respectively. Experimental points for γ_1 are shown (except those at 119 °C, for which a separate curve would be needed). It is a numerical accident that the two standard states for $\gamma_\pm$ yield results so nearly the same as to be indistinguishable on Figure 4. The meaning of these results is discussed in the next section.

Discussion

Most apparent in Figures 4 and 5 is the large electrostatic effect for $\gamma_\pm$ as compared to the small effect for γ_1 in the region of dilute aqueous solution. Thus, without the guidance from Debye–Hückel theory, one would not obtain even approximately correct curves for the activity of the salt on the infinitely dilute standard state. However, on the fused salt standard state, where $\gamma_\pm = 1$ at $x_2 = 1$, the major portion of the curve for $\gamma_\pm$ is reasonably well defined by the experiments on water activity with the simple equations of the nonelectrolyte type.

The postulate mentioned above, that the departure from random distribution of ions is roughly constant from concentrated solutions through to the pure fused salt, is supported by the relative constancy of $\gamma_\pm^{el}$ over that range of composition. There is, of course, some ambiguity in the separation of the electrostatic effect; hence, this postulate cannot be proven exactly from data such as these.

It is interesting to compare volumetric data[20] with the ratio (b_1/b_2) from the activity equations. For $(Li,K)NO_3$–H_2O the ratio of molar volume of water to the average volume per ion is 0.87. The more exact equation with the Debye–Hückel term was fitted with $(b_1/b_2) = 1.0$, whereas the more approximate equation fitted rather well with either 1.2 or 1.0 for this ratio. For the system $(Ag,Tl)NO_3$–H_2O, the experimental volume ratio is 0.82 while the (b_1/b_2) values are 0.56 from eq 18 or 0.50 from eq 1. While the (b_1/b_2) ratios are in the general vicinity of the volume ratios in each case, they depart in opposite directions in the two examples. Thus other factors in addition to molecular volumes affect the (b_1/b_2) value for these systems as is the case for intermetallic solutions and to some extent even for organic molecular solutions.

Further study, both theoretical and experimental, of these fused salt–molecular liquid systems will be interesting.

Acknowledgment. This work was supported by the Division of Chemical Sciences, Office of Basic Energy Sciences, U.S. Department of Energy, under Contract No. W-7405-Eng-48.

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Rates of Proton Transfer between Pyridine Bases in the Gas Phase. Steric and Isotope Effects

Joseph M. Jasinski[1a] **and John I. Brauman***[1b]

Contribution from the Department of Chemistry, Stanford University, Stanford, California 94305. Received June 26, 1979

Abstract: The rates of proton and deuteron transfer between various pyridine bases have been studied in the gas phase by pulsed ion cyclotron resonance spectroscopy. The results show that as the reactants become increasingly substituted in the 2 and 6 positions the reaction efficiencies decrease. Some of the least efficient reactions show a small normal kinetic deuterium isotope effect. These results are interpreted in terms of a general mechanism which includes an intrinsic barrier to proton transfer. The reaction efficiencies and isotope effects are modeled using RRKM theory, and an estimate for the intrinsic barrier height is obtained.

Introduction

Proton transfer is one of the most fundamental and ubiquitous of chemical reactions. It is, therefore, not surprising that it has long been an important area of study, and a great deal of progress has been made in understanding both the thermodynamic and kinetic aspects of the reaction.[2] An increasingly important goal has been to understand the intrinsic (solvent-free) properties of the reaction as well as those properties which are primarily due to the nature of the solvent. A major thermodynamic breakthrough in this regard came with the advent of a variety of methods for studying gas-phase ion–molecule reactions. The quantitative study of acid–base equilibria in the gas phase[3] has resulted in the compilation of extensive tables[4] of intrinsic acidities and basicities. Comparison of these results with solution data has led to a much clearer understanding of substituent effects on the acidity and basicity of many major classes of compounds, as well as providing a means for quantifying solvation effects.[5] In principle, gas-phase ion–molecule kinetic studies should be of comparable value in helping to probe the nature of the potential surface for proton transfer in the absence of complications

0002-7863/80/1502-2906$01.00/0

arising from solvent effects. A major drawback to realizing this goal is that most exothermic proton transfers are extremely rapid in the gas phase, often proceeding at or near the ion-molecule collision rate.[6] As a result, the mechanistic details of any reaction steps subsequent to the ion-molecule collision are frequently obscured. Thus, there have as yet been few gas-phase kinetic studies designed to probe these details.

There are a number of gas-phase proton transfers which are inefficient. In particular, reactions involving delocalized negative ions have been found to be slow in the gas phase,[7,8] just as they are in solution.[9] In an attempt to understand why these reactions are slow in the gas phase, Farneth[8] proposed a mechanism

$$\mathrm{AH} + \mathrm{B} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \mathrm{AH{\cdots}B} \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \mathrm{A{\cdots}HB} \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} \mathrm{A} + \mathrm{HB} \qquad (1)$$

which has the same general features as the mechanism first proposed by Eigen[10] as a model for proton-transfer reactions in solution. Charges have not been shown in eq 1 for simplicity and generality. This mechanism corresponds to the reaction profile illustrated in Figure 1. An argument employing statistical unimolecular rate theory was used by Farneth[8] to show that, even though E_0' (see Figure 1) is below the energy of either the reactants or products, it can still have a marked effect on the reaction rate, primarily for entropic reasons, with the effect becoming more important as $\Delta E = E_0' - E_0$ becomes less negative. This mechanism provided an explanation for all of the trends observed in the study of proton transfers between delocalized negative ions and also explained why most other gas-phase proton transfers are very efficient. If such an interpretation is correct, it suggests that there is a strong tie between the dynamics of proton transfer in solution and the gas phase. It also suggests that a key to probing the nature of the potential surface in the gas phase is to find a means by which the barrier E_0' can be varied relative to E_0.

