state. When the leaving group is methoxy, the basicity of the transition state is probably high enough for this to become the best mechanism (see below); when it is phenoxy the point is debatable.

The fact that k_2 is practically independent of the amine (or even decreases slightly with increasing acidity of MH) is difficult to reconcile with either the concerted or the intramolecular mechanism since one would expect k_2 to increase with increasing acidity of MH. This either suggests a very low sensitivity to the acidity of MH, or, more likely, supports the stepwise mechanism of eq 20.

In dissecting the rate coefficients in 60% dioxane, the possibility of a reduction in k_{3p}^{OH} due to intramolecular hydrogen bonding has to be considered.[4b] The figures given in Table VII are based on a tenfold reduction. We note that the resulting k_2 for the reaction of piperidine with 2,4-dinitrophenyl phenyl ether is ~6 times smaller than in 10% dioxane, which is consistent with the favored mechanism of eq 20.

Reactions with Methoxy as Leaving Group. For the reactions involving methoxy as the leaving group the case against the SB-GA mechanism is less overwhelming than with phenoxy, but still quite strong. The strongest evidence against the SB-GA mechanism is that in 60% dioxane we observe *general* base catalysis for the butylamine reactions, but *specific* base catalysis for the piperidine reactions. If the SB-GA mechanism were operative, this would imply that *n*-$BuNH_3^+$ is a very efficient acid catalyst for methoxide departure whereas $pipH^+$ is so poor that its catalytic effect is undetectable. This is inconsistent with the findings summarized in Table VI which show that $pipH^+$ and *n*-$BuNH_3^+$ are about equally effective catalysts. Also, the k_4^A/k_4^{OH} ratios estimated according to eq 15 for the *n*-butylamine reactions are again much higher than what one could reasonably expect based on the models in Table VI.

Thus a more satisfactory interpretation of the results is that for the *n*-butylamine reactions we have $k_4/k_{-3p} \gg 1$, i.e., the proton transfer mechanism, but for the piperidine reactions we have $k_4/k_{-3p} \ll 1$ and $k_4^A \approx 0$, i.e., the SB mechanism.

In the light of this interpretation we can now offer two possible explanations for the small acceleration by piperidine in the reaction of piperidine with 2,4-dinitroanisole in 10% dioxane. Either the effect is a "small acceleration" of unclear origin and thus the reaction is simply subject to specific base catalysis just as in 60% dioxane, or we deal with a borderline mechanism between the proton transfer and the SB mechanism, as a consequence of k_4 and k_{3p} being of the same order of magnitude.

Estimates of k_4 and k_{-3p} (X = MeO). It is instructive to estimate k_4 and k_{-3p} in order to see whether the above interpretations are reasonable. It should be stressed, however, that there is a considerable uncertainty involved in these estimates, owing to a number of necessary assumptions, particularly in 60% dioxane. In making these assumptions we were guided by known chemical principles and also somewhat by our mechanistic conclusions stated above. Thus the numbers to be discussed are only meant to indicate orders of magnitude.

Estimates of k_{-3p}^{OH} and k_{-3p}^{A} from which k_{-3p} can be calculated are summarized in Table VII, along with the underlying assumptions.

For the reaction of piperidine with 2,4-dinitroanisole we thus obtain

$$k_{-3p}(10\%\ \text{dioxane}) \approx 400 + 2 \times 10^4[RR'NH_2^+] \quad (21)$$

$$k_{-3p}(60\%\ \text{dioxane}) \approx 4 + 3 \times 10^5[RR'NH_2^+] \quad (22)$$

An estimate of k_4 can be based on $k = 42\ s^{-1}$ for reaction 17 with **8b**. This value must be regarded as a lower limit for k_4 because the RR'N group is less electron withdrawing than the methoxy group and, more importantly, because resonance stabilization involving the lone electron pair of the nitrogen is expected to develop in the transition state; both effects enhance methoxide departure. That these effects are probably quite significant can be appreciated by considering the rates of the reverse reactions: methoxide ion attack on 2,4-dinitroanisole, 6×10^{-3} M^{-1} s^{-1};[32] methoxide ion attack on 2,4-dinitrophenylpiperidine, $\sim 2 \times 10^{-4}$ M^{-1} s^{-1} (at 67.9 °C).[39] We thus estimate k_4 to be 100–1000 s^{-1} in 10% dioxane, and, based on

some solvent effect studies involving Meisenheimer complexes such as **3**[26] and others,[26,37] $k_4 \approx 20$–$200\ s^{-1}$ in 60% dioxane.

