reflecting the additional entropic cost of bringing two particles together[18] and demonstrating that any intramolecular kinetic advantage resides in $\Delta S^{\ddagger}$.

The present results provide a fairly detailed thermodynamic/kinetic picture of the reaction coordinate for eq 4. As found by Jones and Feher, the intramolecularly metalated product is thermodynamically more stable than the corresponding intermolecular product under the reaction conditions—for eq 4 because $T\Delta S > \Delta H > 0$. In addition, this study quantitates the change in entropy on releasing an alkyl silane from (or conversely for incorporating an alkyl silane into) a metal complex. This change in entropy, although smaller[19] than predicted by simple physical models, is sufficient to drive the cyclometalation reaction and to overcome the ring strain in the product. As is the case for chelate ring formation,[20] the change in entropy upon cyclometalation is likely a complex composite of a number of factors.

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(19) Had we chosen neat alkyl silane as the standard state, ΔS would have been even smaller ($\Delta S_{neat} = \Delta S_{1M} - R \ln (C_{neat}/C_{1M}) = \Delta S_{1M} - 4.0$ eu, where C_{neat} and C_{1M} are concentrations).[12b]

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"Diffusion-Controlled" Unimolecular Reactions and the Lifetime of a Strong Acid in Water

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There is considerable uncertainty about the rate constant for a "diffusion-controlled" unimolecular reaction. For a bimolecular reaction the encounter rate can be calculated[1] in good agreement with experimental values.[2] When one of the reactants is the solvent, it does not need to diffuse to the other reactant, since it is already there. Consequently the reaction becomes formally first order. Several models have been proposed to treat this situation. In the most widely accepted, the reaction rate is considered to be limited by translational diffusion of two products, A and B, from each other. The rate constant is given[3] by eq 1, where D

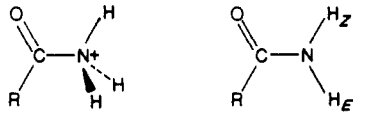
$$k = 4\pi Dr/V \qquad (1)$$

is the sum of the diffusion constants of A and B, r is the sum of their radii, and V is the volume of a spherical shell on the surface of one of the reactants. This leads to $k = 10^{10}$ or 10^{11} s^{-1},[4] but the value is too sensitive to the values assumed for r and V. An alternative model[5] considers the rate to be limited by a rotational reorientation. From dielectric relaxation of the solvent the rate constant can then be estimated as 10^8–10^{12} s^{-1}. The simplest model[6] is to multiply the second-order encounter rate constant by the concentration of solvent or by an estimated "effective molarity" of solvent. This gives estimates for k ranging from 10^{10} to 10^{12} s^{-1}. Experimental values for proton-transfer reactions of $HClO_4$,[7] H_3O^+,[8] OH^-,[8] and electronically excited 1-naphthol[9] with solvent H_2O are 4.35×10^{13}, 6×10^{11}, 1.6×10^{11}, and 2.1×10^{10} s^{-1}, respectively. The first value is unreliable,[10] since hydrogen-bond formation ("nonreactive" motion along the reaction coordinate) also broadens Raman lines, and the latter cases do not involve strongly exergonic proton transfers, required[2] for diffusion control. We now report that the rate constant for deprotonation of the strong acid $RCONH_3^+$ is 6×10^{10} s^{-1}.

This first-order rate constant is $2k_d$, obtainable from the kinetics of acid-catalyzed proton exchange in primary amides (eq 2). (The

$$RCONH_2 + H_3O^+ \underset{2k_d}{\overset{k_p}{\rightleftharpoons}} RCONH_3^+ + H_2O \qquad (2)$$

factor of 2 arises because there are two acidic protons in the preferred conformer, **1**, of the intermediate.) It is essential to use



1 **2**

a primary amide, **2**, with protons H_E and H_Z whose rates of exchange, k_E and k_Z, can be measured separately.[11] From Scheme I (eq 3, 4, and 7) of ref 11 it follows that $k_p[H_3O^+] = 2k_E - {}^1/_2k_Z$. For acrylamide (**2**, R = CH_2=CH) at pH 1.9, $k_E = 49$ s^{-1} and $k_Z = 33$ s^{-1}, so $k_p = 6.5 \times 10^3$ M^{-1} s^{-1}. If K_a ($=2k_d/k_p$), the acidity constant of $RCONH_3^+$, were known, it would then be possible to evaluate k_d. From the thermodynamics of hydrolysis of acyltrialkylammonium ions, pK_a has been estimated[12] as −7.6, and this leads[13] to $k_d \sim 10^{11}$ s^{-1}. However, this estimate has been criticized[14] for neglecting solvation effects on $RCONH_3^+$, and a pK_a of −1.8 (for methacrylamide) was proposed instead, corresponding to $k_d \sim 10^5$ s^{-1}. This is not obviously wrong, since proton transfer is often retarded[13] when it is accompanied by electronic reorganization.

We have sought a more direct determination of $2k_d$. Fortunately this is possible because deprotonation of **1** competes[11] with rotation about its C–N single bond, and $2k_r$, the rate constant of this latter process, can be estimated independently. From Scheme I (eq 3, 4, and 7) of ref 11 it follows that $k_E/k_Z = 1 + k_d/2k_r$, so $k_d/k_r = 0.97$ for acrylamide.