In the present paper we report studies directed toward this goal. We have determined the rates of proton and deuteron transfer and the magnitude of the kinetic deuterium isotope effect for various pyridine-pyridinium ion reactant pairs using pulsed ion cyclotron resonance spectroscopy.[11] Our objectives in studying these systems were to explore the possibility of exerting some control over ΔE by means of steric interactions and to probe the reaction mechanism by means of kinetic deuterium isotope effects. Our choice of alkyl-substituted pyridines as bases and pyridinium ions as acids was based on several considerations. The rigid geometry of the pyridine ring is well suited to manipulating steric interactions around the nitrogen by use of 2 and 6 alkyl substituents, as demonstrated by a number of solution-phase studies.[12] The gas-phase basicities of most of the pyridines used in this study have been determined,[5b,13] thus allowing us some quantitative control over reaction exothermicities. Finally, several solution-phase studies have found large kinetic isotope effects.

The solution studies which are most relevant to our choice of pyridine bases involve kinetic studies of proton and deuteron abstraction from carbon acids by pyridine and 2,6-dialkylpyridines.[14] Lewis and co-workers found that alkyl substitution α to the pyridine nitrogen greatly retarded the reaction rate with 2-nitropropane relative to the rate for pyridine itself[14d] and also led to large isotope effects.[14e-g] They reported k_H/k_D in excess of 20 with 2,6-dimethylpyridine and 2,4,6-trimethylpyridine as bases.[14f] Both the rate retardation and the anomalously large isotope effect have been interpreted in terms of steric interactions in the proton-transfer transition state, with the large isotope effect being attributed to proton tunneling. Recent work has questioned this interpretation of the isotope effect.[15] Regardless of whether or not the interpretation of these data is entirely correct, such studies strongly suggested that sterically hindered pyridines might be good bases for our studies. Pyridinium ions were used as acids for experimental convenience, in order to keep the reactions from becoming too exothermic, and because of the added option of hindering the acid as well as the base.

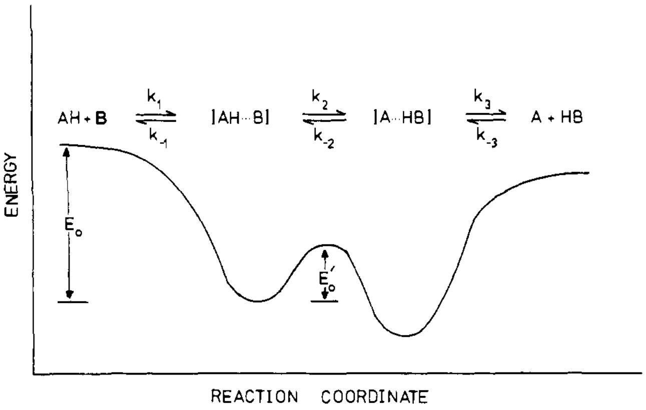


Figure 1. Energy diagram for proton transfer.

While both steric effects[16] and kinetic isotope effects[2,17] have been well developed as probes of reaction mechanism in solution, neither effect has been used extensively in gas-phase ion-molecule studies. Results by Bursey on gas-phase acetylation of phenols[18] and pyridines[19] have been interpreted in terms of steric inhibition as the size of alkyl groups α to the reaction center increases. Possible steric effects have also been reported in S_N2 reactions in the gas phase.[20] Deuterium isotope effects have received some attention in gas-phase ion-molecule studies.[21] However, with the exception of a preliminary study by Riveros,[21f] no purely kinetic isotope effect for a simple exothermic acid-base type proton-transfer reaction has yet been reported and analyzed in the ion-molecule literature.

Our results show that the proton transfers we have studied do indeed become less efficient as the reactants become increasingly hindered with alkyl substituents. As discussed below, however, a complete explanation of this trend requires consideration of several effects in addition to steric interactions. We have also observed a small normal kinetic deuterium isotope effect for some of the slower reactions. These results are interpreted in terms of the energy diagram in Figure 1, and a semiquantitative estimate of ΔE is obtained by the application of RRKM theory to model the observed efficiencies and isotope effects.

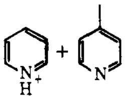
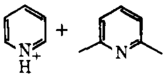
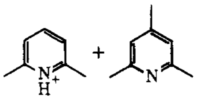
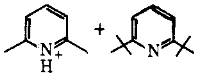
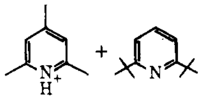
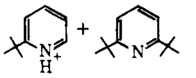
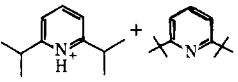
Experimental Section

Instrumentation. All experiments were performed on a pulsed ion cyclotron resonance spectrometer using a trapped ion analyzer cell.[11] The marginal oscillator frequency employed for all of the kinetic studies was 153 kHz. Lower frequencies were used to observe some of the heavier ions during double-resonance studies. The signal from the marginal oscillator was integrated with a boxcar integrator (PAR Model cw-1 or 162). Total pressures were in the 10^{-6}-10^{-5} Torr range and were measured with a Varian Model UHV-24 ionization gauge which was calibrated in the 10^{-5} Torr range against an MKS Baratron capacitance manometer for each neutral reactant gas.

Materials. Pyridine was Mallinckrodt analytical reagent grade; 4-methylpyridine (98%), 2,6-dimethylpyridine (96%), and 2,4,6-trimethylpyridine were obtained from Aldrich; 2-*tert*-butylpyridine (99%), 2,6-diisopropylpyridine (98%), and 2,6-di-*tert*-butylpyridine (99%) were obtained from Chemical Samples Co. All pyridines were vacuum distilled from BaO directly into the ICR foreline following degassing by several freeze-pump-thaw cycles. Methane-d_4 and ammonia-d_3, used as chemical ionization reagents, were obtained from Merck Sharpe and Dohme of Canada.

