have essentially the same slope is evidence that *we are primarily observing a ring current effect which is a function of the HOMO–LUMO energy gap.* The phenyl and naphthyl groups in **2d, 2h, 2i,** and **2k** lower the LUMO relative to the parent anion (**2a**) due to their higher density of π energy levels. These results, when coupled with the uv spectral data (which give an independent measure of the trend in the HOMO–LUMO energy difference), give strong support to the theoretical interpretation of paramagnetic ring currents.[1]

Finally, it is interesting to note that the chemical shifts of H_1 and H_9 in **2b–f** do not correlate as well with σ_p as do those of the other protons. This can be explained by a greater degree of coplanarity of the 9-aryl ring with the eight-membered ring in the case of donor substituents due to greater π-electron delocalization.[12] The chemical shifts of H_1 in **2i** and **2k** (relative to **2d**) also suggest a twisting of the 9-aryl ring, probably for steric reasons. Interestingly, the signals for H_2–H_7 in **2i** (R′ = 1-naphthyl) are shifted *downfield* from the corresponding signals in **2d** (R′ = phenyl) and **2h** (R′ = 2-naphthyl), even though the calculated HOMO–LUMO energy gap in planar **2i** is smaller than those in the latter anions. This is best explained by a greater degree of twisting of the 1-naphthyl group compared to the phenyl and 2-naphthyl groups.[13]

Acknowledgment. We thank the National Science Foundation for support of this work and for a grant (GP 43155) used for the purchase of a 100-MHz NMR spectrometer.

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Nitrogen to Nitrogen Proton Transfer. The Significance of Large Negative Entropies of Activation

Sir:

The activation entropies for transfer of a proton from H_3O^+ to H_2O and from H_2O to ^-OH are −5.8 eu and −0.1 eu, respectively.[1] These values are among the few available for fast proton transfers in protic solvents.[2–4] Corresponding data for

Table I. Rate Constants at 25° and Activation Parameters for Catalyzed Proton Transfer of N,N-Dimethylaminocyclohexylamine Hydrochloride in Chloroform

| Catalyst	$pK_a{}^a$	$10^{-2}k_2$, $M^{-1} s^{-1}$	ΔH^*, kcal/mol	ΔS^*, eu^b
2,4-Lutidine	6.72	700	2.6	−28
4-Picoline	6.02	110	3.2	−29
Pyridine	5.21	13	3.9	−31
2,6-Di-*tert*-butylpyridine	4.91	8.7	3.4	−34
Aniline	4.63	4.3	3.9	−33
Dimethylaminoaceto-nitrile	4.20	1.7	5.2	−31
2-Methoxypyridine	3.28	0.11	5.5	−36
3-Bromopyridine	2.85	0.030	5.0	−40

^{a} In water. ^{b} Calculated from k_2 values at 25° with an uncertainty of ±2.5 eu.

the reactions in aprotic solvents are found even more infrequently.[5,6] We have measured ΔS^* for proton transfer from an aliphatic amine salt to several substituted pyridines in chloroform (eq 1). By using an amine salt/amine system we
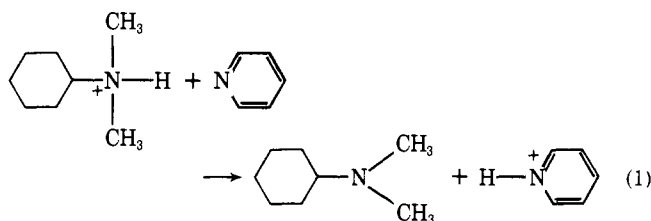
hoped to detect subtle orientation or solvation effects which are unobservable in reactions where charge production or destruction dominates ΔS^*.[7] Unexpectedly, an effect was uncovered which can hardly be called subtle: ΔS^* for eq 1 in chloroform equals −28 to −40 eu depending on the substituents on the pyridine ring (Table I). Such large negative entropies fall in the same range as those for bimolecular reactions which create charge (e.g., ΔS^* = −35 eu for formation of N-methylpyridinium iodide from pyridine and methyl iodide in chloroform[8]). The present communication is devoted to explaining the magnitude of the ΔS^* for eq 1.

