actions return it to $(\eta^5\text{-}C_5H_5)_2Fe_2(CO)_4$.

Having observed two intermediates, we studied their reactivity with added substrates, again by flash photolysis. Two reactions were investigated, substitution and oxidation by CCl_4. For the long-lived intermediate, I, in cyclohexane saturated with CO, a quantitative return to $(\eta^5\text{-}C_5H_5)_2Fe_2(CO)_4$ was observed following flash photolysis and the difference spectrum for the process was unaffected. However, the observed first-order rate constant for return to the dimer had increased from 0.34 s^{-1} to 280 s^{-1} and was no longer light sensitive. The reaction with added potential ligands is not limited to CO. The lifetime of the intermediate was also markedly decreased in solutions containing PPh_3, CH_3CN, and Me_2SO in excess. It is more difficult to obtain reliable rate information under these conditions because net photochemistry is occurring, and only data from the first flash can be used reliably. However, a series of experiments at varying PPh_3 concentrations (10^{-3}–10^{-4} M) in cyclohexane showed that the observed first-order rate constant varies linearly with $[PPh_3]$ and that $k(20 \pm 2\ °C) = 1.5 \times 10^5\ M^{-1}\ s^{-1}$ for the disappearance of I. By contrast, there appears to be no or at best a very small contribution to photosubstitution from the homolytic cleavage pathway, at least for PPh_3 under our concentration conditions. The difference spectrum and recombination rate constants for $(\eta^5\text{-}C_5H_5)Fe(CO)_2$ (eq 2) are *unaffected* by the presence of added CO (saturated) or PPh_3 (0.1 or 0.001 M). Since net photosubstitution to give $(\eta^5\text{-}C_5H_5)_2Fe_2(CO)_3L$ is known to occur under the conditions of the flash experiment,[4,7,10] intermediate I is necessarily the origin of the observed photosubstitution with PPh_3, at least for $[PPh_3] \leq 0.1$ M.[12]

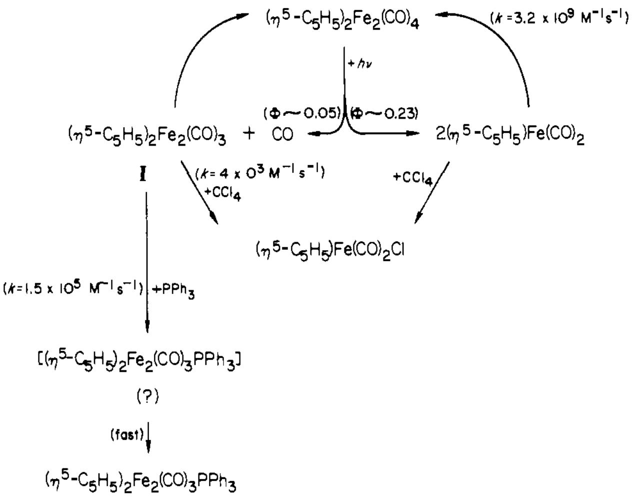
Flash photolysis experiments in cyclohexane with added CCl_4 (0.02–0.002 M), under conditions where photoredox chemistry is known to occur (eq 3), show clearly that I undergoes a reaction

$$(\eta^5\text{-}C_5H_5)_2Fe_2(CO)_4 \xrightarrow[h\nu]{CCl_4} (\eta^5\text{-}C_5H_5)Fe(CO)_2Cl^{2,11} \qquad (3)$$

with CCl_4. The transient decay rate for the intermediate is enhanced ($k(20 \pm 2\ °C) = 4 \times 10^3\ M^{-1}\ s^{-1}$) and the absorbance change observed is consistent with the appearance of $(\eta^5\text{-}C_5H_5)Fe(CO)_2Cl$ as the product. However, it is equally clear that a reaction also occurs between CCl_4 and the monomers as shown by the loss of the transient absorbance increase at 345 nm (Figure 1). Clear evidence for the intervention of two intermediates in a reaction with CCl_4 has also been obtained by Fox and Poë by a kinetic study of the photochemical reaction between $Mn_2(CO)_{10}$ and CCl_4.[13] In fact, at high concentrations of CCl_4 the majority of the photoredox reaction for the iron dimer appears to occur through $(\eta^5\text{-}C_5H_5)Fe(CO)_2$. From the data of Abrahamson et al.[2] and Tyler et al.,[7] the quantum yield at 366 nm for the redox reaction ($\Phi = 0.23$ in CCl_4) is 4–5 times greater than that for PPh_3 substitution ($\Phi = 0.05$ in benzene). The yield for PPh_3 substitution, which only occurs through I, should also be a measure of the contribution of I to the redox yield at sufficiently high concentrations of PPh_3 and CCl_4, and it seems clear that the majority of the reaction with CCl_4 occurs via $(\eta^5\text{-}C_5H_5)Fe(CO)_2$.