Generation of Ions. All primary ions were generated by electron impact of 18-20-eV electrons on the neutral gases. The protonated pyridinium ions were generated from the parent and fragment ions by proton and/or hydrogen atom transfer reactions. The deuterated

Table I

reaction	rate constant $k_H \times 10^{10}$ cm^3 molecule^{-1} s^{-1}	reaction efficiency[b]	$-\Delta G°$, kcal mol^{-1}	k_H/k_D
I 	6.7 ± 0.6^a	0.35	4.0^c	1.1 ± 0.1^a
II 	6.0 ± 0.6	0.35	6.8^c	1.0 ± 0.1
III 	3.3 ± 0.3	0.21	$<5.2^d$	1.1 ± 0.1
IV 	3.4 ± 0.2	0.20	5.2^c	1.2 ± 0.04
V 	1.7 ± 0.3	0.10	$<5.2^d$	1.4 ± 0.3
VI 	0.76 ± 0.1	0.05	5^e	1.8 ± 0.2
VII 	$<1 \times 10^{-11}$	<0.01		

[a] 95% confidence limits. [b] Efficiency = k_f/k_{ADO}. Values of k_{ADO} were calculated as described in ref 25. Polarizabilities for the pyridines were calculated from average parallel and perpendicular bond polarizabilities as described in Hirschfelder, J. O.; Curtis, C. F.; Bird, R. B. "Molecular Theory of Gases and Liquids"; Wiley: New York, 1954; p 947 ff. Dipole moments are from Nouwen, R.; Huyskens, P. *Ann. Soc. Sci. Bruxelles, Ser. 1* **1973,** *87,* 111. The dipole moment of 2,6-di-*tert*-butylpyridine was taken to be the same as that of 2,6-dimethylpyridine. [c] From ref 5b and references cited therein. [d] Gas-phase basicity of 2,4,6-trimethylpyridine unknown. [e] Estimated value from ref 13c.

pyridinium ions were generated by chemical ionization employing either CD_4 or ND_3 as the deuterium source.[22]

Determination of Rate Constants and Isotope Effects. By careful adjustment of the partial pressures of the two pyridines and the CD_4 or ND_3, all of the protonated and deuterated reactant ions could be formed rapidly compared to their rate of decay via the proton or deuteron transfer of interest. Thus, once all of the reactions leading to the formation of reactant ions had gone to completion, decay of the reactant ion signal became exponential. Absolute rate constants were obtained using this limiting pseudo-first-order decay and the pressure of the neutral reactant gas. All reactions studied were confirmed by double resonance ion-ejection experiments.[11] In order to minimize errors due to pressure measurement in determining the ratio k_H/k_D, both the protonated and deuterated reactant ions were generated in the ICR cell at the same time. The decay of each was then recorded under a given set of conditions so that k_H/k_D could be determined directly from the relative rate constants. Each rate constant reported is the average of at least 15 determinations obtained on at least two different days. Each value of k_H/k_D is the average of at least 15 pairs of determinations of k_H and k_D on at least two different days. The error limits reported are 95% confidence limits and reflect the random error in the data. The estimated accuracy of the absolute rate constants is ±20% while relative rate constant comparisons should be considerably more accurate. No corrections have been made for nonreactive ion loss.[20] No competing reactions leading to the decay of reactant ion signal, such as proton-bound dimer formation, were observed under typical experimental conditions.

Results

The results of the kinetic studies are presented in Table I. Both the absolute rate constants and the reaction efficiencies are seen to decrease as the alkyl substituents at the 2 and 6 positions of the reactants increase in size. Neither the reaction between 2,6-diisopropylpyridinium ion and 2,6-di-*tert*-butylpyridine (VII) nor its reverse could be detected in double-resonance experiments. Under the conditions employed this indicates that the reaction is quite slow, and we have conservatively estimated an upper limit of 1×10^{-11} cm^3 molecule^{-1} s^{-1} for k_H. Reactions I–VI in Table I were found to be irreversible under our conditions. This is consistent with the values of $-\Delta G°$ for reactions I, II, IV, and VI and suggests that $-\Delta G°$ for reactions III and V is greater than 2 kcal/mol. The values reported for $-\Delta G°$ in Table I unless otherwise noted were calculated from values of $\delta\Delta G°$ determined by Taft and co-workers and compiled by Arnett.[5b] In some cases these values differ by up to 2 kcal/mol from values of $-\Delta H°$ calculated from pyridine proton affinities recently reported by Hopkins et al.;[13b,c] however, the relative order of reaction exothermicities remains unchanged if these values are used. The relatively large error limits associated with the absolute rate constants result primarily from the necessity of using a low pressure of reactant neutral gas compared to the background pressure due to the other pyridine and the deuterium source gas. This was necessary in order to ensure that the rate of the proton or deuteron transfer under study would be slow compared to the rates of the ion-molecule reactions leading to the formation of reactant pyridinium ions.

The values of k_H/k_D are close to 1.0 for all of the reactions studied. As the error limits show, however, 1.0 is outside the 95% confidence limits for reactions IV, V, and VI. For reactions IV and VI, 1.0 remains outside the confidence limits even at 99.9% confidence. An alternative way to test these data is to use the t test[23] to calculate the probability that the value of k_H/k_D observed is greater than 1.0. For reactions I and III this probability is greater than 95%, for reaction V it is greater than 99.5%, and for reactions IV and VI it is greater than 99.95%.

