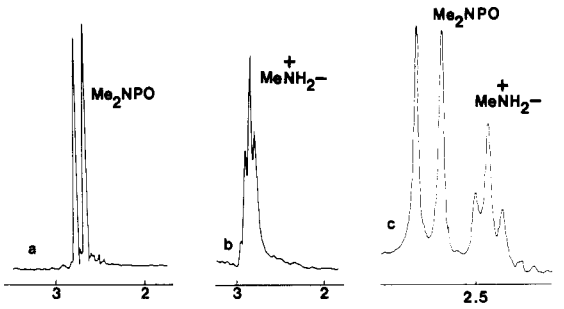

Figure 1. ^{1}H NMR spectra of the *N*-methyl groups, in TFMSA: (a) **2** after 72 h (sweep width 1000 Hz); (b) **3** after 2 min (sweep width 1000 Hz); (c) **5** after 5 min, unchanged after 72 h (sweep width 250 Hz).

tious estimate gives in this case the lower limit of rate acceleration, $k_\Psi(3)/k_\Psi(2) > 10^5$, perfectly in agreement with values observed for solvolysis of other cyclic systems.[9] The behavior of the diamidate **5** in TFMSA conforms well to the pattern observed for other substrates. While the exocyclic dimethylamino group remains unchanged over a long period of time, the cleavage of the endocyclic P–N bond is very fast and quantitative (Scheme V). Figure 1 illustrates the behavior of the acyclic and cyclic phosphoramidates in TFMSA as determined by the ^{1}H NMR of the *N*-methyl substituents.

We believe that our results demonstrate that the acid-catalysed cleavage of the P–N bond in phosphoramidates proceeds via the *N*-protonated species as a reactive form and that the amino group departs directly from the apical position of the trigonal-bipyramidal transition state or intermediate.

Experimental Section

$CDCl_3$ (Aldrich, 99.8 atom % D) was dried with P_4O_{10}, distilled, and stored over molecular sieves. TCAA (May and Baker Ltd.) was distilled under reduced pressure [bp 105 °C (12 mm)] and stored in a desiccator over P_4O_{10}. TFMSA (Aldrich) was distilled from a 10% volume of trifluoromethanesulfonic anhydride with rigorous exclusion of moisture [bp 62 °C (12 mm)] and stored in a desiccator over P_4O_{10}. ^{1}H NMR spectra were recorded at 100 MHz on a Varian XL-100 spectrometer at a probe temperature of 34 ± 1 °C.

Substrates. Amidates **1**, **2**, and **4** were prepared by passing dry dimethylamine through an etheral solution of the corresponding phosphorochloridate at room temperature. Amine hydrochloride was filtered off, the ether removed on a rotary evaporator, and the product purified by distillation.

For **1**: bp 75–76 °C (12 mm) [lit.[17] bp 72–72.5 °C (11 mm)]; ^{1}H NMR δ 2.65 (6 H, d, $J_{H,P}$ = 10 Hz, NMe_2), 3.66 (6 H, d, $J_{H,P}$ = 11 Hz, OMe).

For **2**: bp 95 °C (0.15 mm); mp 50–52 °C [lit.[18] bp 113–114 °C (1 mm); mp 47.5–48.5 °C]. Anal. Calcd for $C_4H_{10}O_3NP$: C, 31.79; H, 6.67; N, 9.27; P, 20.50. Found: C, 31.53; H, 6.64; N, 9.48; P, 20.25; ^{1}H NMR δ 2.74 (6 H, d, $J_{H,P}$ = 10 Hz, NMe_2), 4.20–4.45 (4 H, m, CH_2CH_2).

For **4**: bp 50–51 °C (0.6 mm) [lit.[19] bp 49–50 °C (1 mm)]; ^{1}H NMR δ 2.66 (12 H, d, $J_{H,P}$ = 10 Hz, NMe_2), 3.58 (3 H, d, $J_{H,P}$ = 11 Hz, OMe).

Compound **3** was prepared from methyl phosphorodichloridate, 2-(methylamino)ethanol, and 2 equiv of triethylamine in dry dioxane at 25–30 °C: bp 81–83 °C (0.15 mm); ^{1}H NMR δ 2.71 (3 H, d, $J_{H,P}$ = 10 Hz, NMe), 3.20–3.45 (2 H, m, NCH_2), 3.74 (3 H, d, $J_{H,P}$ = 12 Hz, OMe), 4.10–4.50 (2 H, m, OCH_2). Anal. Found for $C_4H_{10}O_3NP$: C, 31.98; H, 6.89; N, 9.56; P, 20.22.