From our results and the earlier results of Tyler et al. and of Abrahamson et al., it is possible to construct an overall reactivity scheme which accounts for the observed photochemistry of $(\eta^5\text{-}C_5H_5)_2Fe_2(CO)_4$. The basis for the scheme is the thermal reactivity of two distinct photointermediates, both of which appear to be primary photoproducts or are immediately derived from different primary photoproducts. From its reactivity toward added ligands like CO or PPh_3, we assume that intermediate I is a CO-loss products. In order to explain the earlier results of Tyler et al. at low temperature,[7] the suggestion is made in Scheme I that in the reaction between I and PPh_3, there is a second intermediate, the intermediate observed by Tyler et al. The two intermediates are clearly different: from Figure 1, I clearly absorbs strongly in the visible; the second intermediate has no obvious absorption features in the visible.[7] Presumably the second intermediate is a CO-bridged dimer without an Fe–Fe bond which is an unstable isomer of the final product, $(\eta^5\text{-}C_5H_5)_2Fe_2(CO)_3PPh_3$. However, it should be pointed out that we have *no* direct evidence on this point. If a second intermediate is involved, its conversion to the final product is more rapid than its rate of formation under our conditions (20 ± 2 °C).

Scheme I



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Jonathan V. Caspar, Thomas J. Meyer*

Department of Chemistry, University of North Carolina
Chapel Hill, North Carolina 27514

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[10] Haines, R. J.; duPreez, A. L. *Inorg. Chem.* **1969**, *8*, 1459.

[11] Giannotti, C.; Merle, G. *J. Organomet. Chem.* **1976**, *105*, 96.

[12] It seems clear that the reactivity of $(\eta^5\text{-}C_5H_5)Fe(CO)_2$ toward substitution may be strongly dependent on the nature of the added ligand. For example, $(\eta^5\text{-}C_5H_5)_2Fe_2(CO)_2(P(OMe)_3)_2$ is the major photoproduct observed following irradiation of $(\eta^5\text{-}C_5H_5)_2Fe_2(CO)_4$ in the presence of $P(OMe)_3$[2] suggesting a direct reaction between $(\eta^5\text{-}C_5H_5)Fe(CO)_2$ and $P(OMe)_3$.

[13] Fox, A.; Poë, A. *J. Am. Chem. Soc.* **1980**, *102*, 2497.

H-Bond and Deprotonation Effects on the Resonance Raman Iron-Imidazole Mode in Deoxyhemoglobin Models: Implications for Hemoglobin Cooperativity[1]

Sir:

The recent assignment[2,3] of the iron–imidazole stretching mode, $\nu_{Fe\text{-}Im}$, in the resonance Raman (RR) spectrum of deoxyHb (Hb = hemoglobin) has provided a direct monitor of the strength of this important bond. Although no change in this frequency could be observed in R vs. T states of Hb Kempsey,[2] Nagai and Kitagawa,[4] using isolated chains, Hb Milwaukee, Hb Boston, and valency hybrids, have shown that there is an appreciable decrease of the normal (isolated chains or R state) Fe–Im frequency (222 and 224 cm^{-1} for α and β chains) in (T state) deoxyHb A, and that the shift is greater for α chains (207 cm^{-1}) than for β chains (220 cm^{-1}). These shifts were interpreted by Nagai and Kitagawa[4] in terms of the tension model of Hb cooperativity.[5] They assumed a linear force exerted by the protein on the proximal imidazole,

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[1] This work was supported by NIH Grant HL 12526.

[2] Kincaid, J.; Stein, P.; Spiro, T. G. *Proc. Natl. Acad. Sci., U.S.A.* **1979**, *76*, 549–552; 4156.

[3] (a) Kitagawa, T.; Nagai, K.; Tsubaki, M. *FEBS Lett.* **1979**, *104*, 376–378. (b) Nagai, K.; Kitagawa, T.; Morimoto, H. *J. Mol. Biol.* **1980**, *136*, 271–289. (c) Hori, H.; Kitagawa, T. *J. Am. Chem. Soc.* **1980**, *102*, 3608–3613.