Discussion

The values of the rate constants reported in Table I fall roughly between those reported for the majority of exothermic gas-phase proton transfers between small charge localized species[6] and those reported for gas-phase proton transfer involving delocalized systems.[8] Because ion-molecule collision rates are influenced to a large degree by the dipole moment and the polarizability of the neutral reactant, it is difficult and sometimes misleading to compare reaction rate constants for different systems directly and is more useful to compare reaction efficiencies instead. The reaction efficiency is defined as the fraction of collisions which result in reaction and can be calculated for the gas-phase system by dividing the observed rate constant by the ion-molecule collision rate constant. The latter can, in principle, be measured[24] but is more often calculated from a suitable ion-molecule collision theory such as average dipole orientation (ADO) theory.[25] The reaction efficiencies for most exothermic proton transfers between small charge-localized species in the gas phase[6a] are ≥ 0.5. The reaction efficiency for the thermoneutral proton transfer between ammonia and ammonium is reported[26] to be 0.55, and the reaction efficiencies for exothermic proton transfers involving delocalized systems range[8] from 0.4 to 0.002. (Proton transfers between charge-localized species in solution are often diffusion controlled[9,10] and thus have efficiencies close to 1.0.). While it is not certain how well ADO theory approximates the ion-molecule collision rate constants for large organic molecules such as the pyridines used in this study, the values of k_{ADO} appear reasonable when compared with other systems. The calculated values of k_{ADO} used in obtaining the efficiencies reported in Table I range from 1.5 to 1.9×10^{-9} cm^3 molecule^{-1} s^{-1}. This is in the same range as those calculated for the delocalized systems[8] and in the same range as collision rate constants measured for other systems using ICR phase coherence techniques.[24] Thus the absolute reaction efficiencies we have obtained are somewhat smaller than might be expected for exothermic proton transfers between localized systems.

The most obvious trend in the data reported in Table I is that as the reactants become more heavily substituted at the 2 and 6 positions the rate constants and reaction efficiencies decrease. This trend correlates to some degree with reaction exothermicity. For example, reaction II is more efficient than III and reaction IV is more efficient than V. The exceptions to the efficiency-exothermicity correlation are more notable, however. Reaction II is only as efficient as reaction I, although the former is more exothermic, and reaction IV is only as efficient as III and less efficient than I even though IV is more exothermic than either I or III. Most notably, reaction VI is estimated to be one of the more exothermic reactions studied, yet it is surprisingly inefficient. Consistent with both of these trends is our inability to observe proton transfer between 2,6-diisopropylpyridinium ion and 2,6-di-*tert*-butylpyridine. This reaction should be less exothermic than any of reactions I-VI and the reactants are the most heavily substituted. The second trend apparent in Table I is that as the reaction efficiencies decrease there is an increase in $k_{\text{H}}/k_{\text{D}}$. This trend is not dramatic owing to the small nature of the isotope effect and the uncertainties involved. Nonetheless, $k_{\text{H}}/k_{\text{D}}$ is greater than 1.0 with more than 99% certainty for the three slowest reactions (IV, V, and VI). In comparison, Riveros[21f] has also found small normal isotope effects ($k_{\text{H}}/k_{\text{D}}$ ranging from 1.0 to 1.5) for abstraction of a proton or a deuteron from various α-d_1 toluenes by alkoxide ions when the reactions are moderately exothermic (>3 kcal mol^{-1}).

Qualitative Model. The mechanism and energy profile given in eq 1 and Figure 1 can be used to explain the trends discussed above rather well. While recognizing that no kinetic study can hope to determine uniquely the potential-energy surface for a reaction, we have chosen to explain our results in terms of the model discussed below for several reasons. It is the simplest model which is capable of accommodating all of the data presented here as well as the data available on other gas-phase proton transfers. It has been used in the same general form to explain the reaction efficiencies for several other types of ion-molecule reactions such as $\text{S}_\text{N}2$ reactions[20] and carbonyl displacements[27] in the gas phase. There is a strong analogy between this model and the general mechanism for proton transfer in solution first proposed by Eigen.[10] Finally, the central barrier E_0', which is an indispensable part of the model, bears a strong resemblance to the intrinsic barrier to proton transfer suggested by Marcus[28] and measured for several types of systems in solution.[9]

In order to apply this kinetic model to our results either qualitatively or quantitatively it is necessary to make several assumptions which have been discussed and justified in previous work[20,29] and which will only be discussed briefly below. First we assume that these proton transfers proceed through relatively long-lived intermediate complexes which most likely resemble proton-bound species. These complexes are chemically activated owing to the nature of the attractive potential surface for their formation and decompose either back to reactants or to products unless they are collisionally stabilized. At the low pressures used in this study stabilization is not competitive with decomposition. Proton-bound dimers have, however, been observed for a variety of aliphatic amines in high-pressure mass spectrometry[30] and thus the assumption of proton-bound complexes as intermediates for pyridine proton transfers is quite reasonable. Second, we assume that the internal energy of the chemically activated complex is randomized so that its two possible modes of decomposition can be discussed in terms of statistical unimolecular rate theories.

When the mechanism in eq 1 is treated in the steady-state approximation, the overall forward rate constant k_f is given[10] by

$$k_\text{f} = \frac{k_1 k_2 k_3}{(k_{-1} + k_2)k_3 + k_{-2}k_{-1}} \tag{2}$$

Since the reactions under consideration are exothermic, $k_{-2} < k_2$ and $k_{-1} < k_3$; thus $k_{-2}k_{-1} < (k_{-1} + k_2)k_3$ (vide infra). Exactly how small $k_{-2}k_{-1}$ is with respect to $(k_{-1} + k_2)k_3$ depends on the relative values of all the rate constants. For simplicity and without loss of generality in the following description of the features of the model, we will assume that $k_{-2}k_{-1}$ is in fact negligible compared to $(k_{-1} + k_2)k_3$. Physically, this assumption means that once [AH···B] has been converted to [A···HB] it always goes on to products. With this simplification, k_f is given by

$$k_\text{f} = \frac{k_1 k_2}{k_{-1} + k_2} \tag{3}$$

The rate constant k_1 is simply the rate constant for formation of the chemically activated collision complex and is taken as the ion-molecule collision rate constant as calculated from ADO theory. The reaction efficiency is given by

$$\text{efficiency} = k_\text{f}/k_1 = \frac{k_2}{k_2 + k_{-1}} = \frac{1}{1 + k_{-1}/k_2} \tag{4}$$

From eq 4 it can be seen that the overall reaction efficiency is determined by the ratio of two unimolecular rate constants k_{-1}/k_2.