Compound **5** was prepared as for **3**, with Me_2NPOCl_2, 2-(methylamino)ethanol, and Et_3N as substrates: bp 88–89 °C (0.08 mm). Anal. Calcd for $C_5H_{13}O_2N_2P$: C, 36.59; H, 7.98; N, 17.07; P, 18.87. Found: C, 36.71; H, 7.96; N, 16.94; P, 18.61. ^{1}H NMR δ 2.64 (3 H, d, $J_{H,P}$ = 9.8 Hz, *endo*-NMe), 2.72 (6 H, d, $J_{H,P}$ = 10.3 Hz, *exo*-NMe_2), 3.15–3.50 (2 H, m, NCH_2), 4.00–4.40 (2 H, m, OCH_2).

Kinetics. The substrate (ca. 20 mg) was placed in an NMR tube which was equilibrated in a bath at the temperature of the kinetic run. The solution of an equimolar quantity of TCAA in $CDCl_3$ (0.5 mL) was added from a container also kept in the bath, the tube was placed in the spectrometer probe, and measurements were started. The integration curve was plotted repeatedly in the range of the *N*-methyl group signals (between 2 and 3 ppm) at a sweep width of 250 Hz. Second-order rate constants k_2 were determined from changes in intensity of the signals from N-Me protons in the substrate (or product) molecule. For minimization of the complications resulting from the subsequent interactions between TCAA and the reaction product, rate constants were calculated from the initial part of the reaction (up to 30% of conversion). Satisfactory straight-line plots ($r > 0.99$) were obtained; the reported values are the average of three measurements and are reproducible to within ±15%. For reactions in TFMSA, the acid (0.5 mL) was transferred to the NMR tube containing ca. 25 mg of a substrate in a rigorously moisture-free glovebox, the tube cap was wrapped tightly with Parafilm, and the NMR spectrum was recorded.

Acknowledgment. Financial assistance from the Council of the University of Cape Town is gratefully acknowledged.

Registry No. **1**, 597-07-9; **2**, 7114-66-1; **3**, 30982-84-4; **4**, 7393-11-5; **5**, 51833-54-6; TCAA, 76-03-9; TFMSA, 1493-13-6; methyl phosphorodichloridate, 677-24-7; Me_2NPOCl_2, 677-43-0; 2-(methylamino)ethanol, 109-83-1.

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Theoretical Estimation of pK_a Values of Pyrazinylguanidine Derivatives

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The pivotal role which prototropic equilibria play in the action of numerous therapeutic agents has been thoroughly documented.[2] Therefore, the ability to predict quantitatively one of the thermodynamic parameters connected with these events would be particularly useful in drug design and afford a unique advantage in the selection of analogue members. Herein we contribute a practical solution to the question of how well a chemist can predict, a priori, solution-phase pK_a values and present our initial results on the estimation of pK_a values of amiloride[3] (Figure 1) and its derivatives (Figure 2) based on CNDO/2 calculations of gas-phase proton affinities (PAs).[4]

A more detailed understanding of the factors which influence prototropic equilibria has emerged as one of the

(1) (a) West Point, PA. (b) Rahway, NJ.
(2) Ganellin, C. R. In "Drug Action at the Molecular Level"; Roberts, G. C. K., Ed.; University Park Press: Baltimore, MD, 1977; Chapter 1 and references cited therein.
(3) Amiloride is a potassium-sparing diuretic. For conformational studies of amiloride as well as leading references regarding its synthesis and structure–activity relationships, see: Smith, R. L.; Cochran, D. W.; Gund, P.; Cragoe, E. J., Jr. *J. Am. Chem. Soc.* **1979**, *101*, 191 and references cited therein.
(4) Proton affinity (PA) is defined for a base B as the heterolytic bond-dissociation energy for removing a proton from the conjugate acid BH^+.

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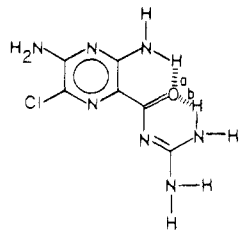

Figure 1. Planar conformation of amiloride (R_1 = NH_2; R_2 = Cl) used in calculations. Distances *a* and *b* are 1.747 and 1.565 Å, respectively.