Most of our runs were carried out with 0.10 M N,N-dimethylcyclohexylamine hydrochloride (I) using a tenfold concentration range of basic catalyst. Observed rate constants were deduced from the slow-passage NMR signal of the N-methyl protons[9,10] which changed from a doublet to a singlet as the catalyst concentration and temperature were raised. If the hydrochloride salt was not free from traces of unprotonated amine, the N-methyl signal gave a singlet even in the absence of added catalyst. Second-order rate constants, calculated from the slopes of linear plots of k_{obsd} vs. [catalyst], are listed in Table I. These k_2's represent proton abstraction by the catalysts against a severe pK_a gradient and were used to obtain the activation entropies. Three different concentrations of I (0.31 M, 0.11 M, and 0.057 M) treated with the same amount of pyridine (4.9 × 10^{-3} M) all yielded the same k_2 (1360 ± 120 $M^{-1} s^{-1}$ at 25°). The poor solubility of I in many aprotic solvents prompted the choice of chloroform for this study. Chloroform was not the ideal solvent because it contained 0.8% ethanol as a preservative, and removal of the ethanol led to immediate solvent decomposition and erratic kinetics. However, ethanol did not appear to be a serious problem because 8.9% ethanol purposely added to the chloroform changed ΔS^* only slightly (3 eu). Moreover, when 1% ethanol was added to a system containing highly purified methylene chloride as the solvent, the kinetics were not perturbed. Spectra were traced in the internal lock mode after temperature equilibration of the sample for 20 min in a Jeol-JNM-MH-100 spectrometer
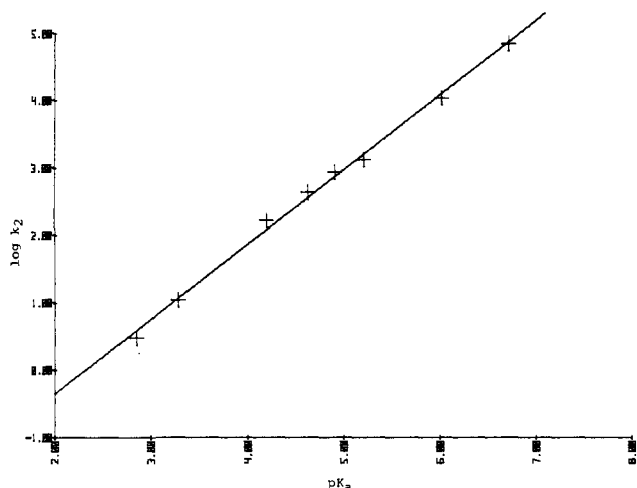
Figure 1. Brönsted plot of log k_2 vs. pK_a for the base-catalyzed proton exchange of N,N-dimethylcyclohexylamine hydrochloride in chloroform at 25°. Rate constants are in $M^{-1} s^{-1}$ and pK_a values are taken from Table 1.

set at an rf field of 0.1 mG, sweep width of 54 Hz, sweep time of 250 s, and filter band width of 20 Hz. An uncertainty of 2.5 eu in our ΔS^* values reflects a 10-15% error in rate constants obtained over a 40-45° temperature interval.