For many years k_r was also uncertain. Rotation was assumed[11] to be fast, by analogy to methyl rotors on a double bond, where the rotational barrier is 1–2 kcal/mol,[15] varying only slightly with substitution. The barrier is **1** itself is unknown, but two MO calculations[16] on $HCONH_3^+$ (**1**, R = H) give barriers of 1.3 and 1.08 kcal/mol. This latter is quite close[16b] to the value of 1.14 kcal/mol calculated for $HCOCH_3$ with the same STO-3G basis. Therefore we might expect the barrier in **1** (R = CH_2=CH) to be 1.2 kcal/mol, as in the isoelectronic ketone.[17] However, this estimate neglects solvation, and it is quite possible that solvation and hydrogen bonding greatly retard the rotation.[18] Nevertheless, the rotational correlation time of aqueous NH_4^+ was recently

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determined[19] to be 1.1×10^{-12} s at 21 °C. This is a measure of the time required for rotation of NH_4^+ by 34° about any axis, within its solvent cage. This time is so short as to signify that solvation and hydrogen bonding hardly retard the rotation. If we convert[20] this value to that for rotation of a tetrahedral NH_3^+ group by 60° about only one axis, subject to an additional barrier of 1.2 kcal/mol, we can calculate that $k_r = 3.0 \times 10^{10}$ s^{-1}. Therefore $2k_d = 6 \times 10^{10}$ s^{-1}.

This value represents quite a fast reaction. It is much too high to be consistent with the suggested pK_a of −1.8. Therefore we reject the conclusion[14] that proton-exchange kinetics support N-protonation of amides. However, the experimental rate constant is distinctly lower than some quite reasonable estimates and slower than two isoenergetic proton transfers.[8] It may be that the necessity for electronic reorganization has reduced the rate slightly. Indeed, an intrinsic barrier[21] $\Delta G_0^{\ddagger}$ of 6 kcal/mol would be sufficient to reduce the rate constant from kT/h to the 6×10^{10} s^{-1} observed.

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Activation of the 2-Alkyl Group of a 2-Alkylindole toward Proton Loss and Subsequent Electrophilic Substitution[1]

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A basic tenant of heterocyclic chemistry[2] is that pyridine-like[3] nitrogen atoms cause the activation of ring C-methyl groups toward proton loss. In its simplest examples, 2- and 4-methylpyridine undergo a range of useful reactions which are initiated by this process. Even β-alkyl group such as those in 3-methylpyridine and 3-methylquinoline can be lithiated by lithium diisopropylamide.[4] Similar reactions are well-known and much employed in the chemistry of azines (six-membered rings with two or more nitrogen atoms) and in generalized azoles (five-membered rings containing two or more heteroatoms).

However, such activation is not caused by a pyrrole-like[5] nitrogen atom, and proton loss from C-methyl groups in pyrroles and indoles is difficult.[6] Although the generation of a γ-lithio enamine or a β-aminoallyl carbanion[7] could be anticipated, only one literature reference has been found for such a reaction of a methylpyrrole or -indole.[8] No report has not been found for the formation of a γ-lithio enamine or β-aminoallyl carbanion from a precursor with an N–H moiety. Indeed, our own effort to generate dilithiated species, such as *N*-lithium 2-(lithiomethyl)-indole failed.[9]

We now report that the 2-alkyl groups of N-unsubstituted 2-alkylindoles can be activated toward proton loss by using carbon dioxide both to protect the N–H position and to enable lithiation at the methyl group. Subsequent reaction with an electrophile affords the corresponding 2-(substituted alkyl)indole-1-carboxylic acid, and loss of CO_2 then occurs to reform the NH group. The whole sequence can be carried out in a one-pot procedure, which comprises the following individual operations:

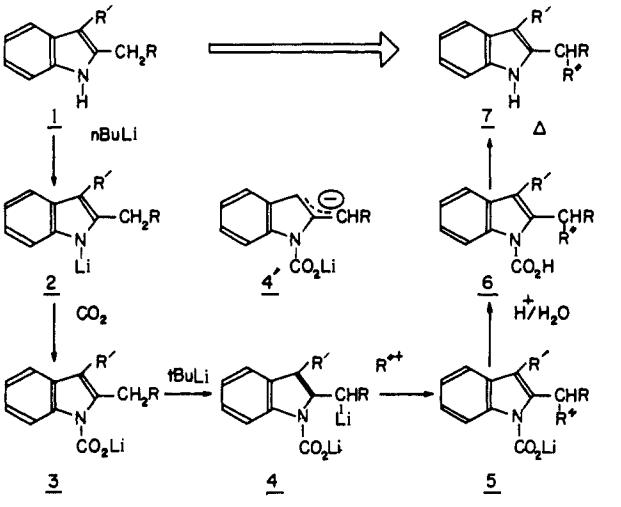
(i) Protection. The 2-alkylindole (**1**) was converted into the corresponding lithium carbamate (**3**) by reaction with *n*-butyllithium in tetrahydrofuran (**1** → **2**), followed by quenching with carbon dioxide (**2** → **3**).

(ii) Lithiation. Lithiation of this lithium carbamate (**3**) was accomplished by the addition of 1.1 equiv of *tert*-butyllithium in tetrahydrofuran at −20 °C for 45 min to give **4**.

(iii) Carbon–Carbon Bond Formation. Intermediate **4** was converted to **5** by adding 1.0 equiv of the electrophile at −70 °C for 2 h.

(iv) Deprotection. Aqueous 2 N sulfuric acid was slowly added to the mixture at −70 °C (**5** → **6**) to give the 1-indolecarboxylic acid (**6**). The isolated acid (**6**) could be decarboxylated under a variety of conditions, e.g., at 100 °C in acid condition. However, we found that brief thermolysis (up to 210 °C for 1 min) was a convenient and high-yielding procedure.

(v) Workup. The crude **7** was chromatographed on silica gel (*n*-hexane) to give the product in high yield.



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