We see now that in 60% dioxane, in strongly basic solution, we have $k_4/k_{-3p} \gg 1$ (or at least > 1) but in a pip-pipH$^+$ buffer $k_4/k_{-3p} \ll 1$. This means that in strongly basic solution OH^- catalysis represents general base catalysis and occurs by the proton transfer mechanism,[40] but in the pip-pipH$^+$ buffer the SB mechanism operates so that no amine catalysis can be observed, as is borne out by the results.

In 10% dioxane, in strongly basic solution, we have $k_4/k_{-3p} \sim 1$ or < 1;[41] in a pip-pipH$^+$ buffer $k_4/k_{-3p} < 1$ or $\ll 1$. Owing to the uncertainty in these estimates we cannot decide between an interpretation of the weak piperidine catalysis in terms of a borderline mechanism ($k_4/k_{-3p} < 1$),[42] or just an SB mechanism ($k_4/k_{-3p} \ll 1$) with piperidine catalysis attributed to a "small effect of unclear origin".[43]

Similar analyses can be made for the other reactions. For example, in the case of piperidine with 1-methoxy-4,7-dinitronaphthalene in 60% dioxane we have

$$k_{-3p} \approx 6 + 5 \times 10^5[RR'NH_2^+] \qquad (23)$$

For the investigated concentration range (Table IVC) this becomes $k_{-3p} \approx 10^4$–$10^5\ s^{-1}$. Since absence of piperidine catalysis implies $k_4/k_{-3p} \ll 1$ this means $k_4 \leq 10^3\ s^{-1}$. This is again a reasonable result because it allows for a higher k_4 than for 2,4-dinitroanisole (20–200 s^{-1}) as expected for the less activated naphthyl system.

In the reaction of *n*-butylamine with 1-methoxy-4,7-dinitronaphthalene we have

$$k_{-3p} \approx 1.6 + 5 \times 10^5[RR'NH_2^+] \qquad (24)$$

which gives $k_{-3p} \approx 5 \times 10^2$ to $5 \times 10^3\ s^{-1}$ in the concentration range where catalysis is observed (Table IVD). Since $k_4/k_{-3p} \gg 1$[44] this implies $k_4 \geq 5 \times 10^4\ s^{-1}$, which is considerably higher than in the piperidine reaction. This could be a consequence of a greater importance of developing resonance (lone pair of nitrogen) in the transition state because of less steric interference with the ortho substituent when dealing with a primary amine.[45] Similar conclusions can be drawn from the reaction of *n*-butylamine with 2,4-dinitroanisole if we assume that the observed catalytic effect represents authentic base catalysis.

k_{-1} and k_2. Without putting too much weight on the actual numbers summarized in Table VII, there are nevertheless two noteworthy observations to be made.

(1) The k_{-1} values are about two orders of magnitude larger in the piperidine compared to the *n*-butylamine reactions, probably as a consequence of release of steric strain in the case of the secondary amine.[10,47]

(2) The k_2 values, at least for the reactions involving piperidine, are considerably higher than the estimated k_4 values, i.e., methoxide ion departure from MH is faster than from M^-. This is in contrast to phenoxide ion departure: k_2 is at least 10 times *slower* then the estimated k_4 value. These findings support the notion that methoxide ion departure from MH is intramolecularly acid catalyzed whereas phenoxide ion departure is not, as suggested earlier.

