Table V, equations of best least-squares planes; Table VI, positional parameters for nonhydrogen atoms; Table VII, anisotropic thermal parameters; and Table VIII, hydrogen atom positions (5 pages). Ordering information is given on any current masthead page.

References and Notes

(1) (a) State University of New York at Stony Brook. The support of this research by the National Science Foundation (Grant No. CHE76-16785) and by the National Institutes of Health (Grant No. GM-20672) is gratefully acknowledged. (b) Williams College. Research partially carried out at Brookhaven National Laboratory under contract with the U.S. Department of Energy and supported by its office of Basic Energy Sciences.
(2) V. Boekelheide and W. Feely, *J. Org. Chem.*, **22**, 589 (1957).
(3) W. L. F. Armarego, *J. Chem. Soc.*, 4226 (1964).
(4) G. Jones and J. Stanyer, *Org. Mass Spectrom.*, **3**, 1489 (1970).
(5) (a) A. Weissberger and E. C. Taylor, Ed., "Special Topics in Heterocyclic Chemistry", Vol. 30, Wiley-Interscience, Somerset, N.J., 1977; (b) F. G. Mann in "The Heterocyclic Derivatives of Phosphorus, Arsenic, Antimony and Bismuth", Vol. 1, 2nd ed., A. Weissberger and E. C. Taylor, Ed., Wiley-Interscience, New York, N.Y., 1970.
(6) F. Ramirez, H. Okazaki, and J. F. Marecek, *Tetrahedron Lett.*, 2927 (1977).
(7) F. Ramirez, J. F. Marecek, and H. Okazaki, *Tetrahedron Lett.*, 4179 (1977).
(8) G. Markl, *Phosphorus Sulfur*, **3**, 77 (1977).
(9) K. Dimroth, *Top. Curr. Chem.*, **38**, 1 (1973).
(10) S. D. Venkataramu, G. D. Macdonell, W. R. Purdum, M. El-Deek, and K. D. Berlin, *Chem. Rev.*, **77**, 121 (1977).
(11) P. Calabresi and R. E. Parks, Jr., "The Pharmacological Basis of Therapeutics", 5th ed., L. S. Goodman and A. Gilman, Ed., Macmillan, New York, N.Y., 1975, p 1248.
(12) A. Takamizawa, S. Matsumoto, T. Iwata, Y. Tochino, K. Katagiri, K. Yamagushi, and O. Shiratori, *J. Med. Chem.*, **18**, 376 (1975), and references therein.
(13) N. Brock, *Cancer Treat. Rep.*, **60**, 301 (1976).
(14) H. J. Hohorst, U. Draeger, G. Peter and G. Voercker, *Cancer Treat. Rep.*, *60*, 309 (1976).
(15) J. C. Clardy, J. A. Mosbo, and J. G. Verkade, *Phosphorus*, **4**, 151 (1974).
(16) (a) E. Hobbs, D. E. C. Corbridge, and B. Raistrick, *Acta Crystallogr.*, **6**, 621 (1953); (b) D. W. J. Cruickshank, *ibid.*, **17**, 671 (1964).
(17) L. N. Beard and P. G. Lenhert, *Acta Crystallogr., Sect. B*, **24**, 1529 (1968).
(18) M. Ul-Haque and C. N. Caughlan, *J. Chem. Soc., Perkin Trans. 2*, 1101 (1976).
(19) F. L. Phillips and A. C. Spaski, *J. Chem. Soc., Dalton Trans.*, **1448** (1976).
(20) J. R. Herriot and W. E. Love, *Acta Crystallogr., Sect. B*, **24**, 1014 (1967).
(21) (a) T. Migchelsen, R. Olthof, and A. Vos, *Acta Crystallogr.*, **19**, 603 (1965); (b) M. J. E. Hewlins, *J. Chem. Soc. B*, 942 (1971).
(22) H. P. Calhoun, N. L. Paddock, and J. Trotter, *J. Chem. Soc., Dalton Trans.*, 38 (1976).
(23) L. Pauling, "The Nature of the Chemical Bond", 3rd ed., Cornell University Press, Ithaca, N.Y., 1960.
(24) D. W. J. Cruickshank, *J. Chem. Soc.*, 5486 (1961).
(25) W. R. Busing and H. A. Levy, *Acta Crystallogr.*, **10**, 180 (1957).
(26) (a) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. B*, **26**, 274 (1970); (b) *Acta Crystallogr., Sect. A*, **27**, 368 (1971).
(27) "International Tables for X-ray Crystallography", Vol. 3, Kynoch Press, Birmingham, England, 1962, Table 3.3.1 A.
(28) R. F. Stewart, F. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, **42**, 3175 (1965).
(29) H. R. Ing, "Heterocyclic Compounds", Vol. 3, R. C. Elderfield, Ed., Wiley, New York, N.Y. 1952, Chapter 5, p 396.
(30) G. R. Clemo and G. R. Romage, *J. Chem. Soc.*, 49 (1931).
(31) In the mass spectrum of indolizine, the molecular ion is also the base peak *m/e* 117; in addition there are strong peaks due to parent HCN (90), parent H_2CN (89), and parent C_2H_2 (64); see ref 4.
(32) (a) E. M. Gaydou, G. Peiffer, and M. Etienne, *Org. Mass. Spectrom.*, **9**, 157 (1974); (b) E. M. Gaydou and G. Pfeiffer, *ibid.*, **9**, 514 (1974).
(33) Indolizine has an absorption band of medium intensity at 270–310 nm with three distinct peaks; in addition it has an intense band at 225–240 nm and a broad, medium intensity band at 330–360 nm; cf. ref 2 and 3.
(34) H. Kwart and K. King, "δ-Orbital Involvement in the Organo-Chemistry of Silicon, Phosphorus and Sulfur", Springer-Verlag, New York, N.Y., 1977.
(35) F. Ramirez, J. S. Ricci, Jr., H. Okazaki, K. Tasaka, and J. F. Marecek, *J. Org. Chem.*, **43**, 3635 (1978).
(36) Covalent bond (van der Waals) radii (Å): H, 0.30 (1.2); C, 0.77 (1.6); N, 0.70 (1.5); O, 66 (1.4); P, 1.10 (1.9); CH_3 (2.0) (ref 23 and 24).