[4] Nagai, K.; Kitagawa, T. *Proc. Natl. Acad. Sci.* U.S.A. **1980**, *77*, 2033–2037.

[5] (a) Perutz, M. F.; Ladner, J. E.; Simon, S. R.; Ho, C. *Biochemistry* **1974**, *13*, 2163–2173. (b) Perutz, M. F.; Heidner, E. J.; Ladner, J. E.; Beetlestone, J. G.; Ho, C.; Slade, E. F. *Ibid.* **1974**, *13*, 2187–2200.

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Table I. $\nu_{\mathrm{Fe-Im}}$ (cm^{-1}) for 5-Coordinate Iron(II) Porphyrins

(2-MeImH)Fe^{II}PP in water	220
(2-MeImH)Fe^{II}PPDME or OEP in benzene	205
(1,2-diMeIm)Fe^{II}PP in water	195
(1,2-diMeIm)Fe^{II}PPDME or OEP in benzene	195
(2-MeImH)Fe^{II}OEP in dimethylformamide	239
(2-MeIm$^-$)Fe^{II}OEP in dimethylformamide	212

superimposed on a Morse potential function for the Fe–Im bond, and calculated Fe–Im displacements of 0.02$_4$ and 0.008$_5$ Å and strain energies of ~31 and ~4 cal/mol for the α and β chains, respectively.

There is, however, an alternative interpretation of these frequency shifts, involving hydrogen bonding of the N_δ proton of the proximal imidazole.[6-11] Partial donation of this proton to a H-bond acceptor is expected to increase the electron-donating propensity of N_ϵ and to strengthen the N_ϵ–Fe bond. Table I gives $\nu_{\mathrm{Fe-Im}}$ frequencies observed for deoxyHb model hemes, prepared with hindered imidazoles, 2-methylimidazole (2-MeImH) and 1,2-dimethylimidazole (1,2-diMeIm), to maintain five-coordination.[12] The band is at 220 cm^{-1} for (2-MeImH)Fe^{II}PP (PP = protoporphyrin IX) in water but 205 cm^{-1} for (2-MeImH)-Fe^{II}PPDME (PPDME = protoporphrin IX dimethyl ester) or (2-MeImH)Fe^{II}OEP (OEP = octaethylporphyrin) in benzene. The difference is not due to the solvent per se or to the porphyrin substituent alteration (required for solubility); (1,2-diMeIm)Fe^{II}PP in H_2O and (1,2-diMeIm)Fe^{II}PPDME in benzene both show $\nu_{\mathrm{Fe-Im}}$ at 195 cm^{-1}. For 2-MeImH, the difference is attributed to H bonding of the N_δ proton to solvent H_2O and a weakening of the H bond in benzene (some H bonding may persist, to dissolved H_2O or to excess 2-MeImH). In 1,2-diMeIm, H bonding is precluded because the N_δ proton is replaced by a methyl group. The decreased Fe–Im frequency in the 1,2-diMeIm complexes, 195 cm^{-1}, is ascribable partly to the increased ligand mass and partly to electronic effects. When (2-MeImH)Fe^{II}OEP in dimethylformamide is deprotonated with sodium *tert*-butoxide, $\nu_{\mathrm{Fe-Im}}$ shifts up from 212 to 239 cm^{-1} (Figure 1). This high frequency reflects the stronger electron donation by imidazolate than by imidazole. (Some H bonding may still be present in a reverse sense, to the bound 2-MeIm$^-$ from the solvent or from excess 2-MeImH in the solution.)

It is reasonable to suppose that the variability of $\nu_{\mathrm{Fe-Im}}$ in heme proteins[3b,4,13] may also be associated with changes in N_δ H bonding. A value of 244 cm^{-1} has recently been reported[13] for reduced horseradish peroxidase (HRP), and the possible role of proximal imidazole H bonding was briefly considered. On the basis of the present data, this frequency is consistent with a deprotonated proximal imidazole ligand, as has been inferred by Mincey and Traylor[14] from absorption spectral shifts. Strong H bonding might also be adequate to account for these spectral features. In Fe^{III}HRP there is NMR evidence[15a] for a proton at N_δ, which does not, however, exchange with solvent H_2O, in contrast to iron(III) myoglobin. It is of considerable interest that the crystal structure of the analogous cytochrome *c* peroxidase shows both a glutamine and a glutamate residue to be within H-bonding range of the proximal imidazole of N_δ.[15b] A carboxylate group would be an especially strong H-bond acceptor.