General Conclusions. We have shown that, when the leaving group is a good one (phenoxy), its departure from M^- is faster than protonation of M^-. This leads to general base catalysis with the deprotonation of MH as the rate-limiting step. When the leaving group is poor (methoxy), its departure can be slower than protonation of M^- so that leaving group departure becomes rate limiting. Absence of *general* base catalysis in these situations shows that acid catalysis of leaving group departure by $RR'NH_2^+$ does not occur or is insignificant, i.e., the SB-GA mechanism is not an important pathway.

These conclusions seem to be generally applicable for reactions in *protic* solvents. On the other hand, in *aprotic* solvents, where leaving group expulsion becomes very difficult and the pK difference between leaving group and acid catalyst ($RR'NH_2^+$) becomes very large, the SB-GA mechanism provides an efficient pathway as shown by the work of Orvik and Bunnett[15] in Me_2SO. This is probably even more true in benzene, another popular solvent for such studies,[1] although there the situation is certainly more complicated because of ion pair formation between M^- and $RR'NH_2^+$.

Experimental Section

Materials. 1,4-Dioxane, piperidine, and *n*-butylamine were purified as described previously.[5,47] 2-Cyano-4-nitrophenyl phenyl ether was prepared by the method of Bost and Nicholson,[48] mp 125–126 °C from ethanol. 1-Methoxy-4,7-dinitronaphthalene was prepared from 1-chloro-4,7-dinitronaphthalene, obtained by described methods.[49] Sodium (78 mg) in 10 mL of methanol was slowly added to 850 mg of the chloro compound in 250 mL of methanol, refluxed for 15 min, and stirred at room temperature for 12 h. After evaporation of half of the methanol the product precipitated and was recrystallized from 2-propanol, mp 176.5–178.5 °C.

N-(2-Cyano-4-nitrophenyl)piperidine, *N*-(2-cyano-4-nitrophenyl)-*n*-butylamine, *N*-(4,7-dinitro-1-naphthyl)piperidine, and *N*-(4,7-dinitro-1-naphthyl)-*n*-butylamine were prepared by the method of Bunnett and Randall[12] starting with the respective chloro compounds; after recrystallization from ethanol we obtained mp 58–59, 127–128, 175–176 (lit.[49] 178), and 160–161 °C, respectively. 2,4-Dinitrophenyl phenyl ether, 2,4-dinitroanisole, *N*-(2,4-dinitrophenyl)piperidine, and *N*-(2,4-dinitrophenyl)-*n*-butylamine were available from previous studies.[5,7,47]

Rate Measurements. The kinetic determinations were generally done under N_2 in the dark; in strongly basic solution in 60% dioxane polyethylene bottles instead of glass flasks were used in order to prevent reaction with the glass. The same photometric procedure as described earlier was used.[5] Good pseudo-first-order kinetic plots were generally obtained over several half-lives. The reactions of 1-methoxy-4,7-dinitronaphthalene in 60% dioxane were very slow at low amine concentrations and in the absence of NaOH; they were followed over the first 10–20% of reaction.

The equilibrium reaction of the amines with water increases the hydroxide concentration and reduces the effective concentration of free amine. Effective concentrations were calculated from estimated pK_a values of the amines in the respective solvents.[5]

Rate coefficients are symbolized and were computed as follows: k_ψ, pseudo-first-order coefficient for the sum of the two reactions (aminolysis and hydrolysis) consuming the substrate, reckoned as 2.30 times the slope of the first-order plots; k_A*, pseudo-first-order coefficient of the aminolysis reaction, k_A* = (fractional yield of aminolysis product) × k_ψ; k_A, second-order coefficient of aminolysis reaction, $k_A = k_A^*/[RR'NH]_{eff}$; k_{OH}*, pseudo-first-order coefficient of the hydrolysis reaction, $k_{OH}^* = k_\psi - k_A^*$; k_{OH}, second-order coefficient of the hydrolysis reaction, $k_{OH} = k_{OH}^*/[OH^-]_{eff}$.

