toward the inward portion of the molecule. This is in full agreement with the predictions based on the arguments of chemical graph theory.[25]

Conclusions

On the basis of the aforementioned examples we believe that the GAPT atomic charges can be a useful tool in the analysis of the electronic structure of molecules. The computed atomic charges are remarkably insensitive to the basis sets used for computing the wave function. Electron correlation effects can be significant in molecules possessing multiple bonds; however, they are predictable since they tend to decrease the atomic charges. This effect is especially pronounced in unsaturated molecules. It should be mentioned that similar observations concerning the influence of electron correlation on natural atomic charges[6] have been published very recently.[26]

Acknowledgment. The U.S. Department of Energy (Contracts No. DE-FC05-85ER250000 and DE-FG09-87ER13811) and the National Science Foundation (Grant CHE880818) contributed to funding of this research.

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Barrier Widths, Barrier Heights, and the Origins of Anomalous Kinetic H/D Isotope Effects

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Abstract: Proton transfer between MeO$^-$ and HOMe has been studied using ab initio molecular orbital theory. At the highest level employed (MP2/6-31+G(d)//6-31G(d) + ZPE), $-\Delta H^{298}$ and $-\Delta G^{298}$ for the formation of the ion-molecule complex MeO$^-\cdots$HOMe from the separated reactants are 26.3 and 15.2 kcal/mol, respectively. At the 6-31G(d)//6-31G(d) level of theory, the (MeO-H-OMe)$^-$ transition structure is 2.19 kcal/mol higher in energy than the ion-molecule complex ($\Delta E^{\ddagger}$ = 2.19), but this barrier disappears when zero-point energies are taken into account. The performance of AM1 on this system is quantitatively different ($-\Delta H^{298}$ = 13.3; $-\Delta G^{298}$ = 6.9; $\Delta E^{\ddagger}$ = 4.91; k_H/k_D = 5.13, increasing to 5.79 when quantum mechanical tunneling is invoked) but appears to be acceptable for the research envisaged in the title. The effect of an enforced separation of the heavy atoms upon proton transfer barriers and isotope effects (which simulates "steric effects") has been studied briefly at the 6-31G(d) level and in some detail using AM1. As predicted by a simplified two-parabola model of the barrier, $\Delta E^{\ddagger}$ increases linearly as the square of the heavy atom distance, and such plots extrapolate to the heavy atom distances of the fully optimized transition structures. The increase in the barriers is accompanied by a small increase in the semiclassical kinetic isotope effect, as expected from KIE theory, and a much larger increase in the tunneling correction, using Bell's treatment, in which the correction factor Q_H/Q_D depends upon the height of the barrier. Because of the relationship between barrier heights and widths, this correction becomes substantial when "steric hindrance" exists. Thus, in proton transfer between pyrrole anions and pyrroles, the KIE including the tunneling correction increases progressively from 6.6 to 9.0 to 15.6 as methyl groups are attached to the 2,5-positions and coplanarity of the two rings is enforced; for proton transfer between pyridinium cations and pyridines, the KIE's including the tunneling correction change from 5.2 to 4.6 to 5285(!) as methyl groups are attached to the 2,6-positions and coplanarity of the two rings is enforced. The energetics of proton transfer between pyridines conform to the Marcus equation, but the isotope effect and tunneling correction are smaller in the exoergic direction. The implications of the present findings for effects of pressure upon proton tunneling and tunneling effects in enzymatic hydrogen-transfer reactions are noted.

It has been the practice for some time to derive conclusions concerning the positions of transition states along the reaction coordinates of hydrogen-transfer reactions on the basis of experimentally determined slopes of Brönsted plots[1] and magnitudes of kinetic H/D isotope effects (KIE).[2] However, since the use of a Brönsted slope to deduce transition-state structure has recently come under attack,[3] the interpretation of a KIE and the factors that contribute to this effect have acquired renewed significance.

If quantum mechanical tunneling were unimportant for the case of a proton-transfer reaction, e.g., eq 1, most of the KIE would originate[2,4] in a zero-point energy difference (dZPE) between H- and D-substituted hydrogen-(deuterium-) bonded reactants (shown as their hydrogen-bonded complexes), which is only partly overcome by a residual dZPE in the transition state. The magnitude of the observed KIE would depend, inter alia, upon the degree of proton (deuteron) transfer in the transition state, and this would depend, in turn, on the separation between the proton donor and proton acceptor (X and Y in eq 1). As this separation increases, ZPE's and dZPE's of hydrogen-(deuterium-) bonded reactants will remain approximately the same. However, since the trans-