Both decomposition paths are energetically accessible as long as E_0' is lower than E_0. If the central barrier E_0' became larger than E_0, the reaction would exhibit normal Arrhenius behavior. However, the available data on the energy dependence of ion-molecule rate constants indicate that even for very slow reactions such behavior is generally not observed.[31] Since the transition state for the process described by k_{-1} (transition state A) is the same as for the ion-molecule collision it should be a very loose transition state. The transition state for the process described by k_2 (transition state B) should be fairly tight since it essentially represents a unimolecular rearrangement of the complex. Thus, although reaction of the complex to yield products is more favorable for energetic reasons, dissociation back to reactants is still energetically feasible and is favored entropically. As the difference in barrier heights, ΔE, becomes less negative, dissociation of the complex back to reactants becomes more favorable compared to further reaction to give products, and the reaction efficiency drops. The statement that $k_{-2} < k_2$ and $k_{-1} < k_3$ can now be justified. Since k_{-2} and k_2 involve the same transition state the entropic considerations are identical. Since the overall reaction is exothermic the complex [A···HB] is more stable than the complex [AH···B]. Thus the two reactions are entropically identical but k_2 is favored energetically. Likewise k_{-1} and k_3 are entropically similar but k_3 is favored energetically for exothermic reactions.

The simplifications introduced in the kinetic model described above render it formally equivalent to the case of a single minimum potential energy surface with a loose transition state at the entrance channel and a tight transition state at the exit channel. It is important to recognize that, if such a surface is accepted for the forward reaction, consideration of the reverse reaction in light of symmetry and the principle of detailed balance requires at least a double minimum in the surface. Thus, we take evidence which supports the kinetic model described above as also supporting the proposed double minimum potential energy surface. The assertions made above regarding the behavior of the rate constant k_f as a function of ΔE have been discussed in greater detail for proton transfer by Farneth[8] and have been shown to be quantitatively correct by Olmstead[20] in the case of S_N2 reactions. We will return to a more quantitative discussion for pyridine proton transfers below. First, however, it is useful to consider the trends observed in our data in terms of the qualitative behavior we have just outlined.

The rough correlation between reaction efficiency and exothermicity for reactions such as II and III or IV and V can be attributed to a lowering of E_0' relative to E_0 in accord with the Hammond postulate and the Bell-Evans-Polanyi principle. The reversals in the efficiency-exothermicity correlation can be attributed to two effects. First, increased steric crowding as the reactants come together in the proton-bound complex may raise the bottom of the well in Figure 1 (i.e., lower E_0) and thus raise any intrinsic barrier to proton transfer with respect to E_0. In addition the actual barrier height E_0' may be raised relative to the well bottom owing to increased steric crowding in transition state B. Any combination of these effects will result in ΔE becoming less negative for more hindered reactant pairs and will thus tend to offset or even overcome effects due to overall reaction exothermicity. There is some evidence for steric effects decreasing the stability of the proton-bound complex and thus effectively raising the bottom of the well. Hopkins[13c] has compared the solution-phase hydrogen bonding basicities of pyridines to phenol with the gas-phase proton affinities of the pyridines. For unhindered pyridines there is a linear correlation between these quantities while 2- and 2,6-substituted pyridines deviate from the correlation in that their hydrogen-bonding basicities are not as great as might be expected from their proton affinities. The deviation becomes greater as the bulkiness of the alkyl substituents on the pyridine is increased and is interpreted as being due to increasingly unfavorable steric interactions in the hydrogen-bonded complex. A second effect which cannot be overlooked in explaining the observed efficiencies is that as the reactants become increasingly heavily substituted their rotational entropy increases. A great deal of this entropy, which is still present in the loose transition state A (see quantitative model below), is lost in forming the proton-bound complex and transition state B. Thus, as the reactants become more heavily substituted, rotational entropy effects as well as sterically induced energy effects will tend to reduce the reaction efficiency. Rotational entropy effects also suggest a possible explanation for why reaction I is somewhat less efficient than exothermic proton transfers between smaller charge-localized species even though this reaction should not have any unfavorable steric interactions.

It is difficult to give a detailed qualitative explanation of the kinetic isotope effect which has been observed since it is actually a combination of competing isotope effects for the two decomposition channels available to the chemically activated complex. One general observation can be made, however. The observation of an isotope effect argues strongly for a barrier to proton transfer at lower energy than the barrier for decomposition back to reactants. If at least one such barrier, E_0', is not present in the well (i.e., if Figure 1 has a single minimum instead of a double minimum), then eq 4 is still applicable to the reaction kinetics. Now, however, transition state B is essentially identical with transition state A except that the proton or deuteron has been transferred, since both transition states now represent ion-molecule collision processes. In this case any differences in vibrational frequencies and zero-point energy for the proton and deuteron transfers would essentially cancel between the pairs of transition states and no isotope effect would be expected. In order to clarify this point and explain fully the observed isotope effect it is necessary to consider a more quantitative version of the kinetic model.