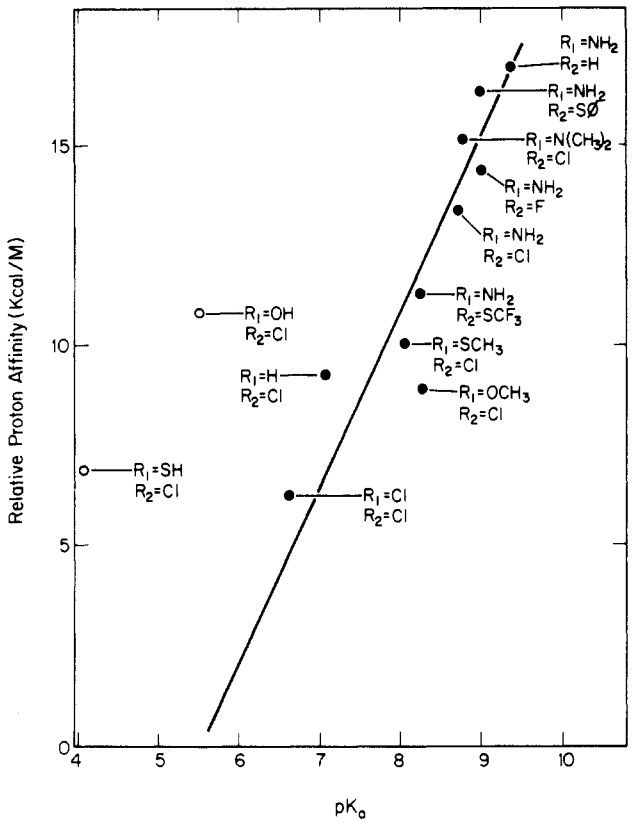

Figure 2. Plot of calculated proton affinity vs. pK_a for substituted pyrazinyl guanidines [(●) included in regression, (○) excluded]. Regression equation: CNDO/2, pK_a(calcd) = (0.22 ± 0.035) × PA_{calcd} + (5.57 ± 0.56), R^2 = 0.82, S = 0.37.

recent significant advances in physical organic chemistry. In this connnection, gas-phase PAs have become available for a wide variety of compounds, using recently developed experimental techniques.[5] The PAs thus obtained have in turn been correlated with experimentally determined, solution pK_a values.[6] By comparison of gas- and solution-phase basicities, solvent effects can now be separated from the intrinsic electronic factors controlling proton affinities. Further, gas-phase PAs may be calculated reliably by ab initio quantum mechanical methods.[7] Such extensive ab initio calculations, however, are currently not practical for complex polyfunctional molecules like amiloride. Consequently, in the present study, we resorted to semiempirical calculational techniques.