Scheme I

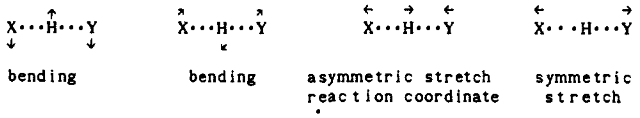

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Table I. Total Energies, Thermodynamic Parameters (298 K, 1 atm) and Kinetic Isotope Effects for the System $MeO^- + MeOH \rightleftarrows MeOH + {}^-OMe$ with Structures Optimized at the HF/6-31G(d) Level

	total energy (hartrees)					
basis set	MeO^-	MeOH	$(MeO\cdots HOMe)^-$	$(MeO{-}H{-}OMe)^-$	ΔE^a	$\Delta E^{\ddagger b}$
6-31G(d)	−114.38447	−115.03542	−229.46358	−229.46009	27.4	2.19
6-31G(d,p)	−114.38954	−115.04669	−229.47997	−229.47752	21.8	1.54
6-31+G(d)	−114.41047	−115.04092	−229.48831	−229.48367	23.2	2.91
MP2/6-31G(d)	−114.70162	−115.34494	−230.09862	−230.09931	32.7	−0.43
MP2/6-31G(d,p)	−114.72826	−115.38128	−230.16190	−230.16400	32.9	−1.32
MP2/6-31+G(d)	−114.74262	−115.35645	−230.14330	−230.14326	27.8	0.03

				k_H/k_D[c]			
basis set	$-\Delta H^d$	$-\Delta G^d$	$\Delta G^{\ddagger d}$	KIE_Z^e	$KIE_{\surd}^f$	Q_H/Q_D^g	KIE_B^h
6-31G(d)	26.0	14.9	4.18	3.95	4.08	*i*	
6-31G(d,p)	20.3	9.3	4.83				
6-31+G(d)	21.7	10.6	3.46				
MP2/6-31G(d)	31.2	20.1	6.80				
MP2/6-31G(d,p)	31.4	20.3	7.69				
MP2/6-31+G(d)	26.3	15.2	6.34				

[a] Refers to the complexation energy, in kcal/mol. [b] Refers to the energy difference between $(MeO{-}H{-}OMe)^-$ and $(MeO\cdots HOMe)^-$ in kcal/mol. [c] Frequencies have been scaled by 0.9. [d] In kcal/mol. [e] Isotope effect at 298 K, based on dZPE. [f] Isotope effect at 298 K, using the Bigeleisen equation (see text). [g] Tunneling correction, using Bell's equation (see text). [h] Isotope effect, after correction for tunneling. [i] The tunneling correction cannot be calculated in this case, because the zero-point energy correction leads to a negative barrier (see text).

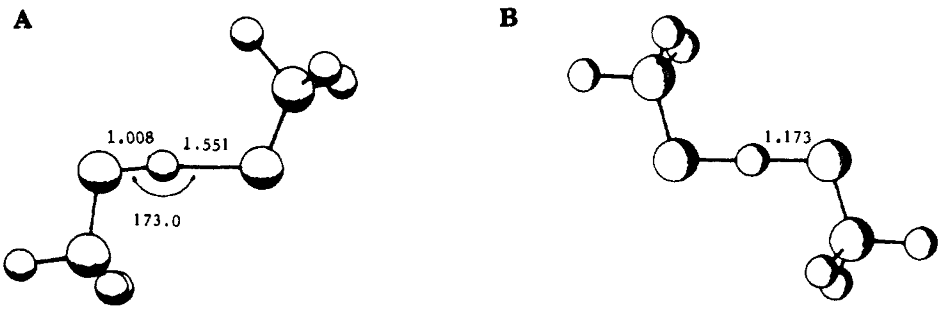

Figure 1. Optimized structures of $(MeO\cdots HOMe)^-$ and $(MeO{-}H{-}OMe)^-$ at the 6-31G(d) level.

ferred proton (deuteron) is less bound, there will be a smaller residual dZPE in the transition state, and the KIE should increase.

$$\underset{C_{XY}}{[XH\cdots Y]^-} \rightleftarrows \underset{TS_{XY}}{[X{-}H{-}Y]^-} \rightleftarrows \underset{C_{YX}}{[X\cdots HY]^-} \qquad (1)$$

The theory of KIE allows a second prediction. In the transition state of a symmetrical proton-transfer reaction (X = Y), the asymmetric stretch depicted in Scheme I[5] is the reaction coordinate and does not contribute to dZPE. Since the hydrogen which is transferred also does not participate in the *symmetric* stretching vibrations, only the bending vibrations can affect dZPE. On the other hand, in an unsymmetrical reaction (X ≠ Y), the transferred hydrogen moves in the symmetric stretch with one of the heavy atoms and contributes to dZPE, thus lowering the KIE.

To our knowledge, the foregoing predictions of the theory of KIE have not previously been tested explicitly. The present research was undertaken as an attempt to illustrate these points computationally, using AM1,[6] to gain some insight into the circumstances in which an enforced X···Y separation may affect a KIE[7] and to assess the consequences of such a separation.

Although AM1 is parameterized to reproduce hydrogen bonding to oxygen and nitrogen, this computational procedure had not previously been applied to a study of the type envisaged here, and it seemed prudent to provide an ab initio benchmark. This was done for the $MeO^- + HOMe$ system, for which some experimental data are available.[8] As is customary for gas-phase ion–molecule reactions,[9] proton transfer in this system is presumed to proceed via an ion–molecule complex, which has been found to be stabilized by ca. 28[8a] or ca. 19–21 kcal/mol[8b] relative to the separated reactants. An experimental investigation of the proton-transfer step is currently in progress.[10] There is no information regarding the primary KIE but, in the related $C_5H_5NH^+ + NC_5H_5$ system,[11] isotope effects close to unity have been reported.