Phosphoric Amides. 1. Phosphorus–Nitrogen vs. Nitrogen–Carbon Bond Cleavage in Acidic Solvolysis of *N*-Alkyl Phosphoramidates and Phosphinamidates

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Received March 6, 1978

N-tert-Butyl phosphinamidates and phosphoramidates, $X_2P(O)NH$-*t*-Bu (X = alkyl, aryl, *O*-alkyl, *O*-aryl), solvolyze in acidic media with both P–N and N–C bond cleavage. The relative contribution of these two pathways depends upon the substrate structure and the proton-donating and nucleophilic properties of the reaction medium. Rates of P–N and N–C bond fission were measured in solutions of $HClO_4$, TFA, and HCO_2H. Rate profiles and KSIE are interpreted in terms of an A2 mechanism for substitution at phosphorus, and a mechanism involving solvent electrophilic assistance for the de-*tert*-butylation pathway. For other *N*-alkyl-substituted phosphoramidates the competition between the P–N and N–R bond cleavage is a function of the ability of the *N*-alkyl group to generate the corresponding carbonium ion. N–C bond fission predominates for R = $CH(CH_3)Ph$ and $CH_2C_6H_4OCH_3$-*p*, but for R = *i*-Pr, CH_2Ph, $CH_2C_6H_4CH_3$-*p*, or CH_2-c-C_3H_5 only the substitution at phosphorus was observed.

The remarkably facile cleavage of the P–N bond under acidic conditions is receiving much attention in terms of mechanistic[1] and stereochemical[2] studies as well as synthetic application.[3] For the phosphacyl[4] derivatives $X(Y)P(O)NR_2$ (**1**), the principal mechanistic problems involve the structure of substrate conjugate acid (N vs. O protonation) and the nature of the rate-determining step (bimolecular displacement vs. unimolecular collapse of the protonated substrate). Although the direct evidence for the N protonation is still lacking, the N-protonated **1** is presently considered as the most probable reactive form of the substrate in solvolysis reaction.[6] The excellent leaving group (amine molecule or ammonia) is then in most cases displaced by the nucleophile in the bimolecular, S_N2-like process; the participation of the unimolecular mechanism can be a function of the leaving group nucleophilicity[7] and perhaps the acidity of the medium[2] (Scheme I).

The postulated structure of the conjugate acid (**1a**) has some additional implications. In the N-substituted system the full charge localized on nitrogen can in principle facilitate both P–N and N–C bond fission (Scheme II), and the reaction pathway should depend upon the relative stability of the intermediates formed and the nucleophilic (and possibly electrophilic) participation of the medium. It is reasonable to expect that these two cleavage patterns should be a function of the properties of the reaction medium and the detailed structure of the organophosphorus amide.

In order to gain some insight into the structure–reactivity

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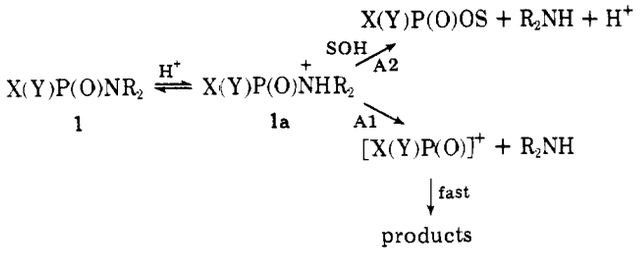
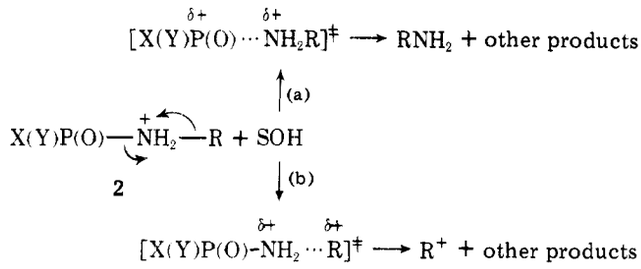
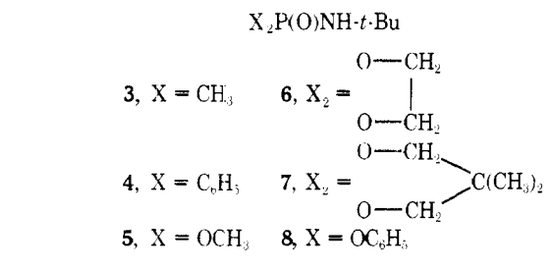
Scheme I



Scheme II



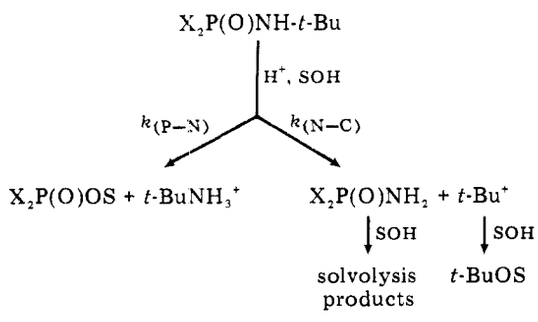
and medium-reactivity relationship in system **2**, we have studied the acidic solvolysis of some *N-tert*-butyl phosphoramidates and phosphinamidates (**3**–**8**) and related compounds.



Results and Discussion

All amidates studied show the ability to react with both P–N and N–C bond cleavage (Scheme III). The orientation and the rate of solvolysis were found to be very sensitive functions of the substrate structure and reaction medium composition. Both orientation and rates of the solvolysis could be easily followed by ^{1}H NMR spectroscopy. Compounds **3**–**8**, comprising the most typical phosphinic and phosphoric structures, provide therefore convenient models for the investigation of the relative reactivity in the acid-catalyzed carbonium ion formation and the acid-catalyzed displacement at phosphorus within the same molecular framework. Table I lists product distribution and rate data for **4** and **5** in aqueous (or aqueous–acetone) solutions of perchloric acid; the corresponding rate profiles are presented in Figure 1. For the P–N bond cleavage, the rate–acidity dependence shows the behavior typical for the A2 reaction mechanism, observed also in acidic hydrolysis of carboxylic amides.[8] The initial increase in rate, followed by the region of leveling off, results most likely from the opposite effects of increasing protonation of the substrate and decreasing availability of the effective nucleophile (water) in the reaction medium. Phosphinate **4**, being more basic than the phsophoramidate **5**,[9] reaches the maximum in rate at lower acidities (rate profiles in aqueous–acetone). For **5**, in aqueous solution, due to a higher acidity of the medium relative to the aqueous–organic solvent,[10] the rates are higher and the leveling off effect is more pronounced at lower content of perchloric acid.[11] The rate profiles for the N–C bond fission show quite different behavior; the rates increase dramatically with acidity over the narrow range of acid concentration. This of course demonstrates the absence of the nucleophilic solvent participation in the rate-determining formation of the *tert*-butyl carbonium ion. Such striking rate–acidity dependence suggests however that the reaction mechanism is more complex than the simple unimolecular collapse of substrate conjugate acid.