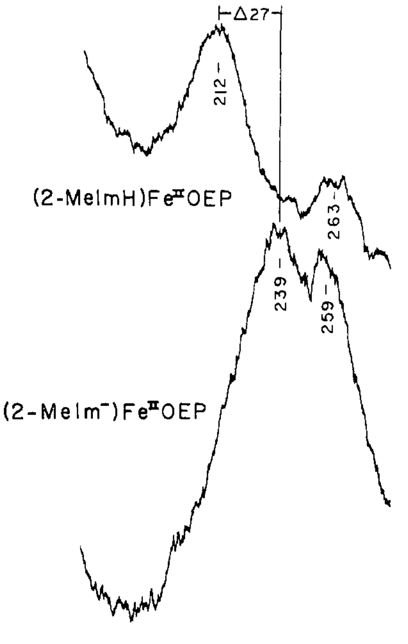

Figure 1. Low-frequency RR spectra of the 2-MeImH adduct of Fe^{II}OEP in DMF (~2 mM) before and after deprotonation with sodium *tert*-butoxide, showing the shift in $\nu_{\mathrm{Fe-Im}}$. Excitation, 457.9 mm, 100 mW; slit width, 10 cm^{-1}; sensitivity, 1000 hertz; scan rate, 0.5 cm^{-1}/s; time constant, 5 s.

In hemoglobin, the N_δ H-bond acceptor is a carbonyl oxygen of the peptide backbone.[16] On the basis of the present results, the observed lowering of $\nu_{\mathrm{Fe-Im}}$ suggests that this H bond is weakened in the T state, particularly in the α chains. A comparison to the X-ray crystallographic coordinates[16] for horse metHb and horse deoxyHb does indicate[11] that the α-chain H bond is indeed weakened in the T state, although the observed differences are of marginal significance in relation to the uncertainty in the coordinates.

The N_δ H bond may play a role in the modulation of heme oxygen affinity and in the mechanism of Hb cooperativity, as has been stressed by Peisach[6] and by Valentine[9-11] and their coworkers. The enhanced electron donation from imidazole to iron, attendant on N_δ H bonding, is also expected to increase the O_2 affinity, since O_2 is a π acid and there is extensive back-donation of iron d_π electrons in O_2Hb.[17] The lowered O_2 affinity of T state Hb could be due to weakened N_δ H bonds. The present interpretation of the Fe–Im frequency shifts is consistent with this hypothesis.

When interpreted as due to molecular tension, the $\nu_{\mathrm{Fe-Im}}$ shifts translate to only a few calories/mole of strain energy.[4] When interpreted as indicators of bond strength, however, they lead to much larger energy changes. The bond energy is expected (from the Morse potential, and from experimental data on related molecules[18]) to be proportional to the stretching force constant and therefore to the square of the stretching frequency (neglecting mixing with other modes). The percentage change in $\nu^2_{\mathrm{Fe-Im}}$ between R and T states is 13% for α chains and 4% for β chains. If the Fe–Im bond energy is ~10 kcal/mol (from the enthalpy of imidazole binding to Co^{II}PPDME[19]), then the change in bond

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(6) (a) Blumberg, W. E.; Peisach, J. *Adv. Chem. Ser.* **1971**, *100*, 271–291. (b) Peisach, J.; *Ann. N.Y. Acad. Sci.* **1975**, *244*, 187–202. (c) Peisach, J.; Mims, W. B.; *Biochemistry* **1977**, *16*, 2795–2799.

(7) Walker, F. A.; Lo, M.-W.; Ree, M. T. *J. Am. Chem. Soc.* **1976**, *98*, 5552–5560.

(8) Satterlee, J. D.; LaMar, G. N.; Frye, J. S.; *J. Am. Chem. Soc.* **1976**, *98*, 7275–7282.

(9) Nappa, M.; Valentine, J. S.; Snyder, P. A. *J. Am. Chem. Soc.* **1977**, *99*, 5799–5800.

(10) (a) Swartz, J. C.; Stanford, M. A.; Moy, J. N.; Hoffman, D. M.; Valentine, J. S. *J. Am. Chem. Soc.* **1979**, *101*, 3396–3398. (b) Stanford, M. A.; Swartz, J. C.; Phillips, T. E.; Hoffman, B. M. *Ibid.* **1980**, *102*, 4492–4499.