Results and Discussion

Ab Initio Calculations of Proton Transfer between MeO^- and MeOH. The most comprehensive theoretical work related to the present study is that of Jorgensen,[12] who found that optimization at the 6-31G(d) level,[13] followed by one-point correlation corrections at the MP2 level[14] with a 6-31+G(d) basis set[15] led to anion–*water* complexation energies in good agreement with experiment. In the case of $CH_3O(H_2O)^-$, four structures with C_s

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Table II. Calculated O–O Separations, Barriers and KIE's for Proton Transfer between RO^- and HOR′ (AM1 Calculations)

	O–O separation (Å)						
R, R′	complex	TS	$\Delta E^{\ddagger}$ (kcal/mol)	KIE_Z[a]	KIE_V[a]	Q_H/Q_D	KIE_B[a]
Me, Me	2.756	2.403	4.91	4.71	5.13	1.13	5.79
Et, Et	2.843	2.403	7.06	4.82	5.13	1.14	5.84
Et, Me	2.760	2.403	5.55	4.61	5.02	1.12	5.63

[a] See footnotes to Table I.

Table III. Effect of an Enforced O–O Separation upon the Barrier to Proton Transfer between MeO^- and HOMe (6-31G(d) Calculations)

O–O separation (Å)	$\Delta E^{\ddagger}$ (kcal/mol)
2.60	6.86
2.75	13.73
2.90	21.84

Table IV. Effect of O–O Separation on the Calculated Barriers and KIE's for Proton Transfer between MeO^- and HOMe (AM1 Calculations)

O–O (Å)	$\Delta E^{\ddagger}$[a]	KIE_Z	KIE_V	Q_H/Q_D	KIE_B
2.5	4.16	4.03	4.63	1.11	5.16
2.6	7.99	4.29	4.80	3.65	17.50
2.7	12.67	4.23	4.74	19.87	94.27
2.8	17.60	4.44	4.95	135.14	668.65
2.9	22.60	4.59	5.13	969.88	4972.41

[a] In kcal/mol.

Table V. Effect of O–O Separation on the Calculated Barriers and KIE's for Proton Transfer between EtO^- and HOEt (AM1 Calculations)

O–O (Å)	$\Delta E^{\ddagger}$[a]	KIE_Z	KIE_V	Q_H/Q_D	KIE_B
2.5	5.45	3.96	4.54	1.65	7.47
2.6	9.64	4.18	4.68	5.90	27.57
2.7	14.72	4.25	4.71	41.95	197.67
2.8	20.05	4.40	4.82	332.41	1601.70
2.9	25.56	4.66	5.07	2738.68	13879.56

[a] In kcal/mol.

Table VI. Effect of O–O Separation on the Calculated Barriers and KIE's for Proton Transfer between MeO^- and HOEt (AM1 Calculations)

O–O (Å)	$\Delta E^{\ddagger}$[a]	KIE_Z	KIE_V	Q_H/Q_D	KIE_B
2.5	4.81	4.07	4.67	1.38	6.45
2.6	9.00	4.31	4.85	4.90	23.76
2.7	13.83	4.22	4.77	30.99	147.72
2.8	19.33	4.44	4.97	269.97	1341.55
2.9	24.88	4.59	5.14	2345.56	12047.12

[a] In kcal/mol.

symmetry were examined, and their energy differences were found to be very small, with an anti-staggered geometry preferred. Accordingly, this geometry of the ion–molecule complex and transition structure for proton transfer in $CH_3O(HOCH_3)^-$ were taken as starting points for optimization at 6-31G(d), using GAUSSIAN 86,[16] and one-point calculations were performed on the optimized structures at 6-31G(d,p), 6-31+G(d), MP2/6-31G(d), MP2/6-31G(d,p), and MP2/6-31+G(d) levels. The results, summarized in Table I and Figure 1, show that the ion–molecule complex is stabilized enthalpically relative to the separated reactants by 26.3 kcal/mol, in fair agreement with Mautner's value.[8a] The proton-transfer barrier ($\Delta E^{\ddagger}$) is 2.91 kcal/mol at the highest HF level (6-31+G(d)//6-31G(d)), but correlation and/or zero-point energy corrections lower the energy of this structure below that of the ion–molecule complex.

GAUSSIAN 86 does not allow calculations on isotopically labeled molecules,[17] and it was necessary to modify LINK 716 to permit frequency calculations on both $CH_3O(HOCH_3)^-$ and $CH_3O(DOCH_3)^-$. A program was written to convert the data to semiclassical KIE's, i.e., isotope effects based on zero-point energy differences or on the Bigeleisen treatment (eq 2),[18]

$$k_H/k_D = [\nu^{\ddagger}{}_H/\nu^{\ddagger}{}_D]\left[\prod_{i}^{3n^{\ddagger}-7}\left(\frac{u^{\ddagger}{}_{Hi}}{u^{\ddagger}{}_{Di}}\,\frac{e^{-u^{\ddagger}{}_{Hi}/2}}{e^{-u^{\ddagger}{}_{Di}/2}}\,\frac{1-e^{-u^{\ddagger}{}_{Di}}}{1-e^{-u^{\ddagger}{}_{Hi}}}\right)\times \prod_{i}^{3n-6}\left(\frac{u_{Di}}{u_{Hi}}\,\frac{e^{-u_{Di}/2}}{e^{-u_{Hi}/2}}\,\frac{1-e^{-u_{Hi}}}{1-e^{-u_D}}\right)\right] \quad (2)$$