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References and Notes

(1) For a recent review dealing mainly with reactions of amines, see C. F. Bernasconi, *MTP Int. Rev. Sci.: Org. Chem., Ser. One*, **3**, 33 (1973).
(2) For general reviews on nucleophilic aromatic substitutions, see (a) F. Pietra, *Q. Rev., Chem. Soc.*, **23**, 504 (1969); (b) T. J. de Boer and I. P. Dirkx in "The Chemistry of the Nitro and Nitroso Groups", Part I, H. Feuer, Ed., Interscience, New York, N.Y., 1969, p 487; (c) J. Miller, "Aromatic Nucleophilic Substitution", American Elsevier, New York, N.Y., 1968; (d) E. Buncel, A. R. Norris, and K. E. Russell, *Q. Rev., Chem. Soc.*, **22**, 123 (1968); (e) S. D. Ross, *Prog. Phys. Org. Chem.*, **1**, 31 (1963); (f) J. F. Bunnett, *Q. Rev., Chem. Soc.*, **12**, 1 (1958); (g) J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 273 (1951).
(3) M. R. Crampton in "Organic Reaction Mechanisms, 1973", A. P. Butler and M. J. Perkins, Ed., Wiley-Interscience, New York, N.Y., 1975, p 225.
(4) (a) C. F. Bernasconi and C. L. Gehriger, *J. Am. Chem. Soc.*, **96**, 1092 (1974);