Quantitative Model. With the assumptions discussed above concerning the mechanism of the reaction and the properties of the intermediate complex, RRKM theory[32] can be used to calculate the overall reaction efficiency as a function of E_0 and E_0'. Thus the reaction efficiency can be calculated as a function of ΔE_H for proton transfer and ΔE_D for deuteron transfer and values of k_H/k_D can be obtained. The treatment outlined below follows that given by Olmstead.[20]

Because of the simplifications made above in the kinetic model, we need only calculate the efficiency for formation of products P in the kinetic scheme

$$A^+ + B \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [AB^+]^* \xrightarrow{k_2} P \tag{5}$$

in order to evaluate the reaction efficiencies for the proton-transfer reactions. In eq 5 $[AB^+]^*$ is a long-lived chemically activated ion-molecule complex. In direct analogy to the discussion given by Forst on the analysis of chemical activation systems,[33] it can be shown that the overall forward rate constant k_f is given by eq 6 and the reaction efficiency by eq 7.

$$k_f = k_{ADO} \int_{E_0}^{\infty} \frac{k_2(E)F(E)\mathrm{d}E}{k_{-1}(E) + k_2(E)} \tag{6}$$

$$\text{efficiency} = \int_{E_0}^{\infty} \frac{k_2(E)F(E)\mathrm{d}E}{k_{-1}(E) + k_2(E)} \tag{7}$$

In eq 7 $k_{-1}(E)$ and $k_2(E)$ are unimolecular rate constants at a specified internal energy E for the reversion of $[AB^+]^*$ to reactants and its conversion to products, respectively. The distribution function $F(E)$ for this type of chemical activation process is given[33] by eq 8 and $k_{-1}(E)$ and $k_2(E)$ are given by eq 9 and 10

$$F(E) = \frac{G_A(E - E_0)e^{-E/kT}}{\int_{E_0}^{\infty} G_A(E - E_0)e^{-E/kT}\,\mathrm{d}E} \tag{8}$$

$$k_{-1}(E) = \frac{G_A(E - E_0)}{hN(E)} \tag{9}$$

$$k_2(E) = \frac{G_B(E - E_0' - \Delta E_{\mathrm{rot}})}{hN(E)} \tag{10}$$

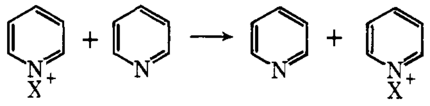
where $N(E)$ is the density of internal vibrational and rotational states of the complex, $G_A(E - E_0)$ is the sum of internal states for transition state A, $G_B(E - E_0' - \Delta E_{rot})$ is the sum of internal states for transition state B, and ΔE_{rot} is a correction to the internal energy of transition state B required by angular-momentum conservation. The value of ΔE_{rot} is calculated[34] from the ratio of the external moments of inertia of transition state A to transition state B, I_A/I_B. Substitution of eq 8, 9, and 10 into eq 7 gives a final expression for the reaction efficiency:

efficiency

$$= \frac{\displaystyle\int_{E_0}^{\infty} \frac{G_B(E - E_0' - \Delta E_{rot}) G_A(E - E_0) e^{-E/kT}}{G_A(E - E_0) + G_B(E - E_0' - \Delta E_{rot})} \mathrm{d}E}{\displaystyle\int_{E_0}^{\infty} G_A(E - E_0) e^{-E/kT} \mathrm{d}E} \qquad (11)$$

which depends only on the properties of transition states A and B and the values of E_0 and E_0'. Once appropriate vibrational frequencies and moments of inertia for the two transition states have been chosen, the sums of states may be evaluated by a direct count of vibrational states and a classical counting of internal rotational states.[35] The integrals in eq 11 must be evaluated numerically. A more rigorous treatment of angular momentum would involve calculating the forward rate constant as a function of both E and the angular momentum J and then averaging over both E and J. Such a treatment is considerably more complicated than the one presented above and unnecessary for our present purposes.

Since all of the reactants in our study are structurally similar, we have chosen to illustrate the quantitative behavior of the model with a calculation of the reaction efficiency and isotope effect for the following reaction:



X = H,D

Although this reaction is experimentally unobservable by ICR, it is the simplest reaction which contains the general features of reactions I–VII. While calculations based on the system will not model any of reactions I–VII exactly, they should give a good estimate of the quantitative behavior of all the reactions for which the efficiency and k_H/k_D could be measured.

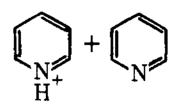
Transition State A. The choice of parameters for transition state A is fairly straightforward. Since A is a transition state for an ion–molecule collision, it is taken to be at the point along the reaction coordinate where the sum of the potential and centrifugal energies is at a maximum.[34] This distance is calculated for the ion-induced dipole (Langevin) potential only, since the appropriate theory for the full ADO potential has not yet been developed. At this point the two species are separated by a sufficient distance (ca. 10 Å) that the vibrational frequencies are taken as those of pyridine and pyridinium ion. The remaining degrees of freedom are a one-dimensional free rotation corresponding to rotation about the hydrogen bond axis, two two-dimensional rotations corresponding to free tumbling of both species about axes perpendicular to the axis of the one-dimensional rotation, and the reaction coordinate. The frequencies and moments of inertia were estimated from those for pyridine and benzene.[36] Benzene was used as a model for pyridinium ion since a complete assignment of vibrational frequencies is not available for the latter. The 57 vibrational frequencies were grouped into seven frequency groups. Three frequencies, which in a local mode description correspond to the NH stretch and in- and out-of-plane NH bends, were each chosen as single groups in order to facilitate consistent modeling of the deuterated pyridinium ion frequencies. Once the frequencies for the protonated transition state were chosen, those for the deuterated transition state were obtained by lowering the three NH frequencies in accord with the Teller–Redlich product rule[37] as applied to the pyridinium ion.