in which $\nu^{\ddagger}{}_H$ or $\nu^{\ddagger}{}_D$ is the imaginary frequency at the saddle point, $u^{\ddagger}{}_{Hi} = h\nu^{\ddagger}{}_{Hi}/kT$, $u^{\ddagger}{}_{Di} = h\nu^{\ddagger}{}_{Di}/kT$, and $u_i = h\nu_i/kT$.[19] It should be noted[10] that kinetic isotope effects calculated in this way assume a Boltzmann energy distribution for the ion–molecule complex, but gas-phase ion–molecule *experiments* are normally conducted at low pressure, and the energy of the complex formed is the energy of the reactants which is above the height of the barrier to proton transfer. Consequently, experimental KIE's in the gas phase are expected to be lower than the theoretically computed values. As seen in Table I, for the reaction $MeO^- + HOMe \rightleftharpoons MeOH + {}^-OMe$, the calculated k_H/k_D is 4.1 at 298 K. However, the significance of this value is questionable, because of the disappearance of the barrier at higher computational levels.

AM1 Calculations of Proton Transfer between MeO^- and MeOH. Table II contains the AM1 results for this reaction (eq 3). The complexation energy is 13.6 kcal/mol, the barrier is 4.91 kcal/mol, and the isotope effect (neglecting tunneling) is 5.1. Compared to the ab initio calculations, the quantitative performance of AM1 seems acceptable, although the ion–molecule complexation energy is underestimated significantly.

AM1 Trends in Symmetrical and Unsymmetrical Proton-Transfer Reactions. Table II also includes the AM1 results for a second symmetrical reaction (eq 4) and an unsymmetrical reaction (eq 5). For reaction 5, the direction shown is exoergic, and the calculated ΔE for the uncomplexed reactants and products is 1.36 kcal/mol, compared to the 3.1 kcal/mol difference in the experimental gas-phase acidities of methanol and ethanol.[20]

$$MeO^-\cdots HOMe \rightleftharpoons [MeO\text{–}H\text{–}OMe]^{\ddagger} \rightleftharpoons MeOH\cdots{}^-OMe \quad (3)$$

$$EtO^-\cdots HOEt \rightleftharpoons [EtO\text{–}H\text{–}OEt]^{\ddagger} \rightleftharpoons EtOH\cdots{}^-OEt \quad (4)$$

$$MeO^-\cdots HOEt \rightleftharpoons [MeO\text{–}H\text{–}OEt]^{\ddagger} \rightleftharpoons MeOH\cdots{}^-OEt \quad (5)$$

The optimized O–O separations (Table II) are almost the same in the C_{XX} and C_{XY} complexes and exactly the same in the transition states. It is noteworthy that the O–O separation decreases by ca. 14% during the process, as is also found in methyl-transfer (S_N2) reactions.[21]

Uncorrected KIE's were calculated initially from the zero-point energies provided by use of the FORCE option of the AMPAC program. However, these were later found to be in error, because the program does not ignore the imaginary frequency of a transition structure.[22] The isotope effects listed in Table II were

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(17) We have been advised by Professor H. B. Schlegel that the forthcoming GAUSSIAN 88 will have this capability.

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(19) This program, which employs calculated frequencies to calculate dZPE, isotope effects from dZPE's, isotope effects using the Bigeleisen equation, and tunneling corrections to semiclassical isotope effects based on the Bell equation (see text) is available as Supplementary Material.

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(22) The problem does not exist in AMPAC if THERMO calculations are performed, but in a FORCE calculation the summation has been taken over $3n-6$ rather than $3n-7$ indices in the case of a transition state. We thank Professor M. J. S. Dewar and Dr. E. F. Healy for a helpful discussion of this point.

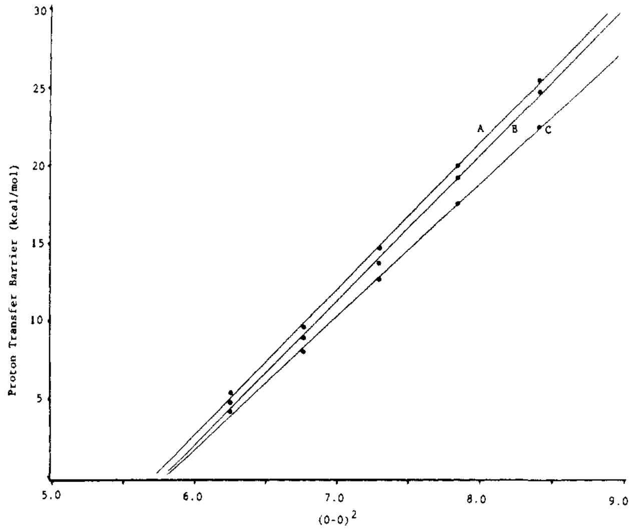

Figure 2. Plots of $\Delta E^{\ddagger}$ for proton transfer between MeO^- and HOMe (C), EtO^- and HOEt (A), and MeO^- and HOEt (B) as a function of the square of the enforced O–O separation (AM1 calculations).

obtained following the appropriate correction of the program. The KIE is marginally larger for reaction 4, which has the larger $\Delta E^{\ddagger}$, compared to reaction 3. The unsymmetrical reaction 5 has $\Delta E^{\ddagger}$ intermediate between the other two but a lower KIE, as predicted by KIE theory.