Scheme III



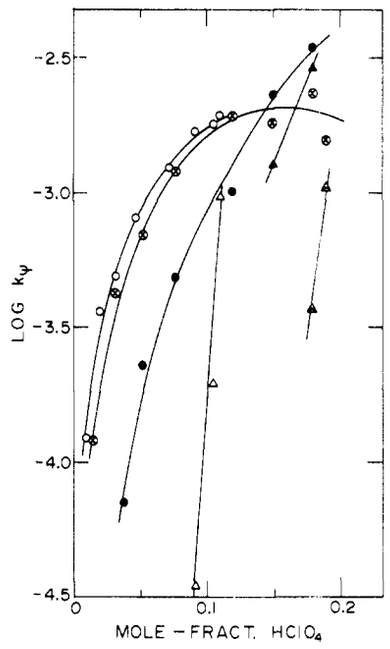


Figure 1. Rates of solvolysis as a function of mole fraction of $HClO_4$. **4** in aqueous $HClO_4$/acetone: (⊕) P–N cleavage; (▲) N–C cleavage. **5** in aqueous $HClO_4$/acetone: (●) P–N cleavage; (▲) N–C cleavage. **5** in aqueous $HClO_4$: (○) P–N cleavage; (△) N–C cleavage.

Solvolysis of substrated **3**–**8** was studied next in trifluoroacetic acid (TFA) and TFA–water mixtures. Product and rate data obtained in anhydrous TFA are listed in Table II. The predominance of one of two concurrent reactions is clearly a function of groups X; the almost exclusive P–N bond cleavage (**3**), comparable contribution from both pathways (**4**), and the exclusive de-*tert*-butylation (**7**, **8**) were observed. The variation in product distribution is mostly a result of variations in rates of substitutions at phosphorus. The rates of the N–C bond cleavage do not change by a factor greater than 10; phosphoramidates **5**–**8** react four to ten times faster than phosphinic derivatives **3** and **4**, due to the higher electronegativity (better leaving ability) of the $(RO)_2P(O)NH_2$ moiety. The accuracy of the experimental technique employed indicates that the values of $k_{\psi(P-N)}$ for **7** and **8** are lower than 1×10^{-4} s^{-1}; this gives the factor of at least 200 for the variation in rates of the reaction involving P–N bond cleavage. The acid-catalyzed hydrolysis of phosphinamidates is known to be significantly slowed down by the increase in steric crowding at phosphorus.[12] We attribute the observed differences in $k_{\psi(P-N)}$ mostly to the steric effects, particularly with respect

Table I. Solvolysis in Aqueous $HClO_4$/Acetone (1:1, v/v) (34 ± 0.5 °C)

$HClO_4$ mol fraction	4				5			
	P–N cleav, %	N–C cleav, %	$10^4k_{\psi(P-N)}$, s^{-1}	$10^4k_{\psi(N-C)}$, s^{-1}	P–N cleav, %	N–C cleav, %	$10^4k_{\psi(P-N)}$, s^{-1}	$10^4k_{\psi(N-C)}$, s^{-1}
0.015	100		1.21					
0.031	100		4.23					
0.038					100		0.71	
0.052	100		7.00		100		2.29	
0.077	100		12.2		100		4.93	
0.12	100		19.7		100		10.3	
0.15	100		18.4		65	35	24[a]	13[a]
0.18	86.5	13.5	24[a]	4[a]	55	45	34[a]	29[a]
0.19	60	40	16[a]	11[a]				

Solvolysis of **5** in Aqueous $HClO_4$ (34 ± 0.5 °C)

$HClO_4$ mol fraction	P–N cleav, %	N–C cleav, %	$10^4k_{\psi(P-N)}$, s^{-1}	$10^4k_{\psi(N-C)}$, s^{-1}	$HClO_4$ mol fraction	P–N cleav, %	N–C cleav, %	$10^4k_{\psi(P-N)}$, s^{-1}	$10^4k_{\psi(N-C)}$, s^{-1}
0.009	100		1.22		0.072	100		12.5	
0.020	100		3.66		0.091	98	2	16.9	0.34
0.032	100		4.93		0.105	90.5	9.5	18.3	1.92
0.047	100		8.20		0.110	74	26	20[a]	10[a]

[a] ±20%.

Table II. Solvolysis in Anhydrous TFA (34 ± 0.5 °C)

compd	registry no.	P–N cleav, %	N–C cleav, %	$10^4 \cdot k_{\psi(P-N)}$, s^{-1}	$10^4 \cdot k_{\psi(N-C)}$, s^{-1}
3	68036-30-6	96	4	≥160[a]	6[a]
4	68036-31-7	45	55	3.67	4.70
5	68036-32-8	8	92	2.60	30[a]
6	64067-51-2	20	80	5.47	22[a]
7	944-23-0		100		51[a]
8	3335-12-4		100		23[a]

[a] ±20%.

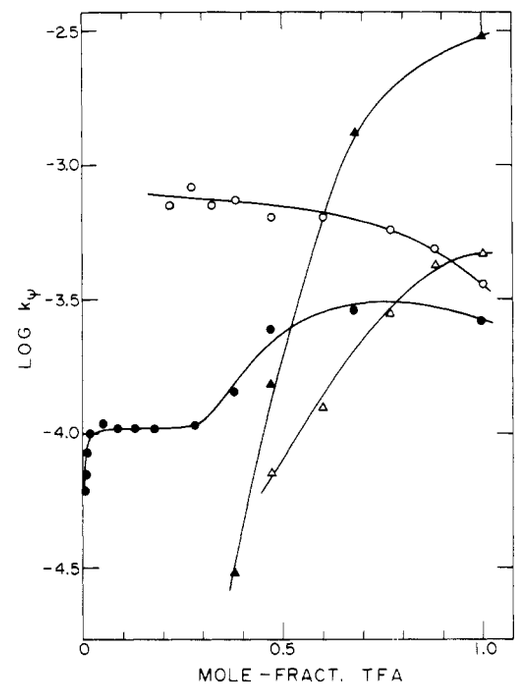


Figure 2. Rates of solvolysis as a function of mole fraction of TFA. **4**: (○) P–N cleavage; (△) N–C cleavage. **5**: (●) P–N cleavage; (▲) N–C cleavage.

to such a weak nucleophile as the TFA molecule. Compound **3** represents the system with the least hindrance at phosphorus and it undergoes displacement reaction at least 30 times faster than the next most reactive substrate. In phosphoramidates **5–7**, the polar effects should be to a first approximation the same. The steric hindrance for the nculeophilic attack at phosphorus increases in the order **6** < **5** < **7**,[13] which corresponds to the order of decreasing rate constants (5.5, 2.6, ≤1).

