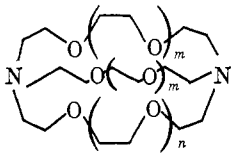
Table I. ^{13}C and ^{23}Na Nmr Spectral Data, Calculated Correlation Times, and ^{23}Na Quadrupolar Coupling Constants for Sodium Cryptates of Ligands **1**–**4**[a]

Cryptate	$T_1(^{13}C)$,[b] sec (±15%)	$\tau_c(^{13}C)$,[b] psec (±15%)	$\delta(^{23}Na)$,[c] ppm (±2%)	$\Delta\nu(^{23}Na)$,[c] Hz	$T_q(^{23}Na)$,[d] msec (±5%)	χ_{Na},[d] MHz (±10%)
[**1**,Na^+]Cl^-	1.05	21.5	+11.15	132 ± 3	2.4	2.20
[**2**,Na^+]Cl^-	1.25	18.0	−4.25	46 ± 2	6.9	1.43
[**3**,Na^+]Cl^-	1.00	22.5	−11.40	29 ± 1	11.0	1.01
[**4**,Na^+]Cl^-	1.10	20.5	−6.20	49 ± 2	6.5	1.38

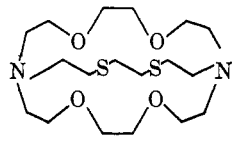
[a] See ref 26 for experimental details. [b] ^{13}C relaxation times T_1 and correlation times τ_c calculated according to eq 2. The values given are averages over all carbons in the molecules. The spread of T_1 values is about ±10%. In the case of τ_c an error of ±0.009 Å in r_{CH} leads to an error of ±5% in τ_c. τ_c is given in picoseconds; 1 psec = 10^{-12} sec. [c] δ, shift of ^{23}Na resonance downfield (<0) from 0.25 *M* NaCl in water (8 Hz line width). $\Delta\nu$, full line width at half-height of ^{23}Na resonance. A 0.25 *M* NaCl solution in methanol–water has δ −2.70 ppm and $\Delta\nu$ = 19.5 Hz. [d] ^{23}Na nuclear quadrupolar relaxation time, T_q, and coupling constant, $\chi_{Na} = (e^2qQ/h)$, calculated using eq 1 and $\tau_c(^{13}C)$ values. T_q is obtained from the full line width $\Delta\nu$; the inhomogeneity contribution to $\Delta\nu$ is probably less than 1–2 Hz leading to an error (over estimation) in χ_{Na} of about 3% or less.

culated from the Debye relation ($\tau_c \sim 110$ psec for a molecular radius of about 5 Å).

The *^{23}Na chemical shifts* show an interesting trend. Whereas oxygen containing organic solvents shift the ^{23}Na resonance downfield, amines give an upfield shift.[7,10] Indeed the ^{23}Na resonance is upfield from the reference when the ligand shell contains four oxygens and two nitrogens and shifts downfield as the number of oxygens increases from four to six. Sulfur sites lead to a small downfield shift (Table I).



1, $m = 0$; $n = 1$
2, $m = 1$; $n = 0$
3, $m = n = 1$



4

The *^{23}Na nuclear quadrupolar coupling constants* decrease when the number of oxygens in the ligand shell increases. The electric field symmetry increases as more and more oxygen sites are disposed around the cation. The replacement of two oxygens in **3** by sulfur in ligand **4** causes about the same increase in field gradient as the removal of one oxygen (in **2**). The present values of χ_{Na} (Table I) are by a factor of 2–3 higher than those which would be obtained by approximating τ_c with the Debye relation. A linear relation has been proposed[4b] between χ_{Na} and the paramagnetic shielding term which dominates[4,7] the ^{23}Na chemical shifts. Indeed the plot of χ_{Na} against δ(Na) (Table I) gives a straight line within experimental accuracy.

Finally, when excess NaCl is added to the cryptate solutions two separate ^{23}Na signals (free and complexed Na^+) are observed, showing that cation exchange is slow at 35°. In the case of [**3**, Na^+] coalescence occurs at about +58° giving a free energy of activation $\Delta G^{\ddagger}_{58}$ of about 15.4 kcal/mol in agreement with previous proton resonance work[27] and with a recent ^{23}Na nmr study of cation exchange rates in the same compound in ethylenediamine.[28] In [**1**,Na^+] and [**2**,Na^+] one still observes separate ^{23}Na resonances at +58° ($\Delta G^{\ddagger} > 16$ kcal/mol).[29]

Double probe ^{13}C, ^{23}Na nmr studies may provide detailed information on the electric effects produced by ligand structure, binding sites, ion pairing, and medium[15] as well as on molecular tumbling. Complexes of other metal cations may also be investigated (lithium and cesium for instance).[30]

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(29) The cation exchange rates in cryptates may be obtained most conveniently from variable temperature ^{13}C nmr spectra of 1/1 cryptate–ligand mixtures (forthcoming report).
(30) The use of nitrogen-14 as the quadrupolar nucleus allows similar studies to be performed on nitrogen-containing substances of chemical or biological interest.[24,25]
(31) ERA No. 265 from CNRS.