(b) C. F. Bernasconi and F. Terrier, *ibid.*, **97**, 7458 (1975); (c) C. F. Bernasconi, C. L. Gehriger, and R. H. de Rossi, *ibid.*, **98**, 8541 (1976).
(5) J. F. Bunnett and C. F. Bernasconi, *J. Am. Chem. Soc.*, **87**, 5209 (1965).
(6) J. F. Bunnett and R. W. Nichols, unpublished results.
(7) C. F. Bernasconi, *J. Org. Chem.*, **32**, 2947 (1967).
(8) J. F. Bunnett and R. H. Garst, *J. Am. Chem. Soc.*, **87**, 3879 (1965).
(9) J. F. Bunnett and C. F. Bernasconi, *J. Org. Chem.*, **35**, 70 (1970).
(10) J. F. Bunnett and R. H. Garst, *J. Am. Chem. Soc.*, **87**, 3875 (1965).
(11) It should be noted that in a more general treatment the expressions for k_{3p}, k_{-3p}, and k_4 would include terms like k_{3p}^{S} (for deprotonation by the solvent), $k_{-3p}^{S}[H^+]$ (for protonation by the solvated proton), and $k_4^{S}[H^+]$ (for leaving group departure catalyzed by the solvated proton), respectively. However, under the reaction conditions of the present study (basic solutions) these terms are negligible.
(12) J. F. Bunnett and J. J. Randall, *J. Am. Chem. Soc.*, **80**, 6020 (1958).
(13) M. Eigen, *Angew. Chem., Int. Ed. Engl.*, **3**, 1 (1964).
(14) J. F. Bunnett and G. T. Davis, *J. Am. Chem. Soc.*, **82**, 665 (1960), footnote 27.
(15) J. A. Orvik and J. F. Bunnett, *J. Am. Chem. Soc.*, **92**, 2417 (1970).
(16) H. Suhr, *Chem. Ber.*, **97**, 3268, 3277 (1964).
(17) (a) S. D. Ross, *Tetrahedron*, **25**, 4427 (1969); (b) S. D. Ross and R. C. Petersen, *Tetrahedron Lett.*, 4699 (1968).
(18) A. J. Kirby and W. P. Jencks, *J. Am. Chem. Soc.*, **87**, 3217 (1965).
(19) D. M. Brewis, N. B. Chapman, J. S. Paine, J. Shorter, and D. J. Wright, *J. Chem. Soc., Perkin Trans. 2*, 1787 (1974).
(20) B. Capon and C. W. Rees, *Annu. Rep. Prog. Chem.*, **60**, 278 (1963).
(21) In 10% dioxane $K_a^A/K_W \approx 10^3$ for piperidine, $\approx 3 \times 10^4$ for *N*-methylbenzylamine, $\approx 5 \times 10^5$ for morpholine, $\approx 3 \times 10^3$ for *n*-butylamine. In 60% dioxane, $pK_w \approx 16.5$[22] whereas the pK_a^A of piperidine decreases by ≈ 0.8, that of *n*-butylamine by ≈ 0.7 units, respectively;[23] thus $K_a^A/K_w \approx 2 \times 10^6$ for piperidine, $\approx 5 \times 10^6$ for *n*-butylamine.
(22) H. S. Harned and L. D. Fallon, *J. Am. Chem. Soc.*, **61**, 2374 (1939).
(23) P. Rumpf, G. Girault-Vexlearschi, and R. Schaal, *Bull. Soc. Chim. Fr.*, 554 (1955).
(24) C. F. Bernasconi and H.-C. Wang, *J. Am. Chem. Soc.*, **98**, 6265 (1976).
(25) C. F. Bernasconi and C. L. Gehriger, unpublished observations.
(26) C. F. Bernasconi and J. R. Gandler, in preparation.
(27) W. P. Jencks, *J. Am. Chem. Soc.*, **94**, 4731 (1972).
(28) W. P. Jencks, *Chem. Rev.*, **72**, 705 (1972).
(29) The pK_a of phenol in 60% dioxane is ~ 12.7: R. Gaboriaud and D. Meeroff, private communication.
(30) C. F. Bernasconi and M. C. Muller, in preparation.
(31) J. H. Fendler, E. J. Fendler, and C. E. Griffin, *J. Org. Chem.*, **34**, 689 (1969).
(32) C. F. Bernasconi, *J. Am. Chem. Soc.*, **90**, 4982 (1968).
(33) M. R. Crampton and M. J. Willison, *J. Chem. Soc., Perkin Trans. 2*, 1681 (1974).
(34) C. R. Hart and A. N. Bourns, *Tetrahedron Lett.*, 2995 (1966).
(35) C. B. Sawyer and J. F. Kirsch, *J. Am. Chem. Soc.*, **95**, 7375 (1973).
(36) C. F. Bernasconi, R. H. de Rossi, P. Schmid, J. F. Bunnett, and A. N. Bourns, unpublished results.
(37) C. F. Bernasconi and R. H. de Rossi, *J. Org. Chem.*, **38**, 500 (1973).
(38) The pK_a of *N,N*-dimethyl-2,4-dinitroanilinium ion is ~ -1.0: K. N. Bascombe and R. P. Bell, *J. Chem. Soc.*, 866 (1963).
(39) J. F. Bunnett and R. H. Garst, *J. Org. Chem.*, **33**, 2320 (1968).
(40) The virtual sameness of k_3^{OH}/k_{-1} for the reactions of piperidine with 2,4-dinitroanisole and with 2,4-dinitrophenyl phenyl ether in 60% dioxane further supports this conclusion; since k_{-1} is not expected to significantly depend on the leaving group, the sameness of k_3^{OH}/k_{-1} must mean that k_3^{OH} refers to the same process (proton transfer) in both reactions.
(41) Just as the virtual sameness of k_3^{OH}/k_{-1} in 60% dioxane, for the reactions of piperidine with 2,4-dinitroanisole and with 2,4-dinitrophenyl phenyl ether, showed that $k_4/k_{-3p} \gg 1$,[40] the considerably lower k_3^{OH}/k_{-1} ratio for 2,4-dinitroanisole compared to 2,4-dinitrophenyl phenyl ether in 10% dioxane further supports the conclusion that a borderline mechanism operates due to $k_4/k_{-3p} \sim 1$ or < 1.
(42) This interpretation requires a plot of k_A vs. piperidine concentration to be curvilinear because of an increase in k_{-3p}. Whether the slight curvature in our plot (not shown) is real or whether the plot should rather be considered to be a straight line within experimental error is difficult to decide. In any event, if the plateau region ($k_4/k_{-3p} \ll 1$) has already been approached, the curvature would be slight and the plot could give the appearance of linearity.
(43) An interpretation of this small effect in terms of $pipH^+$ catalysis of methoxide ion departure (SB-GA) is a possibility; however, it is then difficult to rationalize the total absence of such an effect in 60% dioxane, where the pK difference between $pipH^+$ and MeOH is more favorable for such a mechanism.
(44) The fact that k_A is independent of the buffer ratio at amine concentrations ≥ 0.01 M, i.e., when the plateau is reached (Figure 1), indicates that $k_4/k_{-3p} \gg 1$ and not just > 1.
(45) The importance of steric hindrance of resonance can be appreciated by comparing the pK_a of *N*-methyl-2,4-dinitroanilinium ion ($pK_a = -4.8$)[46] with that of *N,N*-dimethyl-2,4-dinitroanilinium ion ($pK_a = -1.0$).[36]
(46) E. A. Halevi, M. Nussim, and A. Ron, *J. Chem. Soc.*, 866 (1963).
(47) C. F. Bernasconi and R. H. de Rossi, *J. Org. Chem.*, **41**, 44 (1976).
(48) R. W. Bost and F. Nicholson, *J. Am. Chem. Soc.*, **57**, 2368 (1935).
(49) P. Beltrame, L. Bonomi, P. Da Re, and M. Simonetta, *Gazz. Chim. Ital.*, **97**, 470 (1967).