Four of the substrates were studied in aqueous solutions of TFA over a wide range of medium composition. The pertinent data are collected in Table III and rate profiles presented in Figures 2 and 3. All systems are capable of reacting according to pathway (a) or (b) (Scheme II); the proportion of products depends entirely upon the composition of the medium. In the case of **8**, it is even possible to produce at two extremes of acid concentration range the exclusive expulsion of the amine or exclusive formation of the *tert*-butyl carbonium ion. For all compounds the solvolysis of the P–N bond shows very low sensitivity to changes in medium composition (except in the very dilute acid region where the initial protonation of the substrate is necessary for the reaction to proceed with measurable rate). This behavior remains in full agreement with the A2 mechanism for the P–N bond cleavage. The increase in concentration of substrate conjugate acid with the increase of acidity is counterbalanced by the effect of replacement of good nucleophile (water) by the poor one (TFA). The values of k_ψ vary with concentration of TFA in a monotonic fashion; this indicates no change in reaction mechanism (e.g., for the A2 to A1 model), even in the region of low water content (or in anhydrous acid), i.e., the nucleophilic assistance of the solvent is necessary in the rate-determining transition state. It seems hard to accept that the leveling off of the rate profiles observed at ca. 0.1 mol fraction TFA results solely from the protonation of a substrate. This would require the amidates studied to be farily strongly basic ($pK_a \geq 0.4$). Haake demonstrated[1] that the pK_a values for some *N*-alkyl phosphinamidates are of the order of −2 to −3; the phosphoramidates $(RO)_2P(O)NHR$ have to be still considerably less basic.[9]

As in perchloric acid, the dealkylation reaction shows rapid acceleration within a relatively narrow range of acidity. The change in the medium composition from 0.4 to 1.0 mol fraction TFA results in ca. 100-fold rate increase, an effect greater than that expected solely on the basis of the increased concentra-

Table III. Solvolysis in Aqueous TFA (34 ± 0.5 °C)

TFA mol fraction	P–N cleavage, %				N–C cleavage, %				$10^4k_{(P-N)}$, s^{-1}				$10^4k_{(N-C)}$, s^{-1}			
	4	5	6	8	4	5	6	8	4	5	6	8	4	5	6	8
0.005	*a*	100		*a*	*a*			*a*	*a*	0.61		*a*	*a*			*a*
0.010	*a*	100	100	*a*	*a*			*a*	*a*	0.71	9.25	*a*	*a*			*a*
0.012	*a*	100		*a*	*a*			*a*	*a*	0.84		*a*	*a*			*a*
0.013	*a*		100	*a*	*a*			*a*	*a*		11.4	*a*	*a*			*a*
0.017	*a*	100		*a*	*a*			*a*	*a*	1.00		*a*	*a*			*a*
0.052	*a*	100	1100	*a*	*a*			*a*	*a*	1.09	17.8	*a*	*a*			*a*
0.085	*a*	100		*a*	*a*			*a*	*a*	1.04		*a*	*a*			*a*
0.086	*a*		100	*a*	*a*				*a*		15.0	*a*	*a*			*a*
0.13	*a*	100		*a*	*a*				*a*	1.04		*a*	*a*			*a*
0.18	*a*	100	100	*a*	*a*				*a*	1.05	8.25	*a*	*a*			*a*
0.20				100								0.37				
0.22	100								7.07							
0.27	100								8.40							
0.28		100								1.06						
0.30				100								0.44				
0.32	100								7.03							
0.38	100	91	100			9			7.38	1.44	4.55			0.30		
0.40				85				15				0.59				0.10
0.47	94	62			6	38			6.49	2.48			0.72	1.52		
0.50				54.5				45.5				1.24				1.03
0.51			93				7				3.61				0.27	
0.60	89			29	11			71	6.51			1.32	1.26			3.23
0.68		22				78				2.88				13.1		
0.70				17				83				1.73				8.44
0.75			66	12			34	88			6.21	1.89			12.1	13.8
0.77	73				27				5.72				2.80			
0.80				8				92				1.74				20[b]
0.88	57				43				4.87				4.24			
0.90				7				93				2.03				27[b]
1.00	45	8	20		55	92	80	100	3.67	2.60	5.47		4.70	30[b]	22[b]	23[b]

[a] Measurements not possible due to solubility limitations. [b] ±20%.

tion of protonated substrate in the pre-equilibrium step.[14] Such high sensitivity to the medium composition suggests the possibility of the additional involvement of the acid in the de-*tert*-butylation reaction. Kinetic solvent isotope effect measurements are usually employed to provide information about the role of the proton transfer in the acid-catalyzed process. KSIE has been determined for the solvolysis of amides **3–8** in TFA; the pertinent data are listed in Table IV. The KSIE results demonstrate the obvious mechanistic difference between the P–N and N–C bond cleavage pathways. For the substitution at phosphorus, the k_H/k_D values are typical for

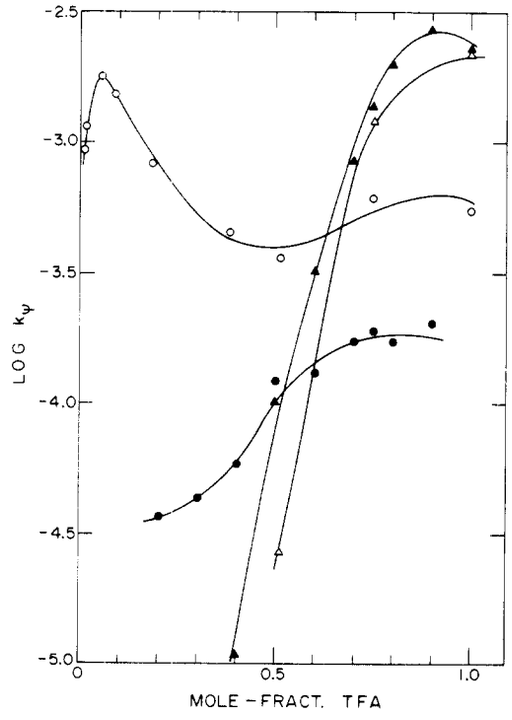


Figure 3. Rates of solvolysis as a function of mole fraction of TFA. **6**: (○) P–N cleavage; (△) N–C cleavage. **8**: (●) P–N cleavage; (▲) N–C cleavage.