Effect of Enforced Separation (Increasing Barrier Widths) on Barrier Heights and Kinetic Isotope Effects. If the barrier of a symmetrical proton-transfer reaction, e.g., eqs 3 and 4, is taken as the crossing point of two parabolas separated by a distance d, it is qualitatively apparent that an increase in d leads to an increase in the barrier.[23] Analysis of this model as in the two-parabola derivation of the Marcus equation[24,25] leads to the prediction that the height of the barrier is proportional to d^2.

Since this specific relationship between barrier heights and widths had not previously received comment, it was first tested using 6-31G(d) ab initio calculations on reaction 3, with the results summarized in Table III. As the O–O separations in the ion–molecule complexes are made equal and then increased progressively from 2.6 to 2.9 Å, $\Delta E^{\ddagger}$ increases progressively from 6.86 to 21.84 kcal/mol. The plot of $\Delta E^{\ddagger}$ versus the square of the O–O separation (not shown) is linear, and the extrapolated O–O separation for $\Delta E^{\ddagger} = 0$ is 2.58 Å; this is close to the optimized value (2.55 Å) in the ion–molecule complex.

The corresponding AM1 data are presented in Tables IV–VI, for reactions 3–5. Figure 2 summarizes the variation of $\Delta E^{\ddagger}$ with $(O–O)^2$. Each of these plots extrapolates to $(O–O)^2 = 5.70–5.75$ at $\Delta E^{\ddagger} = 0$, corresponding to O–O = 2.39–2.40, the O–O separation in the optimized transition structures. It seems clear that, for these proton-transfer reactions, barrier heights are related to barrier widths.

The third and fourth columns of Tables IV–VI are the uncorrected KIE's (based on dZPE) and the KIE's provided by the Bigeleisen equation, all at 298 K. Although there is a progressive increase in both data sets with an increase in barrier height (barrier width), as predicted by the theory of KIE, it is evident that an analysis based only on bending and symmetric stretching vibrations cannot account for the anomalous isotope effects observed experimentally in sterically hindered proton-transfer reactions.[2]

Table VII. Calculated Barriers and Kinetic Isotope Effects for Proton Transfer between Pyrrole Anions and Pyrroles (Eq 7)

	N–N separation (Å)						
R	complex	TS	$\Delta E^{\ddagger\,a}$	KIE_Z	KIE_V	Q_H/Q_D	KIE_B
H	2.825[b]	2.570[c]	4.77	4.08	4.30	1.54	6.64
Me	2.882[b]	2.575[c]	6.05	4.33	4.57	1.97	9.01
Me	2.882[b]	2.602[d]	7.19	4.34	4.57	3.41	15.61

[a] In kcal/mol. [b] The two rings are coplanar. [c] The two rings are twisted ($\phi = 45°$). [d] Coplanarity of the two rings enforced.

We have, therefore, computed the tunneling corrections for the data of Tables IV–VI, using eq 6 given by Bell,[2]

$$Q_t = \frac{0.5u^{\ddagger}_t}{\sin 0.5u^{\ddagger}_t} - \sum_{n=1}^{\infty}(-1)^n \frac{\exp\left(\dfrac{u^{\ddagger}_t - 2n\pi}{u^{\ddagger}_t}\alpha\right)}{\dfrac{u^{\ddagger}_t - 2n\pi}{u^{\ddagger}_t}} \qquad (6)$$

where t = H or D, $u^{\ddagger}_t = h\nu^{\ddagger}_t/kT$, and α $(=\Delta E^{\ddagger}/kT)$ includes dZPE. These corrections, expressed as Q_H/Q_D,[19] are given in the fifth columns of Tables IV–VI, and the final KIE's are shown in the last columns of these tables. Equation 2 is derived with the assumption that the shape of the barrier can be treated as an inverted parabola, and it has been suggested[2b] that the first term leads to a reasonable approximation when the imaginary frequency of the transition state is less than about 1000 cm^{-1}. Our data confirm this point: with a standard correction factor of 0.9 for the frequencies, only the transition states of Table II exhibit imaginary frequencies less than 1000 cm^{-1}, and only in these cases is the second term of eq 2 negligible. It has also been stressed[2b] that the barrier height used in the second term of eq 2 includes the zero-point energy difference between the transition state and the initial state and, therefore, depends upon the nature of the isotopic species. This is taken into account in the calculations.[19] Since, as we have already noted (Table I), the ab initio barrier for the reaction of MeO^- with HOMe disappears when the zero-point energy correction is applied, a tunneling correction to the semiclassical isotope effect would be meaningless.

Since Q_t depends on α, the tunneling correction will vary with the height of the barrier. The data of Tables IV–VI illustrate this point clearly. Indeed, taking 20–30 as the range of anomalously large KIE's that has typically been observed for sterically hindered proton-transfer reactions,[2] our data suggest that, with the assumption of tunneling, this kind of KIE can be achieved by an 8% increase (from 2.4 to 2.6 Å) in the heavy atom distance and that this increase in the width of the barrier approximately doubles the barrier height.