Aromatic Substitution in the Gas Phase. Predominant O-Alkylation in the Attack of t-$C_4H_9^+$ Ions to Anisole

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Abstract: The reaction of anisole with t-$C_4H_9^+$ ions, obtained in the dilute gas state from the γ-radiolysis of neopentane, yields exclusively *o*- and *p-tert*-butylanisole. Both the reactivity of anisole relative to toluene and the isomeric distribution of its alkylated products depend markedly on the composition, and especially on the pressure, of the gaseous reaction environment. The apparent $k_{anisole}:k_{toluene}$ ratio increases from 0.8, in neat neopentane at 720 Torr, to 4–5 in neopentane at 20 Torr containing a few mol % of a gaseous base, e.g., NH_3. Concurrently, the $^1/_2$ ortho:para ratio decreases from 1.3 at 720 Torr to <0.2 at 20 Torr. These results, and the effects of gaseous additives, including NH_3, $(CH_3)_3N$, and $(CH_3)_2O$, are consistent with a mechanism involving kinetically predominant O-alkylation of anisole, and subsequent isomerization of the excited dialkylaryloxonium ions to thermodynamically more stable para-alkylated arenium ions. The *substrate* and *positional* selectivity of the gas-phase *tert*-butylation, and the mechanism of isomerization, involving intermolecular alkylation of the para position of anisole by the dialkylaryloxonium ion, are discussed and compared with the gas-phase data concerning *tert*-butylation of phenol, and with those of related alkylation reactions occurring in solution.

In the preceding paper of this series[1] the gas-phase attack of t-$C_4H_9^+$ ions to phenol was shown to occur predominantly at the n-type nucleophilic center of the ambident substrate, leading to kinetically predominant O-alkylation.

The present paper reports the extension of the study to anisole, which represents a particularly interesting substrate, since the dialkylaryloxonium ion formed from the t-$C_4H_9^+$ attack to the oxygen atom cannot collapse into isolable alkylation products without some kind of isomerization to a C-substituted arenium ion.

Consequently, the alkylation of anisole with *tert*-butyl cations in the dilute gas state was expected to confirm, in the first place, the kinetically prevalent role of O-alkylation established for phenol,[1] and to give further information concerning the extent and the nature of the isomerization processes of the dialkylaryloxonium ion, and its alkylating ability.