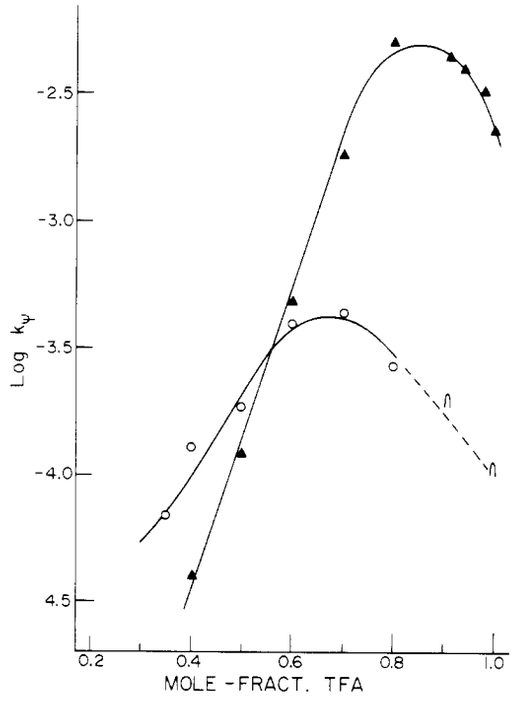


Figure 4. Rates of solvolysis of **9a** as a function of mole fraction of TFA: (○) P–N cleavage; (▲) N–C cleavage.

Table IV. Kinetic Solvent Isotope Effect for Solvolysis in TFA

compd	medium	k_H/k_D P-N cleavage	k_H/k_D N-C cleavage
3	100% TFA	0.56	*a*
4	100% TFA	0.58	1.37
5	100% TFA	0.73	1.36
5	5.8% TFA	0.64	
6	100% TFA	0.67	1.43
7	100% TFA		1.72
8	100% TFA	*b*	1.64

[a] Evaluation of k_H/k_D not possible due to negligible N-C cleavage in TFA-*d*. [b] In TFA-*d* 5% of the P-N bond cleavage was observed.

the reaction of an A2 mechanism;[16] rate acceleration in the deuterated medium results from the higher concentration of substrate conjugate acid. However, for the nitrogen–carbon bond cleavage, rather unexpectedly, the inverse isotope effect was found in anhydrous TFA for all systems, despite the fact that the first protonation pre-equilibrium producing the intermediate common for both reactions is subject to the "normal" effect ($K_H/K_D < 1$). Corrected to the magnitude of the KSIE upon the first protonation step, the values of k_H/k_D for the de-*tert*-butylation reaction in anhydrous trifluoroacetic acid are in the range 1.8–2.4, demonstrating unambiguously that the additional proton transfer must be involved in the transition state of the N-C bond fission. Such a transition state can be envisaged in this medium as a system in which the leaving group ability is increased by the proton transfer from the TFA to the phosphoryl oxygen, synchronous with the cleavage of the nitrogen–carbon bond (Scheme IV). The directly formed protonated (unsubstituted) amide can tautomerize to its reactive N-protonated form and the above sequence explains the high dependence of the debutylation rate on the acid concentration. Such a mechanism, involving specific, electrophilic solvation of the transition state by TFA, is reminiscent of the TFA-catalyzed ortho-Claisen rearrangement of allyl aryl ethers for which the KSIE of the value $k_H/k_D = 1.4$ has been found.[18]

Solvolysis of the phosphorus–nitrogen bond depends therefore upon the acidity (because of the pre-equilibrium step) and nucleophilicity (substitution at phosphorus) of the medium; de-*tert*-butylation is entirely the function of its proton-donating properties. This can be demonstrated by comparing solvolysis of **5** in aqueous solutions of $HClO_4$ and TFA. The medium containing 0.1 mol fraction of $HClO_4$ is characterized[19] by the same value of the acidity function as the solution containing 0.57 mol fraction of TFA[15] ($H_0 = -2.24$); these two solutions differ of course significantly in their nucleophilicity. The rates of the de-*tert*-butylation are in these two media approximately the same; the P-N bond cleavage proceeds in perchloric acid ca. eight times faster than in the corresponding TFA solution of the same H_0 value but with a much lower content of water.

Since the two modes of the acidic solvolysis of amides studied are characterized by different requirements with respect to medium acidity and nucleophilicity, it seems possible to modify the relative contributions of these two pathways by simply changing the reaction medium. On the other hand, the behavior of the compounds of the type **3–8** can provide information about the specific properties of a given acidic solution. For example, formic acid has a proton-donating ability considerably weaker (by ca. 0.5 in H_0 units) than TFA.[15,19] Haake and Ossip demonstrated[5] that HCO_2H is about 40 times more nucleophilic than TFA for displacement at the P^V atom. According to the mechanism proposed, the change of reaction medium from TFA to HCO_2H should produce quite different effects upon the solvolysis of P–N and N–C bonds. The solvolysis in these two media has been compared for some amidates and the results are presented in Table V. The change in product composition is indeed dramatic. In formic acid the almost exclusive P–N bond cleavage is observed even for compounds which in TFA react with predominant or exclusive N–C bond fission. The changes in rates of substitution at phosphorus are rather small. The effects caused by the greater nucleophilicity of HCO_2H are counterbalanced by its lower acidity. The rates of de-*tert*-butylation decrease however in formic acid enormously (for **8** by a factor of 2.8×10^3) as expected for a reaction with a high demand for the proton-donating ability of the medium, both in the pre-equilibrium step and in the electrophilic assistance in the rate-determining transition state.

It is evident that both patterns of the solvolytic cleavage are characterized by energies of activation of comparable magnitudes, so small variations in substrate structure or reaction medium can essentially change the reaction pathway. We decided to investigate also the structural dependence of the N–C bond cleavage for various N-alkylated phosphoric amides **9** and **10**. Thus the solvolytic cleavage has been tested as a probe for the relative easiness of the carbonium ion formation (Scheme II, b) by various groups R.

$(PhO)_2P(O)NHR$	$Ph_2P(O)NHR$
9a, R = $CH(CH_3)Ph$	**10a**, R = $CH(CH_3)Ph$
b, R = CH_2Ph	**b**, R = CH_2Ph
c, R = $CH_2C_6H_4CH_3$(p)	**c**, R = CH_2-c-C_3H_5
d, R = $CH_2C_6H_4OCH_3$(p)	
e, R = *i*-Pr	

Results of the solvolysis in anhydrous TFA are presented in Table VI. The position of the cleavage depends rigorously upon the structure of the substituent at nitrogen. Only for systems able to produce highly stabilized carbonium ions, such