(11) Valentine, J. S.; Sheridan, R. P.; Allen, L. C.; Kahn, P. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 1009–1013.

(12) Collman, J. P.; Reed, C. A. *J. Am. Chem. Soc.* **1973**, *95*, 2048–2049.

(13) Teraoka, J.; Kitagawa, T. *Biochem. Biophys. Res. Commun.* **1980**, *93*, 694–700.

(14) Mincey, T.; Traylor, T. G. *J. Am. Chem. Soc.* **1979**, *101*, 765–766.

(15) (a) LaMar, G. N.; Ropp, J. S. *Biochem. Biophys. Res. Commun.* **1979**, *90*, 36–41. (b) Poulos, T. L.; Kraut, J. *J. Biol. Chem.*, in press.

(16) (a) Bolton, W.; Perutz, M.F. *Nature (London)* **1970**, *228*, 551–552. (b) Ladner, R. C.; Heidner, E. J.; and Perutz, M. F. *J. Mol. Biol.* **1977**, *114*, 385–414.

(17) (a) Spiro, T. G.; Strekas, T. C. *J. Am. Chem. Soc.* **1974**, *96*, 338–345. (b) Spiro, T. G.; Burke, J. M. *Ibid.* **1976**, *98*, 5482–5489.

(18) Nakamoto, K. "Infrared and Raman Spectra of Inorganic and Coordination Compounds"; 3rd ed.; Wiley-Interscience: New York, 1978.

energy is 1.3 and 0.4 kcal/mol for α and β chains. These values are significant on the scale of the free energy of cooperativity, ~3.4 kcal/mol (heme).[20] But the contribution is of the wrong sign, since the decrease in the Fe–Im bond energy implies a destabilization of the unligated heme in the T state and therefore an increase in the O_2 affinity, if everything else were equal. However, the H-bond effect is expected to be greater for O_2-heme and should outweigh the deoxy contribution. This is because the binding of the π-acid ligand O_2 should increase the polarization of the Fe–Im bond (there is much spectral evidence that the electron distribution in HbO_2 is similar to that in low-spin Fe^{III} hemes[17]) and thereby increase the strength of the N_δ H bond. Model calculations[11] suggest that the H-bond energy scale is more than adequate to support cooperativity. The key determinant is the strength of the H bond in the oxy forms of the R and T states. This could be monitored with ν_{Fe-Im}, but unfortunately, the Fe–Im mode has not yet been located in the RR spectrum of O_2-Hb.

Experimental. Aqueous (2-MeImH)Fe^{II}PP and (1,2-di-MeIm)Fe^{II}PP were prepared by adding an ~3-fold excess of 2-MeImH and sodium dithionite to an aqueous solution (~1 mM) of hemin chloride. The 2-MeImH and 1,2-diMeIm adducts of Fe^{II}PPDME and OEP were prepared by shaking the porphyrin-iron(III) chloride in benzene with aqueous sodium dithionite (buffered with Na_2HPO_4) containing 2-MeImH or 1,2-diMeIm. (2-MeImH)Fe^{II}OEP (~2 mM) in dimethylformamide (DMF) was prepared as follows: Fe^{III}OEPCl and an ~5-fold excess of 2-MeImH were dissolved in DMF and the solution was degassed by freeze–thawing in a transparent NMR tube in which Raman spectra were subsequently obtained via the spinning back scattering arrangement.[21] A small excess of solid sodium dithinoite and a small drop of water (for dithionite dissolution) were added to the frozen sample; the tube was evacuated and the sample was thawed under N_2. This complex was deprotonated by refreezing the sample, adding excess solid sodium *tert*-butoxide, sealing the tube under vacuum, and bringing the sample back to room temperature. A precipitate formed (probably sodium dithionite and hydroxide) and was spun to the bottom with a centrifuge. The Raman spectrum was obtained from the overlying solution via backscattering. The absorption spectrum showed peaks at 375, 427 (Soret), 515 (sh), 547 (β), 581 (α) nm compared to 361, 418 (Soret), 500 (sh), 543 (β) 575 (sh) nm for (2-MeImH)Fe^{II}OEP. These spectral shifts are similar to those observed by Mincey and Traylor[14] for the analogous PP complexes (but all PP specta are red-shifted relative to OEP due to the vinyl conjugation). The Raman spectrometer has been described elsewhere.[2]

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[19] Drago, R. S.; Beurgelsdijk, T.; Breese, J. A.; Canady, J. P. *J. Am. Chem. Soc.* **1978**, *100*, 5374-5381.