Transition State B. The structure and frequencies of this transition state are less well defined. We have taken the structure to be that of a symmetrical proton-bound dimer with an N–N distance of 3.0 Å as suggested for the N–N distance in $N_2H_7^+$ by ab initio studies.[38] Most of the frequencies were again estimated from those of pyridine and benzene. In this transition state, however, the pyridine NH stretch has been replaced by an N···H···N symmetric stretch which was taken to be at 668 cm^{-1} as calculated[38] for $N_2H_7^+$. The N···H···N asymmetric stretch is the reaction coordinate. The N···H···N bending modes were assigned a frequency of 1200 cm^{-1} in analogy to those[39] in F_2H^-. The remaining degree of freedom is the one-dimensional free rotation also present in transition state A. The two-dimensional rotations present in transition state A have become bending modes and hence the loss of rotational entropy discussed above in the qualitative model. The frequencies for the deuteron transfer were again calculated in accordance with the Teller–Redlich product rule. In order to apply the product rule properly in this case, the ratio of the imaginary frequencies for proton and deuteron transfer must be known. This was calculated by treating the transition state as triatomic and following the method of Bigeleisen.[40]

Zero Point Energy Effects. Because of zero point energy differences between the transition states for proton and deuteron transfer, ΔE will be different for the two reactions even though the potential surface for both is the same. This difference in zero-point energy is readily calculated for a given set of frequencies and has a significant effect on the magnitude of the calculated values of k_H/k_D. Since the correct frequencies to use for the NH stretch and bends in the pyridinium ion are not known accurately, two sets of choices reflecting a reasonable range of possible values were used. These choices were based on the infrared spectra of pyridinium ions in various salts.[41] In model I the NH stretch was chosen at 2700 cm^{-1} and the bends at 1200 and 700 cm^{-1}. In model II the NH stretch was chosen at 2400 cm^{-1} and the bends at 1000 and 600 cm^{-1}. In both models the total vibrational entropy was kept constant and equal to the sum of the vibrational entropies of pyridine and benzene by adjusting the value of the lowest frequency group for proton transfer. The frequencies of transition state B were not varied because there is no experimental evidence as to what might be a reasonable range. The parameters for transition states A and B for proton transfer are given in Table II. Those for deuteron transfer are given in Table III. The zero-point energy corrections, $\Delta E_D - \Delta E_H$, are 1.0 kcal/mol for model I and 0.6 kcal/mol for model II.

Calculation. The calculated reaction efficiencies for proton transfer and the calculated values of k_H/k_D are tabulated as a function of ΔE_H over the range of interest in Table IV. Although neither model is in perfect quantitative agreement with the experimental results, both models reproduce the trends observed in the experimental data, with model II giving somewhat better agreement than model I. More nearly quantitative agreement might be obtained by further adjusting the frequencies for the NH and NHN vibrational modes in both transition states. This would, however, serve no useful purpose given the present state of knowledge about the true physical properties of such species. The results show that, as discussed qualitatively above, the reaction efficiency decreases as ΔE_H becomes less negative, and as the reaction efficiency decreases k_H/k_D increases. These results can also be used to estimate the error introduced in neglecting the terms $k_{-1}k_{-2}$ in eq 2. For reactions which are only exothermic by 1–2 kcal/mol this simplification results in an overestimation of the

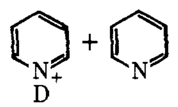
Table II. Parameters Used in the Calculation of Reaction Efficiencies for (i)[a]


(i)

	transition state A model I	transition state A model II	transition state B
ν_i	3060 (10)	3060 (10)	3000 (10)
	2700 (1)	2400 (1)	1500 (12)
	1500 (5)	1500 (5)	1200 (2)
	1200 (1)	1000 (1)	900 (19)
	900 (35)	900 (35)	700 (13)
	700 (1)	600 (1)	668 (1)
	406 (4)	454 (4)	400 (4)
I_i, σ_i	41.8, 2 (1)	41.8, 2 (1)	41.8, 2 (1)
	122, 1 (4)	122, 1 (4)	
I_A/I_B	5.6	5.6	

[a] Degeneracies are in parentheses. Frequencies (ν_i) are in cm^{-1}; moments of inertia (I_i) are in amu Å^2; σ_i are the symmetry numbers of the internal rotors.

Table III. Parameters Used in the Calculation of Reaction Efficiencies for (ii)[a]


(ii)

	transition state A model I	transition state A model II	transition state B
ν_i	3060 (10)	3060 (10)	3000 (10)
	1900 (1)	1700 (1)	1500 (12)
	1500 (5)	1500 (5)	900 (19)
	900 (35)	900 (35)	850 (2)
	850 (1)	700 (1)	700 (13)
	506 (1)	454 (4)	668 (1)
	406 (4)	436 (1)	400 (4)
I_i, σ_i	41.8, 2 (1)	41.8, 2 (1)	41.8, 2 (1)
	122, 1 (4)	122, 1 (4)	
I_A/I_B	5.6	5.6	

[a] See Table II for explanation and units.

reaction efficiency by approximately 5-10%, which is less than accuracy of the calculations and about the same as the precision of the experimental data. For more exothermic reactions the error is even less.

The general properties of the transition states used in these calculations have met with success in other calculations modeling related ion-molecule reactions. Transition states of the same form as A have proven useful in calculating the rates of formation of proton-bound dimers of small molecules[29] such as ammonia, methylamine, water, and hydrogen sulfide. Transition states similar to both A and B have also been used by Bowers et al.[42] in a phase space study of the proton transfer from *tert*-butyl cation to ammonia, although these authors do not use a double minimum potential surface to describe the reaction. Thus there is a small but growing body of theoretical work which supports the validity of this general form of quantitative model for those gas-phase proton-transfer reactions which can reasonably be assumed to proceed via long-lived intermediate complexes.