Scheme IV

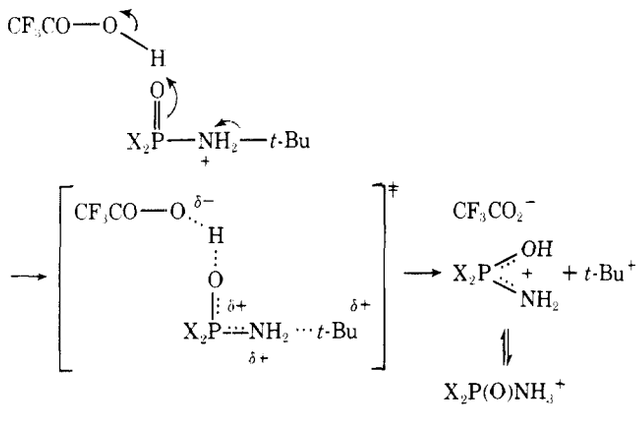


Table V. Comparison of Solvolysis in TFA and in Formic Acid

compd	TFA mol fraction	P–N cleav, %	N–C cleav, %	$10^4 k_{\psi(P\text{-}N)}$, s^{-1}	$10^4 k_{\psi(N\text{-}C)}$, s^{-1}
4	0.88	57	43	4.87	4.24
	1.00	45	55	3.67	4.70
5	0.68	22	78	2.88	13.1
	1.00	8	92	2.60	30
8	1.00		100		23
	HCO_2H mol fraction				
4	0.98	100		6.43	
5	0.98	100		0.58	
8	0.98	96	4	0.20	0.008

Table VI. Solvolysis in Anhydrous TFA (34 ± 0.5 °C)

compd	registry no.	P–N cleav, %	N–C cleav, %	$10^4 k_{\psi(P-N)}$, s^{-1}	$10^4 k_{\psi(N-C)}$, s^{-1}
9a	68036-33-9		100	<1	23[a]
9b	33985-75-0	100		1.26	<0.03
9c	68036-34-0	100		1.85	<0.05
9d	68036-35-1		100	<1.5	60[a]
9e	5756-04-7	100		0.51	<0.012
10a	67764-56-1	78	22	*b*	*b*
10b	27127-08-8	100		2.66	<0.07
10c	68036-36-2	100		*b*	*b*

[a] ±20%. [b] No reliable rate constant could be determined due to the overlap of the NMR signals of the substrate and products.

as α-methylbenzyl or *p*-methoxybenzyl, was the N–C cleavage observed in anhydrous TFA. Since the structural environment at phosphorus in all derivatives **9a–e** is practically constant, only small variations in rates of the P–N cleavage are observed. Rates of the dealkylation vary markedly reflecting large differences in the stability of the corresponding carbonium ions. It is worthwhile to point out the virtually identical values of $k_{\psi(N-C)}$ for compounds **9a** and **8** (Table II) indicating very similar stability of the α-methylbenzyl and *tert*-butyl carbonium ions. The same result has been reported in the solvolysis of the corresponding alkyl chlorides.[20] Data in Table VI demonstrate also sharp differences in the easiness of the formation of the tertiary vs. secondary (**8** vs. **9e**) or secondary vs. primary (**9a** vs. **9b**) carbonium ions. Since among *N*-benzyl derivatives only the *p*-methoxy compound gives the dealkylation product, determination of the ρ^+ constant for this reaction is not possible. However, the accuracy of the kinetic method enables one to estimate the upper limit of the $k_{\psi(N-C)}$ values for **9b** and **9c**, hence the upper limit of the reaction constant. It follows that for the debenzylation reaction $\rho^+ \leq$ ca. −4, clearly indicating the highly advanced formation of the carbonium ion in the rate-determining step, comparable to that observed in such reactions as solvolysis of cumyl chlorides, diphenylmethyl *p*-nitrobenzoates, or hydration of styrenes.[21]

Amidate **9a** was studied in aqueous TFA solutions. The rate–acidity dependence closely parallels that observed for the *tert*-butyl derivatives; the rate profiles for the P–N and N–C cleavage are shown in Figure 4. For the cleavage at phosphorus the rate profile is again compatible with an A2 model. Low variation in rate is observed with the possible decrease in rate in the range of low water content, what is indicated by the dashed line, based upon the upper limit of the k_ψ values for the (not observed) P–N cleavage. The rate profile for the dealkylation shows the distinct maximum at 0.8–0.9 mol fraction of TFA, which corresponds exactly to the maximum of the acidity function in aqueous TFA.[15] The plot of the log $k_{\psi(N-C)}$ vs. $-H_0$ is however not linear and increases rapidly at high concentrations of TFA. This indicates strongly the general acid catalysis in the region of the undissociated TFA and remains in full agreement with the rate-determining proton-transfer model for the N–C cleavage reaction (Scheme IV).

Experimental Section

Melting points are uncorrected. Aqueous solutions of $HClO_4$ were prepared by diluting the concentrated acid with distilled water. The concentrations of these solutions were determined from their densities; densities were measured with a DMA 02C digital precision density meter at 25.0 °C. TFA (Eastman) was distilled from trifluoroacetic anhydride with exclusion of moisture. Aqueous solutions of TFA were prepared from the calculated amounts of the acid and distilled water. Deuteriotrifluoroacetic acid (Aldrich, 99 atom % D) was used as supplied. Formic acid (Fischer) was distilled under reduced pressure from anhydrous cupric sulfate and its concentration was determined by standard titration against sodium hydroxide. ^1H NMR spectra were recorded at 60 MHz on a Varian T-60 spectrometer at a probe temperature of 34 ± 0.5 °C.

Reagents. Dimethylphosphinic chloride was prepared from the dimethylphosphinic acid[22] and PCl_5,[23] mp 68 °C (lit.[23] mp 67–68 °C). Diphenylphosphinic chloride was prepared from the diphenylphosphinic acid (Aldrich) and thionyl chloride,[24] bp 147 °C (0.3 mm) [lit.[24] bp 135–136 °C (0.07 mm)].

Dimethyl phosphorochloridate was prepared from methanol, PCl_3, and sulfuryl chloride,[25] bp 80 °C (18 mm) [lit.[25] bp 65–67 °C (11 mm)].

2-Chloro-2-oxo-1,3,2-dioxaphospholane was prepared from 2-chloro-1,3,2-dioxaphospholane[26] by oxidation with oxygen,[27] bp 68–69 °C (0.15 mm) [lit.[27] bp 79 °C (0.4 mm)].

2-Chloro-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane was prepared from 2,2-dimethylpropane-1,3-diol and $POCl_3$,[28] mp 100–101 °C (lit.[28] mp 104–106 °C).

Diphenyl phosphorochloridate (Aldrich) was distilled before use.

Amides **3–8** were prepared from *tert*-butylamine (2 equiv) and the corresponding acid chloride in anhydrous ether at 8–10 °C and purified by crystallization.

3, mp 90.5–91.5 °C (from ether). Anal. Calcd for $C_6H_{16}ONP$: C, 48.31; H, 10.81; N, 9.39; P, 20.76. Found: C, 47.68; H, 10.41; N, 9.82; P, 20.37.