The rate constants in Table I cover a range of 2×10^4 and correlate closely with the basicity of the catalysts. A Brönsted plot, with a slope $\beta = 1.1$ (Figure 1), points to a well-formed catalyst/proton bond in the transition state. Since this Brönsted plot utilizes aqueous pK_a values (not pK_a's in chloroform), the value of β is meaningful only under the assumption that the pK_a shift from water to chloroform is constant for all pyridine bases. However, a $\rho = -6.4$ for a Hammett plot based on 3- and 4-substituted pyridines (not shown) confirms that proton transfer in eq 1 is virtually complete in the transition state.[6] In the light of a nearly identical charge content of the ground state and transition state, how can the large negative ΔS^* values be explained? One possibility is that the solvation requirements for protonated aliphatic amine and protonated pyridine differ substantially despite their identical charges. The validity of this rationale is demonstrated from the ΔS^* values for the substituted pyridines (Table I) which gravitate from -28 to -40 eu as the basicity of the catalysts decreases. The poorer the base, the greater the solvation needs of the corresponding conjugate acid, and the more negative the ΔS^*. We add parenthetically that the marked dependence of ΔS^* on the nature of the positive charge demands great caution when using ΔS^* as a criterion for the creation of charge.

Solvation differences between the reactant and product cations did not seem to be the sole explanation for the large negative entropies because ΔS^* approximates -30 eu even for the more basic catalysts. We therefore investigated whether or not the *anion* of I might also influence the proton transfer. The relative rate of pyridine-catalyzed proton exchange of I in chloroform increases from 1.0 to 7.6 to 52 as the counterion of I is changed from chloride to bromide to benzenesulfonate. Corresponding entropies are -31, -23, and -20 eu. These results can be best explained by an ion-pair dissociation (eq 2)[11] which precedes the rate-determining proton abstraction and which of course contributes to the observed ΔS^*.

$$R_3NH^+Cl^- \rightleftarrows Cl^- + R_3NH^+ \xrightarrow{C_6H_5N} R_3N + C_6H_5NH^+$$

$$(2)$$
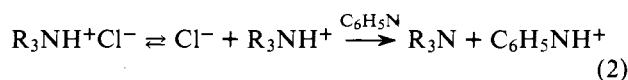
Since disengaging X^- from an ion-pair immobilizes solvent according to the charge density on X^-, the chloride salt would be expected to have the most negative ΔS^*. Equation 2 is also

consistent with another observation, namely that ΔS^* for the pyridine-catalyzed proton exchange of I (chloride salt) in pure ethanol is only -18 eu. Dissociation of an anion from a "loose" ion-pair within a protic solvent demands less *additional* solvent stabilization of the anion. In summary, the exceptionally negative entropy of activation of eq 1 stems from several factors: the bimolecularity of the reaction; solvation differences between the donor and acceptor amines; freezing of solvent around the anion following ion-pair dissociation.

Interestingly, the severely hindered base 2,6-di-*tert*-butyl-pyridine displays normal reactivity (its k_2 lies on the Brönsted line, not below it).[12] No doubt steric interactions between two bulky amines sharing a proton are reduced by the late transition state for eq 1. Freedom of k_2 and ΔS^* from steric effects also suggests that the two nitrogens and the proton in eq 1 prefer a rather inflexible linear orientation in the transition state.[13,14]

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(15) Recipient of a Camille and Henry Dreyfus Foundation Teacher–Scholar Grant and a National Institutes of Health Research Career Development Award.

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Nybomycin. 8. Biosynthetic Origin of the Central Ring Carbons Studied by ^{13}C-Labeled Substrates[1,2]

Sir:

The antibiotic nybomycin (**1**) possesses two structural features of biosynthetic interest, a fused pyridoquinolone ring system and an angularly fused oxazoline ring. Both features have not been reported elsewhere in nature except for the naturally occurring deoxynybomycin (**2**).[3] We recently established by use of ^{14}C- and ^{13}C-labeled precursors that the single-carbon units C-11' and C-2 (N-CH$_3$ and N-CH$_2$-O, respectively) are derived from methionine, while the exterior carbons of the pyridone rings (C-4 to C-6, C-6', C-8 to C-10, C-8') arise from acetate.[4] The ^{13}C-labeled acetate feeding also showed that the central ring carbons are not derived from this source and, thus, eliminated the possibility of the aromatic system's arising from a phloroglucinol-type pathway.[5] We now present evidence which supports the intermediacy of a shiki-