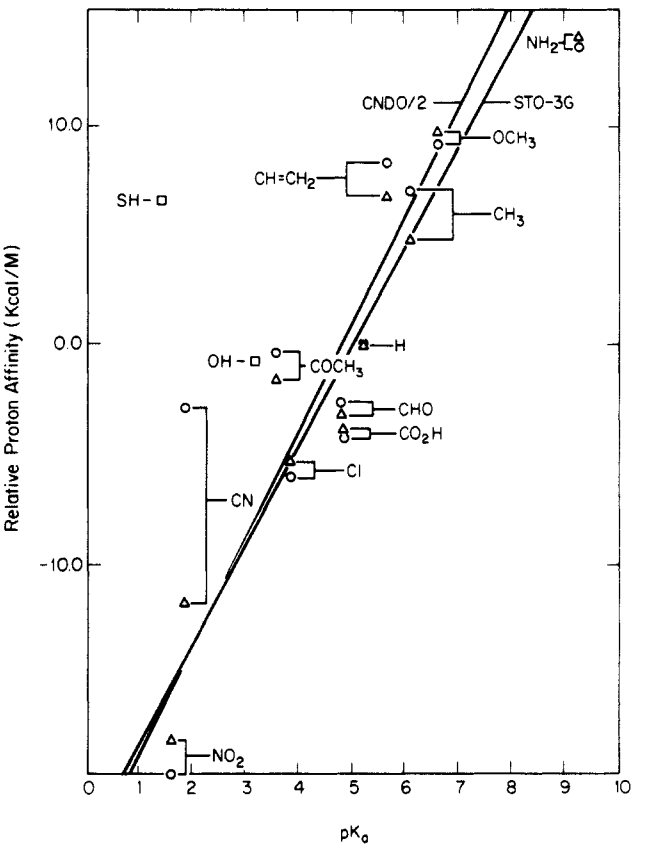

Figure 3. Plot of calculated proton affinity [(○) CNDO/2, (△) STO-3G] vs. pK_a for eleven para-substituted pyridines; values for the unsubstituted structure have been taken as zero and superimposed. (OH values, pK_a(calcd) = 11.12, PA = 6.27 kcal/mol; SH values, pK_a(calcd) = 8.86, PA = −0.60 kcal/mol). Regression equations: CNDO/2, pK_a(calcd) = (0.20 ± 0.038) × PA_{calcd} + (0.84 ± 1.3), R^2 = 0.73, S = 1.11; STO-3G, pK_a(calcd) = (0.22 ± 0.024) × PA_{calcd} + (1.07 ± 0.82), R^2 = 0.89, S = 0.70.

To gauge the suitability of the CNDO/2 approximation,[8] minimal basis set STO-3G ab initio calculations[9] were carried out on a variety of anilines and pyridines, two model systems for which dependable experimental data are available.[10] Figure 3 shows the correlation between aqueous solution pK_a values and the relative PAs calculated by CNDO/2 and ab initio methods for 4-substituted pyridines. Analogous data for a series of *p*-aniline derivatives are presented in Figure 4. For both methods, the calculated PAs correlate well with the measured pK_a values, indicating that semiempirical calculations give meaningful results for related molecules within a given series. There are two notable exceptions. The sizeable discrepancy between the two computations for the cyano derivative PA can be traced to difficulties in the CNDO/2 technique (cf. trends in experimental gas-phase PAs[4]). For the hydroxyl and particularly the sulfhydryl groups in the pyridine case, keto–enol tautomerism very likely accounts for the observed deviation from the norm.[11]

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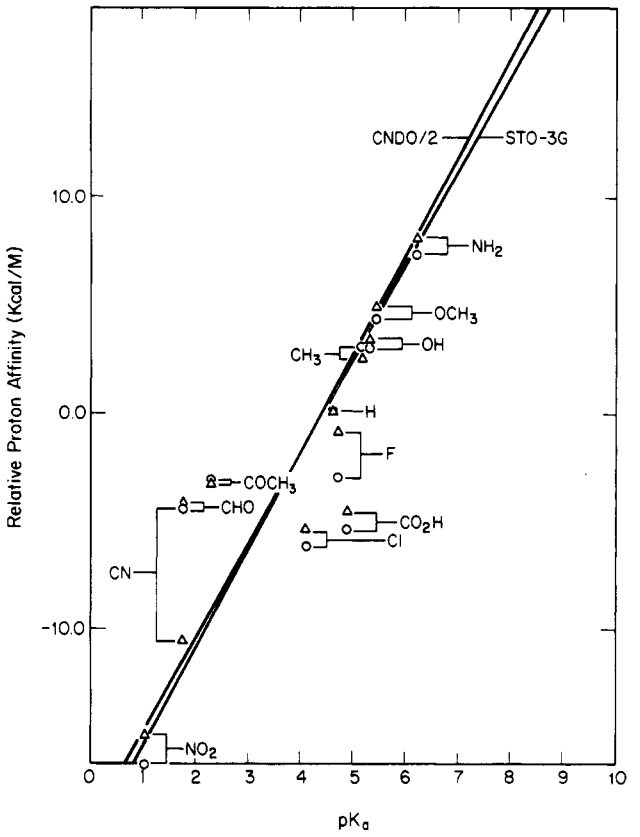
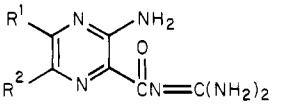


Figure 4. Plot of calculated proton affinity [(○) CNDO/2, (●) STO-3G] vs. pK_a for 12 para-substituted anilines. The values for the unsubstituted structures have been taken as zero and superimposed. Regression equations: CNDO/2, pK_a(calcd) = (0.22 ± 0.052) × PA_{calcd} + (0.82 ± 1.3), R^2 = 0.62, S = 1.07; STO-3G, pK_a(calcd) = (0.23 ± 0.040) × PA_{calcd} + (0.98 ± 1.0), R^2 = 0.75, S = 0.87.