A final result which is suggested by our calculations is a rough estimate of the size of the actual barrier to proton transfer, E_0'. For a calculated reaction efficiency of 0.35, which corresponds to the efficiency of the unhindered reaction I, $-\Delta E_H$ is found to be 15.0 kcal/mol. A reasonable estimate of the well depth may be obtained from the bond dissociation energy of the proton-bound dimers of ammonia and methylamines, all of which are approximately[30] 20 kcal/mol.

Table IV. Results of RRKM Calculations[a]

	model I		model II	
$-\Delta E_H$	efficiency	k_H/k_D	efficiency	k_H/k_D
12.0	0.04	2.3	0.05	1.6
13.0	0.10	2.1	0.11	1.5
14.0	0.19	1.8	0.21	1.4
15.0	0.32	1.6	0.35	1.3
16.0	0.42	1.4	0.50	1.2
17.0	0.61	1.3	0.64	1.1
18.0	0.74	1.2	0.76	1.1

[a] ΔE_H is in kcal mol^{-1} and is the difference $E_0' - E_0$ for the proton-transfer reaction. Efficiencies are for the proton-transfer reaction, calculated from eq 7.

Therefore we obtain a barrier height of 5 kcal/mol. This value is in the middle of the range of values reported for intrinsic barriers to proton transfer obtained by the application of Marcus theory to solution results.[9] These values range from 2 kcal/mol for "normal" oxygen and nitrogen bases to 10 kcal/mol for protonation of aromatic compounds. This agreement suggests a close tie between the intrinsic barriers to proton transfer in both phases.

Conclusion

In summary, the reaction efficiencies obtained in this study indicate that steric interactions can inhibit the rate of proton transfer between pyridine bases. A small normal kinetic isotope effect has been observed for the less efficient reactions. These results are accommodated qualitatively and semiquantitatively by a potential surface which has two minima separated by a small intrinsic barrier to proton transfer. The observation of a kinetic isotope effect provides evidence for the existence of this barrier. The magnitude of the barrier is estimated to be in reasonable agreement with the magnitudes of intrinsic barriers to proton transfer obtained from the application of Marcus theory to solution-phase results.

Acknowledgment. We are grateful for the support of the National Science Foundation and the donors of the Petroleum Research Fund, administered by the American Chemical Society.

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Proton Exchange between Nucleic Acid Bases in Nonaqueous Solvents

Hideo Iwahashi and Yoshimasa Kyogoku*

Contribution from the Institute for Protein Research, Osaka University, Suita, Osaka 565, Japan. *Received August 8, 1979*

Abstract: The saturation transfer method of nuclear magnetic resonance reveals that protons exchange between nucleic acid bases in nonaqueous solvents. The exchange takes place between the imino proton of 1-cyclohexyl-5-bromouracil (BrU) and the amino proton of 9-ethyladenine (9EA), and between the amino proton of 1-methylcytosine (1MC) and the imino proton of 9-ethylguanine (9EG), while the amino proton of 9EG does not exchange at all with the other protons. Experiments at low temperature show that, of the two amino protons of cytosine, only the proton directly participating in the hydrogen bond exchanges with the imino proton of 9EG. Activation energies of the proton exchange between some 1-cyclohexyluracil derivatives and 9EA in chloroform were determined. They vary from 7 to 16 kcal/mol, increasing in the following order: 1-cyclohexyl-5-bromouracil, 1-cyclohexyluracil, 1-cyclohexylthymine, and 1-cyclohexyl-5,6-dihydrouracil. It is unlikely that all the protons exchange through water protons in the solvent because the water-proton signal is only partially saturated even when the imino- or amino-proton signals are completely saturated.

The molecular basis of nucleic acid base–base interaction has been studied extensively using various physicochemical techniques including infrared spectroscopy[1] and nuclear magnetic resonance.[2] These experiments demonstrated that a specific interaction between complementary nucleic acid bases exists in nonaqueous solvents even at the monomer level. In spite of much knowledge about specificity, little is known about the dynamic properties of base-pair formation.[3] Specificity or selectivity in base pairing is a fundamental process in genetic coding, but fluctuation in the paired structure should also be relevant to the biological phenomena.[4] In previous work we showed that at the monomer level the adenine–uracil pair using the C(2) carbonyl group as a proton acceptor site coexists extensively with the Watson–Crick type base pair which uses the C(4) carbonyl group.[5] It has also been suggested that the keto-enol tautomerism of thymine (uracil) and guanine and the amino–imino tautomerism of adenine and cytosine may explain spontaneous mutation and wobble pairing in codon–anticodon recognition,[6] although there is almost no experimental evidence supporting the idea. In a previous paper we demonstrated the exchange of protons between complementary nucleic acid bases by applying the saturation transfer method of proton magnetic resonance.[9] The evidence may be relevant to fluctuation in the structure of the bases, particularly tautomerism. Saturation transfer is a well-known phenomenon[7] and has usually been employed to elucidate the sites and rates of exchangeable nuclei.[8] In the present experiment we analyze the observed proton saturation transfer on nucleic acid base pairs in nonaqueous solvents and discuss the mechanism of proton exchange between the bases.

Experimental Section

Materials. 9-Ethyladenine (9EA), 1-cyclohexyluracil (U), 1-cyclohexylthymine (T), 1-cyclohexyl-5-bromouracil (BrU), 1-cyclohexyl-5,6-dihydrouracil (DU), 9-ethylguanine (9EG), and 1-methylcytosine (1MC) were purchased from Cyclo Chemical Co., Los

0002-7863/80/1502-2913$01.00/0