4, mp 131–132 °C (lit.[29] mp 134–136 °C).

5, mp 64–65 °C (from hexane). Anal. Calcd for $C_6H_{16}O_3NP$: C, 39.77; H, 8.90; N, 7.73; P, 17.09. Found: C, 38.93; H, 9.60; N, 7.46; P, 16.69.

6, mp 113–115 °C (from hexane/CH_2Cl_2, 10:1). Anal. Calcd for $C_6H_{14}O_3NP$: C, 40.22; H, 7.88; N, 7.82; P, 17.29. Found: C, 40.32; H, 8.07; N, 7.75; P, 16.91.

7, mp 159–161 °C (from cyclohexane/CH_2Cl_2, 10:1). Anal. Calcd for $C_9H_{20}O_3NP$: C, 48.86; H, 9.11; N, 6.33; P, 14.00. Found: C, 48.60; H, 9.15; N, 6.18; P, 14.95.

8, mp 115–116 °C (lit.[30] mp 114–115 °C).

Amides **9** and **10** were prepared in the same manner from 2 equiv of the amine and the corresponding acid chloride.

9a, mp 104–106 °C (from cyclohexane). Anal. Calcd for $C_{20}H_{20}O_3NP$: C, 67.98; H, 5.71; N, 3.96; P, 8.77. Found: C, 67.51; H, 5.55; N, 3.80; P, 8.68.

9b, mp 92–94 °C (lit.[31] mp 101–102.5 °C).

9c, mp 93–94.5 °C (from cyclohexane/CH_2Cl_2, 10:1). Anal. Calcd for $C_{20}H_{20}O_3NP$: C, 67.98; H, 5.71; N, 3.96; P, 8.77. Found: C, 67.66; H, 5.88; N, 3.94; P, 8.75.

9d, mp 62–63 °C (from cyclohexane). Anal. Calcd for $C_{20}H_{20}O_4NP$: C, 65.04; H, 5.46; N, 3.79; P, 8.39. Found: C, 64.75; H, 5.51; N, 3.68; P, 8.54.

9e, mp 72–74 °C (lit.[30] mp 75–76 °C).

10a, mp 147–149 °C (from cyclohexane). Anal. Calcd for $C_{20}H_{20}ONP$: C, 74.75; H, 6.27; N, 4.36; P, 9.64. Found: C, 74.53; H, 6.41; N, 4.23; P, 9.49.

10b, mp 110–112 °C (lit.[32] mp 111–112 °C).

10c, mp 73–76 °C (from ether). Anal. Calcd for $C_{16}H_{18}ONP$: C, 70.83; H, 6.69; N, 5.16; P, 11.42. Found: C, 69.80; H, 6.60; N, 4.33; P, 12.07.

Product Determination. The substrate was dissolved in the acidic solution and the solvolysis was followed by recording the NMR spectrum of the solution. For **3–8** the *tert*-butyl groups of substrates and both products (P–N and N–C cleavage) appear as easily identified sharp singlets. For example, chemical shifts of the *t*-Bu group (in TFA) of **4**, *tert*-butylamine, and de-*tert*-butylation product are 1.43, 1.58, and 1.67 ppm, respectively.

When the reaction was complete, the cleavage products were identified by adding authentic samples of *tert*-butyl alcohol and *tert*-butylamine to the sample tube. When two solvolysis products were formed (P–N and N–C cleavage), the products ratio was determined from the intensities of the two *tert*-butyl signals.

For substrates **9** and **10** solvolysis products were identified and determined in the same way. The following signals were used to identify reaction products and to follow reaction kinetics: **9a**, CH_3 (d, J = 6 Hz); products, N–C cleavage, CH_3 (d, J = 6 Hz), $\Delta\delta$ = 9 Hz, and P–N cleavage, CH_3 (d, J = 6 Hz), $\Delta\delta$ = 15 Hz.

9b, CH_2 (d, $J_{H,P}$ = 11 Hz); product, P–N cleavage, CH_2 (q, J = 6 Hz), $\Delta\delta$ = 3 Hz.

9c, CH_2 (d, $J_{H,P}$ = 11 Hz); product, P–N cleavage, CH_2 (q, J = 6 Hz), $\Delta\delta$ = 5.5 Hz.

9d, CH_3 (s), CH_2 (d, $J_{H,P}$ = 11 Hz); product, N–C cleavage, CH_3 (s),

$\Delta\delta = -4.5$ Hz; also the broad band, $\Delta\delta \simeq -30$ Hz (relative to the CH_2 signal of **9d**), resulting from subsequent reactions of the *p*-methoxybenzyl carbonium ion in acidic medium.

9e, $(CH_3)_2$ (d, $J = 7$ Hz); product, P–N cleavage, $(CH_3)_2$ (d, $J = 7$ Hz), $\Delta\delta = 13$ Hz.

10a, CH_3(d, $J = 7$ Hz); products, N–C cleavage, CH_3 (d, $J = 7$ Hz), $\Delta\delta = 6$ Hz; P–N cleavage, CH_3 (d, $J = 7$ Hz), $\Delta\delta = 13$ Hz.

10b, CH_2 (d, $J_{H,P} = 7$ Hz); product, P–N cleavage, CH_2 (q, $J = 6$ Hz), $\Delta\delta = 11$ Hz.

10c, CH_2 (d of d), $\delta = 2.8$ (relative to Me_4Si) changed to the multiplet, $\delta = 2.8$ (relative to Me_4Si), identical with that from the authentic sample of the cyclopropylmethylamine.

Kinetics. The substrate (25 mg) was placed in an NMR tube which was equilibrated in a bath at the temperature of the kinetic run. The acid (0.5 mL) was pipetted from a container also kept in the bath and added to the substrate. Immediately after mixing, the tube was placed in the spectrometer probe and measurements were started. The integration curve was plotted repeatedly in the range of the *tert*-butyl groups signals (between 1 and 2 ppm) or in the appropriate range for substrates **9** and **10**, at the sweep width 100 or 50 Hz. Even for fast runs ($t_{1/2} < 5$ min) it was possible to collect not less than five points, first of which corresponded to not more than 30% of conversion. For these runs the reported rate constants are the average of at least three measurements and are reproducible to ca. ±20%. For slower runs ($t_{1/2} > 5$ min), reaction was followed for about 3 half-lives. The pseudo-first-order rate constants k_ψ were determined from changes in the intensity of the signals from the selected protons in the substrate molecule. Good straight-line plots ($r > 0.998$) were obtained in all cases. Identical results were obtained by following the decrease in the intensity of the signal from the substrate or by following the increase in the intensity of the signals derived from the reaction products. Rates obtained for slower runs are reproducible to within ±5%.