For amiloride and its derivatives, various substituents were placed at the 5- and/or 6-position of the pyrazine ring. The site of protonation, the guanidine nitrogen bearing the acyl group, and its immediate environment remained constant throughout the series. In these cases, the site of substitution was far removed from the protonation site and, therefore, it was expected that the various substituents would have comparable influences on the solvation shell surrounding the site of protonation. With these restrictions, semiempirical methods could reproduce adequately the trend among the pK_a values. The PAs for the amiloride series calculated by the CNDO/2 method and experimental pK_a values are given in Table I. A least-squares analysis of the data shows a correlation which is similar in quality to that found for both the pyridine and aniline series (Figure 2). Here again, the deviations of the values observed for the hydroxyl and sulfhydryl groups may be attributed to tautomerism, since the OCH_3 and SCH_3 derivatives, which cannot tautomerize, afford PAs which fall predictably on the line.

Since the ionization state of a molecule, particularly that of a drug, may have profound effects on its solubility, absorption, membrane penetration, and conformation, a rapid first approximation of its pK_a value can be a valuable aid in target compound selection. The pK_a values derived for the amiloride series fall within a limit of 0.4 pK_a units. In our view, 0.4 pK_a units is within an acceptable range for making judgments concerning the choice of key compounds to synthesize from potentially hundreds of candidates. The usefulness and practicality of this method are therefore demonstrated. It is our expectation that this method of analysis, with suitable precautions, will prove to be of general utility as a means for predicting pK_a values.

Table I. Pyrazinylguanidine Data



1

	R_1	R_2	concn, mM	pK_a	PA, kcal/mol
1	NH_2	H	1.66	9.30	16.91
2	NH_2	SC_6H_5	0.91	9.00	14.45
3	$N(CH_3)_2$	Cl	1.33	8.76	15.18
4	NH_2	F	1.60	9.00	16.39
5	NH_2	Cl	1.66	8.70	13.36
6	NH_2	SCF_3	1.33	8.22	11.13
7	CH_3O	Cl	1.33	8.25	8.89
8	SCH_3	Cl	1.33	8.05	10.12
9	H	Cl	1.33	7.10	9.30
10	OH	Cl	1.33	5.45	10.80
11	SH	Cl	1.33	4.00	6.84
12	Cl	Cl[a]	1.66	6.60	6.30

[a] All measurements were carried out at 24 °C, using water as solvent; entry 12 was determined in 30% aqueous ethanol.

Experimental Section

Calculations were performed by using the Merck molecular modeling system.[12] Standard bond lengths and angles were used to construct the pyrazine series. A single tautomer of the guanidine moiety was used as shown in Figure 1. The neutral guanidine geometry was as follows: C=N, 1.29 Å; C—N, 1.406 Å. A single value of 1.355 Å was used for the guanidinium geometry.

Acknowledgment. We thank Dr. P. Gund for helpful discussions and are especially grateful to Mr. Y. Lee for physical measurements in the pyrazine series and to Ms. J. de Solms for cataloguing and providing these data for us. We extend our appreciation to Drs. P. S. Anderson and R. L. Smith for their encouragement and support throughout the course of these studies.

Registry No. 1 (R^1 = NH_2; R^2 = H), 1134-13-0; 1 (R^1 = NH_2; R^2 = SC_6H_5), 70296-90-1; 1 (R^1 = $N(CH_3)_2$; R^2 = Cl), 1214-79-5; 1 (R^1 = NH_2; R^2 = F), 64078-02-0; 1 (R^1 = NH_2; R^2 = Cl), 2609-46-3; 1 (R^1 = NH_2; R^2 = SCF_3), 70296-89-8; 1 (R^1 = CH_3O; R^2 = Cl), 1863-23-6; 1 (R^1 = SCH_3; R^2 = Cl), 1140-85-8; 1 (R^1 = H; R^2 = Cl), 1203-87-8; 1 (R^1 = OH; R^2 = Cl), 76599-74-1; 1 (R^1 = SH; R^2 = Cl), 1136-97-6; 1 (R^1 = Cl; R^2 = Cl), 76599-75-2.

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Oxidative Cleavage of 1,2-Diols with *N*-Iodosuccinimide

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As part of our continuing interest in the reactions of *N*-iodosuccinimide (NIS, **2**) with alcohols[1] we have found that 1,2-diols are easily cleaved with NIS. In organic synthesis the two major reagents presently used to cleave

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