J. P. Kintzinger, J. M. Lehn*
Institut de Chimie, Université Louis Pasteur
67-Strasbourg, France[31]
Received October 25, 1973

A Linear Relationship between Substituted Pyridine Lone Pair Vertical Ionization Potentials and pK_a

Sir:

A recent communication[1] on the gas-phase proton affinities, PA, of five 4-substituted pyridines pointed out the importance of the question whether solution phase substituent constants apply in the gas phase.

PA's for a series of bases, B:, will be linear functions of vertical lone pair ionization potentials, IP, provided that the rehybridization energies of $B\cdot_v^+$ and homolytic $B{:}H^+$ bond dissociation energies are constant or are themselves linear functions of IP. If, in addition, the differences in solvation energies between bases, B:, and conjugate acids, BH^+, are linear functions of IP, a linear relationship should also exist between pK_a and B: lone pair IP. These restrictions preclude the observation of any simple relationship between IP(B:) and pK_a for dissimilar bases, and until now a satisfactory linear pK_a–IP(B:) relationship has not been demonstrated for Brønsted bases.

The photoelectron spectra of ten substituted pyridines have been measured and combined with reported spectra for seven chloropyridines,[2] methylpyridines,[3] and fluoropyridines[4] from the literature. Spectra were determined on a Perkin-Elmer Model 16 pe spectrometer and calibrated with argon (15.76 eV). To ensure valid

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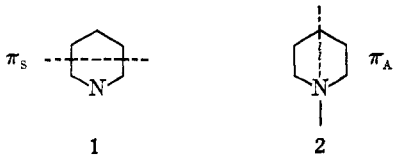
Table I. Substituted Pyridine Ionization Potentials[a]

Pyridine[b]	π_A[c] Exptl	π_A[c] Calcd	π_S[c] Exptl	π_S[c] Calcd	n[c] Exptl	n[c] Calcd
4-Me_2N	(9.3)	10.56	7.82	9.85	(9.1)	11.70
4-H_2N	9.57	10.66	8.77	10 27	(9.2)	11.84
4-MeO	>10.0	10.70	(9.7)	10.48	(9.3)	11.82
2,4,6-Me_3	(8.9 ± 0.1)	10.10	9.60	10.84	(9.2 ± 0.1)	11.49
3,5-Me_2	9.25	10.10	10.12	11.05	9.52	11.72
3,4-Me_2	9.15	10.28	9.83	10.88	9.43	11.65
4-Me[3]	9.60	10.65	10.05	10.97	9.50	11.80
2-Me	9.20	10.37	10.25	11.34	9.50	11.81
H[3]	9.75	10.68	10.50	11.41	9.60	11.97
2-Cl[2]	9.89	10.92	10.93	11.75	10.3	12.24
3-Cl[2]	9.5	10.90	10.48	11.71	9.85	12.21
4-C≡N	(10.7)	11.10	(11.2)	11.28	(10.3)	12.29
3-C≡N	10.37	10.75	11.12	11.74	10.17	12.24
3,5-Cl_2	9.88	11.11	10.43	11.92	10.26	12.44
4-Cl[2]	(10.4)	11.03	(10.6)	11.53	(10.0)	12.22
2-F[4]	9.70	10.81	10.83	11.79	10.37	12.37
3-F[4]	9.64	10.76	10.60	11.70	10.09	12.33

[a] Numbers in parentheses are obtained from overlapping bands. [b] Superscripts refer to references in text. [c] See text.

comparison between different measurements, the instrument was further calibrated with methyl iodide (9.54 eV) against argon.

In general only three ionization potentials below 11 eV were found in the pe spectra of the substituted pyridine molecules reported here. These must be assigned to the nitrogen "lone pair" n and to the two highest filled π orbitals, π_S and π_A, according to the *nodal* properties of the molecular orbitals as given by **1** and **2**.



1 2

The assignment of Heilbronner, *et al.*,[3] for the N lone pair ionization potentials of pyridine and methyl-substituted pyridines was adopted, *i.e.*, an n, π_3, π_2 sequence in pyridine. Modified CNDO/2[5] calculations were then carried out on all substituted pyridines, and the ionization potential assignments of n, π_A, and π_S were made on the basis of agreement with the calculated changes in ionization potential relative to pyridine and correlation consistency between molecules (Table I). A satisfactory linear relationship between calculated and assigned ionization potentials then results in which the n ionization potentials form a family of points well separated from the two π ionization potentials which are correlated by a single regression line.