Tunneling is thus the major factor leading to anomalously large kinetic isotope effects, as has long been conjectured.[26] Interestingly, both narrow[26] and wide barriers[27a] have been postulated for sterically congested proton-transfer reactions. Although our results are consistent with the latter view,[27b] they do refer to model systems, and it seemed desirable to obtain additional information regarding the relationships between barrier widths, barrier heights, and kinetic isotope effects. The systems selected for study are shown in eq 7 and 8, with R = H, Me. It was recognized that nonplanar (twisted) structures would probably be preferred en-

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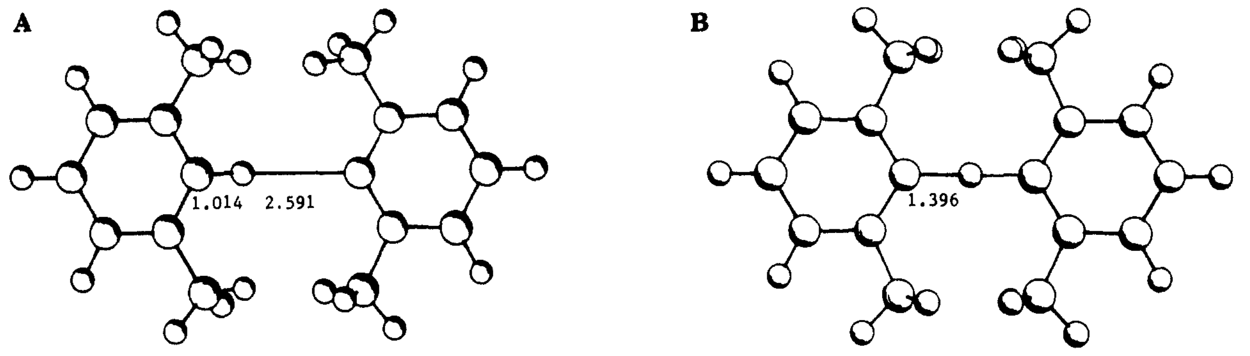


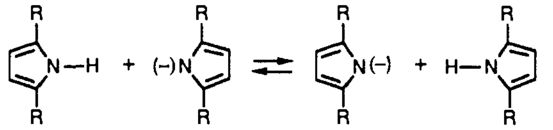
Figure 3. Structures of the ion–molecule complex and transition state for proton transfer between ArH^+ and Ar (Ar = 2,6-dimethylpyridine) when the two rings are constrained to planarity (AM1 calculations).

Table VIII. Calculated Barriers and Kinetic Isotope Effects for Proton Transfer between Pyridinium Cations and Pyridines (Eq 8)

R	N–N separation (Å) complex	N–N separation (Å) TS	$\Delta E^{\ddagger a}$	KIE_Z	KIE_V	Q_H/Q_D	KIE_B
H	2.825	2.600	4.11	3.88	4.06	1.28	5.20
Me[b]	2.876	2.606	4.39	4.18	4.38	1.05	4.60
Me[c]	3.605	2.792	21.72	5.45	5.80	912.11	5285.59

[a] In kcal/mol. [b] The two rings are twisted (ϕ = 90°). [c] Coplanarity of the two rings enforced.

ergetically to minimize steric effects.[28] Constraining the two rings to planarity would then allow such effects to be "turned on".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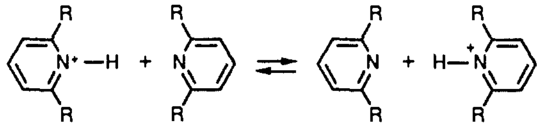
(8)

Proton Transfer between Pyrrole Anions and Pyrroles. Table VII summarizes the results obtained for reaction 7, using AM1. With R = H, the ion–molecule complex is planar, but the ca. 9% decrease in the N–N separation that accompanies the proton transfer causes the transition structure to be twisted. The introduction of four methyl groups leads to an increase in the N–N separation in the ion–molecule complex, which remains planar. Since the N–N separation in the twisted transition state is only marginally increased by the attachment of the methyl groups, the decrease in the N–N separation that accompanies the proton transfer is ca. 11%. The barrier, the semiclassical isotope effect, and the tunneling correction all increase slightly.

When the transition state is now constrained to planarity for R = Me, the N–N separation of this structure and the barrier increase slightly, *but the semiclassical isotope effect is unchanged.* The "steric effects" are manifested mainly in the increase in the tunneling correction that accompanies the increase in the width of the barrier and leads to an anomalous KIE.

Proton Transfer between Pyridinium Cations and Pyridines. Some of the effects just described are reproduced in reaction 8, but the consequences of enforced planarity in the R = Me transition state are much more pronounced (Table VIII). That proton transfer in this system is inherently more hindered than in the pyrrole system follows from the observation that all optimized structures are twisted, for R = H and R = Me. The attachment of the methyl groups therefore has only a small effect upon the barrier and upon the isotope effects.