Acknowledgments. The financial assistance of the National Research Council of Canada is gratefully acknowledged.

Registry No.—*tert*-Butylamine, 75-64-9; dimethylphosphinic chloride, 111-92-8; diphenylphosphinic chloride, 1499-21-4; dimethyl phosphorochloridate, 813-77-4; 2-chloro-1,3,2-dioxaphospholane 2-oxide, 6609-64-9; 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphorinane 2-oxide, 4090-55-5; diphenyl phosphorochloridate, 2524-64-3; α-methylbenzylamine, 98-84-0; benzylamine, 100-46-9; *p*-methylbenzylamine, 104-84-7; *p*-methoxybenzylamine, 2393-23-9; isopropylamine, 75-31-0; cyclopropylmethylamine, 2516-47-4.

References and Notes

(1) T. Koizumi and P. Haake, *J. Am. Chem. Soc.*, **95**, 8073 (1973), and references cited therein.
(2) M. J. P. Harger, *J. Chem. Soc., Perkin Trans. 1*, 2057 (1977), and references cited therein.
(3) A. Zwierzak and I. Podstawczynska, *Angew. Chem., Int. Ed. Engl.*, **16**, 702 (1977).
(4) This term was proposed by Haake[5] to include phosphoryl, phosphonyl, and phosphinyl groupings.
(5) P. Haake and P. S. Ossip, *J. Am. Chem. Soc.*, **93**, 6924 (1971).
(6) See, for example, K. E. De Bruin, A. G. Padilla, and D. M. Johnson, *Tetrahedron Lett.*, 4279 (1971).
(7) D. A. Tyssee, L. P. Bausher, and P. Haake, *J. Am. Chem. Soc.*, **95**, 8066 (1973).
(8) See, for example, C. R. Smith and K. Yates, *J. Am. Chem. Soc.*, **93**, 6578 (1971).
(9) A. G. Cook and G. W. Mason, *J. Inorg. Nucl. Chem.*, **35**, 2090 (1973).
(10) J. F. Coetzee and C. D. Ritchie, "Solute–Solvent Interactions", Marcel Dekker, New York, N.Y., 1969, Chapter 3.V.
(11) For the full discussion of the A2 vs. A1 mechanism of solvolysis at phosphorus more complete rate profiles are needed. If the A2 mechanism operates over the whole range of acidity, rate decrease should be observed at high acidities, where substrates are fully protonated. Any change in a rate profile at high acidity should also indicate the change in reaction mechanism. However, more complete rate profiles are not available in the medium such as aqueous $HClO_4$, since above 0.2 mol fraction of $HClO_4$ solvolysis is extremely fast and involves almost exclusively the N–C bond cleavage.
(12) M. J. P. Harger, *J. Chem. Soc., Perkin Trans. 1*, 514 (1975); 605 (1977).
(13) For **7**, the approach of the nucleophile is particularly hindered because of the interactions with two 4,6-axial hydrogens and the *cis*-5-methyl group.
(14) The acidity function of aqueous TFA increases in the 0.4–1.0 mol fraction range by ca. 1.4 H_0 units.[15]
(15) U. A. Spitzer, T. W. Toone, and R. Stewart, *Can. J. Chem.*, **54**, 440 (1976).
(16) For the acid-catalyzed hydrolysis of some *N*-alkyl-substituted phosphoramidates similar values of $k_H/k_D = 0.5$–0.6 have been found.[17]
(17) A. W. Garrison and C. E. Boozer, *J. Am. Chem. Soc.*, **90**, 3486 (1968).
(18) U. Svanholm and V. D. Parker, *J. Chem. Soc., Perkin Trans. 2*, 169 (1974).
(19) Reference 10, Chapter 3.III.
(20) A. Streitwieser, *Chem. Rev.*, **56**, 571 (1956).
(21) D. Bethel and V. Gold, "Carbonium Ions", Academic Press, London, 1967, p 96–98.
(22) H. Reinhardt, D. Bianchi, and D. Mölle, *Ber.*, **90**, 1656 (1957).
(23) G. M. Kosolapoff and R. M. Watson, *J. Am. Chem. Soc.*, **73**, 5466 (1951).
(24) N. Kreutzkamp and H. Schindler, *Arch. Pharm. (Weinheim, Ger.)*, **293**, 296 (1960).
(25) B. Fiszer and J. Michalski, *Rocz. Chem.*, **26**, 688 (1952).
(26) H. J. Lucas, F. W. Mitchell, and L. N. Scully, *J. Am. Chem. Soc.*, **72**, 5491 (1950).
(27) R. S. Edmundson, *Chem. Ind. (London)*, 1828 (1962).
(28) R. S. Edmundson, *Tetrahedron*, **21**, 2379 (1965).
(29) N. L. Smith and H. H. Sisler, *J. Org. Chem.*, **26**, 5145 (1961).
(30) J. A. Stock, W. J. Hopwood, and P. D. Regan, *J. Chem. Soc. C*, 637 (1966).
(31) V. F. Kucherov, *Zh. Obshch. Khim.*, **19**, 126 (1949).
(32) V. Gutmann, G. Mörtl, and K. Utvary, *Monatsh. Chem.*, **93**, 1114 (1962).

Characteristics and Reactions of Cation Radicals and Quinone Imines Derived from Hydroxylated Chlorpromazine Derivatives

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Received July 27, 1978

The mechanisms of the chemical and electrochemical oxidations of two monohydroxylated and one dihydroxylated derivative of chlorpromazine, an N-substituted phenothiazine, are presented. In aqueous solutions at low pH, all three compounds form protonated cation radical oxidation products, and one derivative forms an uncharged radical center at neutral pH. The radicals are much more stable in aqueous solutions than radical ions derived from similar heterocyclic systems. Comparatively unstable quinone imines may be formed from the radicals, either by electrochemical oxidation or disproportionation of the radical ions. These quinone imines undergo a variety of reactions, including hydrolysis to quinones, hydroxylation, and nucleophilic substitution of chloride by hydroxide. The products and relative rates of these reactions are presented, and the overall pathways of the oxidations of the chlorpromazine derivatives are discussed.

Of the many radical ions which have been examined in recent years, the aromatic heterocyclic cation radicals have been of particular interest. The large majority of efforts in this area have been carried out in nonaqueous solvents due to the very short aqueous lifetimes of the radicals derived from such precursors as anthracene,[1-3] thianthrene,[4,5] and phenothiazine.[6,7] Recently, it was reported[8] that the radical of an N-substituted phenothiazine, chlorpromazine (CPZ, 1), has a

0022-3263/78/1943-5006$01.00/0