The resultant IP assignments are further supported by the observation of a reasonably linear correlation between the pyridine π_S ionization potentials and Brown[6] σ^+ values (Figure 1), except for 4-$Me_2NC_5H_4N$. The CNDO/2 calculations, however, indicate that the first π_S ionization potential of 4-$Me_2NC_5H_4N$ correlates with the $Me_2\ddot{N}$– lone pair rather than the pyridine π-orbital. It is interesting to note that substituents at the 2 position (open circle) CH_3, F, and Cl are also reasonably well correlated by σ^+ para. The Hammett relationship obtained in Figure 1 is IP(eV) = $2.1\sigma^+$ + 19.4.

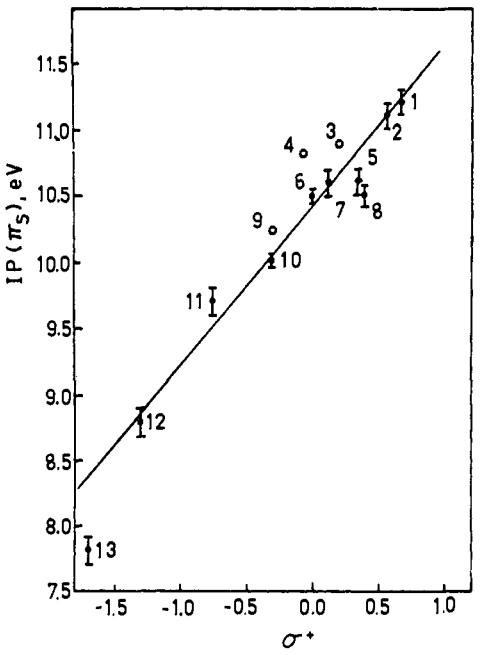


Figure 1. A plot of π_s vertical ionization potentials of substituted pyridines (see text) *vs.* σ^+ para for 2- and 4-substituents and σ^+ meta for 3-substituents. The 2-substituents are indicated by open circles: (1) 4-CN, (2) 3-CN, (3) 2-Cl, (4) 2-F, (5) 3-F, (6) H, (7) 4-Cl, (8) 3-Cl, (9) 2-CH_3, (10) 4-CH_3, (11) 4-CH_3O, (12) 4-NH_2, (13) 4-NMe_2.

We now wish to report that the lone pair vertical ionization potentials of 17 substituted pyridines as determined by pe spectroscopy show an astonishingly good linear correlation with values of reported[7] aqueous pK_a's, Figure 2, such that pK_a = −6.80IP(eV) + 70.7 with an average deviation of ±0.2 pK_a units.

If the regression line of Figure 2 is used to calculate ionization potentials of 4-NO_2- (10.2 eV) and 4-CF_3-C_5H_9N (10.05 eV), within experimental error, published[1]

(5) A CNDO/2 program was used, modified according to the method of H. Jaffe and J. Del Bene, *J. Chem. Phys.*, 48, 1807 (1968), and programmed by J. Kroner and W. Fuss, University of Munich, Munich, Germany; see also J. Kroner, D. Proch, W. Fuss, and H. Bock, *Tetrahedron*, 28, 1585 (1971).

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(7) (a) A. Fischer, W. J. Galloway, and J. Vaughn, *J. Chem. Soc.*, 3591 (1964); (b) A. Albert, *Phys. Methods Heterocycl. Chem.*, 4, 1 (1971); 1, 1 (1963); (c) J. M. Essery and K. Schofield, *J. Chem. Soc.*, 3939 (1961); (d) N. Ikebawa, Y. Sata, and T. Maeda, *Pharm. Bull.*, 2, 205 (1954); (e) H. H. Jaffe and H. L. Jones, *Advan. Heterocycl. Chem.*, 3, 224 (1964); (f) J. M. Essery and K. Schofield, *J. Chem. Soc.*, 3939 (1961).