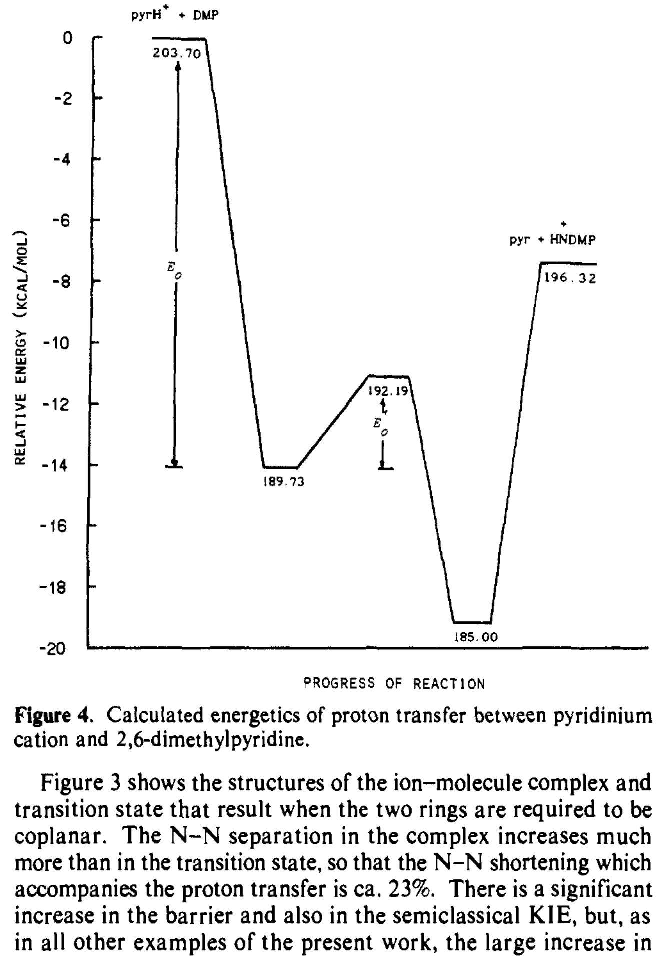

Figure 4. Calculated energetics of proton transfer between pyridinium cation and 2,6-dimethylpyridine.

Figure 3 shows the structures of the ion–molecule complex and transition state that result when the two rings are required to be coplanar. The N–N separation in the complex increases much more than in the transition state, so that the N–N shortening which accompanies the proton transfer is ca. 23%. There is a significant increase in the barrier and also in the semiclassical KIE, but, as in all other examples of the present work, the large increase in the barrier that is caused by the steric effects is accompanied mainly by a large increase in the tunneling correction.

In the experimental work of Jasinski and Brauman,[11] gas-phase proton transfer between pyridine bases was analyzed in terms of the double well reaction coordinate shown in Figure 4, and RRKM theory was employed to estimate the overall reaction efficiency as a function of E_0 and E_0'; with the assumption of a 20 kcal/mol well depth for the ion–molecule complex, the barrier for proton transfer in the parent system (eq 8, R = H) was found to be 5 kcal/mol, with k_H/k_D = 1.3–1.6. The calculated barrier for this reaction (Table VIII, AM1, $\Delta E^{\ddagger}$) is 4.11 kcal/mol, with k_H/k_D = 5.2, i.e., larger than the experimental value, as predicted by Brauman.[10] The calculated well depth is 13.3 kcal/mol; since AM1 appears to underestimate this quantity (op cit), Jasinski and Brauman's estimate of 20 kcal/mol seems reasonable.

These workers[11] also examined a number of unsymmetrical proton transfers between pyridine bases, including the reaction of pyridinium cation with 2,6-dimethylpyridine, for which the overall energy change, $-\Delta G$, is 6.8 kcal/mol. The data included in Figure 4 refer to the calculated results for this reaction. The

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[28] Wheland, G. W. *Advanced Organic Chemistry*; 3rd ed.; John Wiley: New York, 1960; pp 272–288.

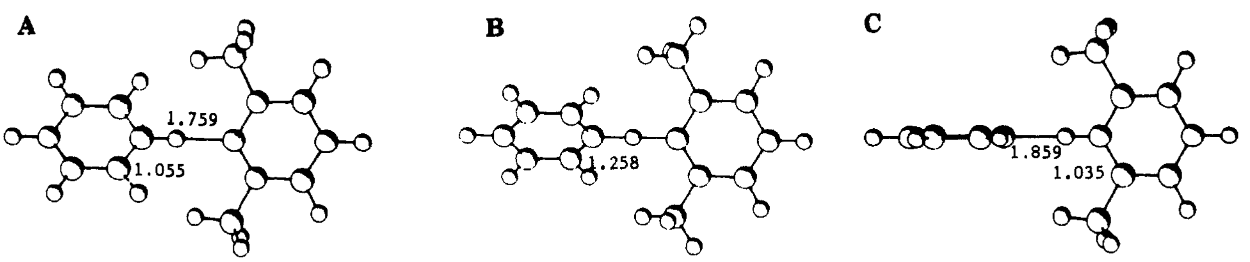

Figure 5. Optimized structures of the reactant and product ion–molecule complexes and transition state for proton transfer between pyridinium cation and 2,6-dimethylpyridine (AM1 calculations).

calculated $-\Delta E$ is 7.38 kcal/mol, and the well depths on the reactant and product sides of the reaction are 14.0 and 11.3 kcal/mol, respectively. The barrier in the exoergic direction is 2.46 kcal/mol, and the isotope effect, after correction for tunneling, is 2.10. Figure 5 shows the optimized structures of the reactant and product ion–molecule complexes and transition state of this reaction. All of these are twisted, with the result that any steric effects associated with the presence of the methyl groups are minimized. Interestingly, the tunneling correction in this case is 0.54, less than unity. Since each of Q_H and Q_D is calculated as the difference between the first and second terms of eq 2, there is no a priore requirement that Q_H/Q_D always be greater than unity. For the endoergic direction of this reaction, the barrier is 7.19 kcal/mol, and the isotope effect, after a 2.43 correction for tunneling, is 11.05. Such KIE differences in the exoergic and endoergic directions have been discussed by Melander and Saunders.[2b]

The internal consistency of the data of Figure 4 and Table VIII can be tested by using the Marcus equation (eq 9),[25] where $\Delta E = -4.73$ (the energy difference between the reactant and product ion–molecule complexes), and $\Delta E^{*}_{0} = 0.5\ (4.11 + 4.39)$ kcal/mol, respectively. This predicts ΔE^{*} for the cross reaction to be 2.21 kcal/mol, compared to the 2.46 kcal/mol computed directly.[21]

$$\Delta E^{*} = \Delta E^{*}_{0}\left(1 + \frac{\Delta E}{4\Delta E^{*}_{0}}\right)^{2} \qquad (9)$$

Barriers Widths and the Effect of Pressure upon KIE's. The effect of pressure on proton-transfer rate constants and on kinetic isotope effects has been studied for systems that exhibit both normal and anomalous KIE's[29,30] and commented upon by Kreevoy and Truhlar.[27,2f] Since the volume of activation is directly related to the separation of reactants at the transition state, our results lead to the expectation that an increase in pressure will lead to a decrease in the width of the barrier; this should lead, in turn, to an increase in the reaction rate (decreased barrier height), a decrease in the tunneling contribution, and a decrease in the observed KIE.

The reaction of diphenyldiazomethane with benzoic acid in dibutyl ether proceeds via rate-determining proton transfer and exhibits a normal KIE ($k_H/k_D = 4.5$). Increasing the pressure from 1 to 1090 atm leads to an increase in reaction rates, but no change in the KIE.[29a] On the other hand, in aqueous *tert*-butyl alcohol, the enolization of 2-nitropropane, catalyzed by 2,4,6-trimethylpyridine, exhibits $k_H/k_D = 16.4$. In this case, increasing the pressure from 1 to 1285 bar leads to a 3–4-fold increase in the rate and a *decrease* in the KIE to 11.4.[29b] The volumes of activation for ^{1}H and ^{2}H are −31 and −40 cm^3 mol^{-1}, respectively. Although the latter results are consistent with the view that tunneling and, therefore, an anomalous KIE will decrease with an increase in pressure, we note that other workers find these effects to be sensitive to solvent and to the nature of the reaction.[30] In addition, Truhlar argues[27b] that the "critical configuration" is often far removed from the saddle point, and the barrier width at the saddle point does not control the reaction dynamics.

Barrier Heights, Barrier Widths, and the Role of Tunneling in Enzymatic Reactions. In a classic series of papers,[7a–e] Schowen and his co-workers demonstrated, mainly through the use of multiple isotope effect studies, that the transition state for O-methylation of 3,4-dihydroxyacetophenone enolate anion by *S*-adenosylmethionine (a methyl transfer reaction) is *tightened* by 0.15–0.30 Å per bond when the reaction is catalyzed by catechol *O*-methyltransferase. This tightening (narrowing of the barrier) is accompanied by a rate enhancement of 10^{16}. Since tunneling is probably not a factor in the case of methyl transfer, much of this rate enhancement must result from the decrease in the barrier height that is associated with the decrease in barrier width. However, the overall effect seems larger than that suggested by the data of Table II and may reflect desolvation of the transition structure.[31]

For the transfer of a particle having a mass smaller than that of a methyl group, tunneling can be significant, as we have seen, but its role will be reduced by a tightening of the transition structure. Conversely, when tunneling is found to play a greater role in an enzymatic hydrogen-transfer reaction[7f–h] than in the corresponding nonenzymatic process, a *loosening* of the transition structure should be inferred. It will be of interest to obtain KIE data for enzyme-substrate and drug-receptor interactions having a nonoptimal fit between enzyme and substrate or between drug and receptor.

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Registry No. MeOH, 67-56-1; EtOH, 64-17-5; D_2, 7782-39-0; pyrrole, 109-97-7; 2-methylpyrrole, 636-41-9; 2,5-dimethylpyrrole, 625-84-3; pyridine, 110-86-1; 2-methylpyridine, 109-06-8; 2,6-dimethylpyridine, 108-48-5.

Supplementary Material Available: Listing of a computer program for the calculation of kinetic isotope effects based on zero-point energies, the Bigeleisen equation, and Bell's equation and typical input, which contains the calculated barrier (corrected for dZPE), the number of frequencies, and the scaling factor (if desired) (3 pages). Ordering information is given on any current masthead page.

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