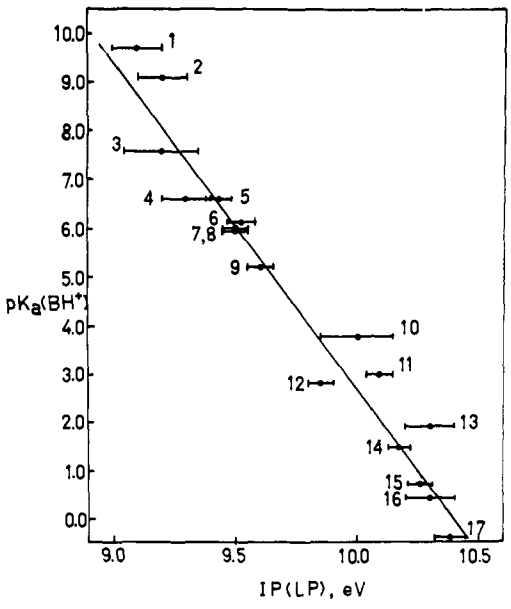

Figure 2. A plot of substituted pyridine pK_a's *vs.* nitrogen lone pair ionization potential: (1) 4-Me_2N, (2) 4-H_2N, (3) 2,4,6-Me_3, (4) 3,4-Me_2, (5) 4-MeO, (6) 3,5-Me_2, (7) 4-Me, (8) 2-Me, (9) H (pyridine), (10) 4-Cl, (11) 3F, (12) 3-Cl, (13) 4-CN, (14) 3-CN, (15) 3,5-Cl_2, (16) 2-Cl, (17) 2-F.

relative proton affinities for 4-NO_2-, 4-CF_3-, 4-H-, 4-CH_3-, and 4-$CH_3OC_5H_9N$ are found to be linear functions of lone pair ionization potentials; PA(R) − PA(H) = −0.3(kcal/eV)IP + 29 kcal.

These results support: (1) the conclusion that a separate order of gas phase and solution phase substituent effects for electron ionization, gas phase proton affinities, and solution phase pK_a's of substituted pyridines is unnecessary, (2) the Heilbronner assignment[8] n, π, π for the pyridine pe IP's, and (3) the proposal that substituent effects on differences in heats of solvation $\delta(\Delta H_5(B:) - \Delta H_5(BH^+))$ of closely related bases and conjugate acids may be linear functions of gas phase proton affinities or lone pair ionization potentials.

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Brian G. Ramsey,* F. Ann Walker
Department of Chemistry, California State University San Francisco, California 94132
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Geldanamycin Biosynthesis and Carbon Magnetic Resonance[1,2]

Sir:

The ansamycin antibiotics—rifamycin, streptovaricin, tolypomycin, geldanamycin, and their derivatives—are of considerable current interest, both for their novel structures and for their biological properties, which include potent inhibition of RNA-dependent DNA polymerase (reverse transcriptase).[3] Biosynthetic results on two of the naphthoquinonoid ansamycins—streptovaricin[2,4] and rifamycin[5]—have recently been reported. We report here our biosynthetic results on geldanamycin,[6] the only benzoquinone representative among the ansamycins, and show that this antibiotic, although structurally different, follows the same biosynthetic pathways as streptovaricin[2,4] and rifamycin.[5]

A number of ^{14}C-labeled precursors (Table I) were fed to fermentation cultures (0.5–1.0 l.) of *Streptomyces hygroscopicus* var. *geldanus* var. *nova* 2 days after inoculation; after a total of 4–5 days' growth the geldanamycin produced was isolated by minor modification of the procedure described earlier.[7] The results in Table I, showing that [methyl-^{14}C]methionine and [carboxy-^{14}C]propionate are incorporated very well, acetate and malonate less well, and formate very little, suggest a biosynthetic pathway like that of streptovaricin and rifamycin, with the *ansa* chain being formed from propionate and acetate; methionine should label the three *O*-methyl groups. Treatment of methionine-labeled geldanamycin (**1**, 3.74 μCi/mmol) with barium hydroxide in water and tetrahydrofuran gave des-*O*-methylgeldanamycin (**2**, 2.52 μCi/mmol), indicating that one-third of the label resided in the 17A-methoxyl carbon.

To identify the other carbons labeled by methionine and propionate, we have employed carbon-13 magnetic resonance (cmr) spectroscopy. Geldanamycin's cmr absorptions were assigned[8] by off-resonance decoupling experiments, standard chemical shift correlations,[9] specific proton decoupling, and comparison to chemical shifts in the cmr spectra of geldanamycin derivatives[6] and model compounds.[8-11]

Experiments with [methyl-^{13}C]methionine and [carboxy-^{13}C]propionate followed the procedures employed with ^{14}C-labeled compounds (above); results are shown in Table I. ^{13}C-Labeled geldanamycin was analyzed mass spectrometrically (flat topped peaks). That from methionine was 81% unlabeled, 10% mono-, 5% di-, and 4% trilabeled, or an average of 11% labeled at

(1) Presented in part at the 166th National Meeting of the American Chemical Society, Chicago, Ill., Aug 1973, ORGN 124.

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