[20] Perutz, M. F. *Br. Med. Bull.* **1976**, *32*, 195-207.

[21] Shriver, D. F.; Dunn, J. B. R. *Appl. Spectrosc.* **1974**, *28*, 319.

Paul Stein, Melody Mitchell, Thomas G. Spiro*
Department of Chemistry, Princeton University
Princeton, New Jersey 08544

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Correlation of Kinetic Isotope Effects with Free Energies of Reaction

Sir:

Marcus rate theory[1] provides a particularly useful formalism for correlating rates and equilibria of proton-transfer reactions.[2] Application of the simple theory to kinetic isotope effects, however, leads to an expression which might be interpreted in a way which violates a basic tenet of isotope effect theory. We wish to show how this difficulty may be overcome.

Marcus theory relates the barrier for a chemical reaction, $\Delta G^{\ddagger}$, to its standard free energy change, ΔG°, through the parameter $\Delta G_0^{\ddagger}$, which is the value of $\Delta G^{\ddagger}$ when $\Delta G^{\circ} = 0$ (eq 1). This

$$\Delta G^{\ddagger} = (1 + \Delta G^{\circ}/4\Delta G_0^{\ddagger})^2\Delta G_0^{\ddagger} \qquad (1)$$

parameter is therefore a purely kinetic barrier free of any thermodynamic drive or impediment; it is generally called the intrinsic barrier and its magnitude serves to characterize the potential energy surface for a reaction series; i.e., it identifies the series as consisting of inherently slow or inherently fast reactions.[2,3]

An equation relating kinetic isotope effects to ΔG° may be obtained by taking the difference between two Marcus theory expressions of the form of eq 1.[1,2a,4] The assumption that there is no isotope effect on ΔG° ($\Delta G_H^{\circ} = \Delta G_D^{\circ} = \Delta G^{\circ}$, i.e., no equilibrium isotope effect) then leads to eq 2. This expression

$$\Delta G_H^{\ddagger} - \Delta G_D^{\ddagger} = (\Delta G_{0,H}^{\ddagger} - \Delta G_{0,D}^{\ddagger})[1 - (\Delta G^{\circ}/4(\Delta G_{0,H}^{\ddagger}\Delta G_{0,D}^{\ddagger})^{1/2})^2] \qquad (2)$$

predicts a parabolic dependence of the isotope effect $\Delta G_H^{\ddagger} - \Delta G_D^{\ddagger}$ upon ΔG° with a maximum effect, equal to the difference between H- and D-intrinsic barriers, $\Delta G_{0,H}^{\ddagger} - \Delta G_{0,D}^{\ddagger}$, occurring at $\Delta G^{\circ} = 0$. There is now considerable experimental support for such behavior.[4,5]

The fact that this expression contains different intrinsic barriers, however, might be taken to mean that the H and D reactions are intrinsically different in the sense that they occur on different potential energy surfaces. This, of course, is in violation of the fundamental principle upon which isotope effect theory is built, namely, that isotopic substitution does not alter the potential energy of a chemical system (Born–Oppenheimer approximation).[6] These intrinsic barriers as written in eq 2, however, are free energy quantities measured from vibrational energy levels which lie above potential energy minima, and isotopic substitution does alter vibrational energy levels. All of the difference between $\Delta G_{0,H}^{\ddagger}$ and $\Delta G_{0,D}^{\ddagger}$ may therefore be attributed to differences in isotopically sensitive vibrational energy levels situated in the same isotopically-invariant potential energy wells, and the principle of isotopically different reactions occurring on a single potential energy surface may thus be preserved. Unfortunately, it is not clear from the model upon which simple Marcus theory is based why isotopic vibrational energy differences should depend upon ΔG° in the parabolic fashion required by eq 2. Such dependence, however, can be obtained by combining Marcus theory with the Melander–Westheimer principle.[7]

Consider a system in which hydrogen is transferred between two heavy atoms, eq 3. Replacement of H by D will change the

$$\text{A-H} + \text{B} \rightarrow [\text{A-H-B}]^{\ddagger} \rightarrow \text{A} + \text{H-B} \qquad (3)$$

zero-point energy of the transition state of this reaction by an amount $\delta(\text{ZPE})^{\ddagger}$ whose magnitude, according to an idea first put forward by Melander and Westheimer,[7] will vary with the symmetry of the transition state. When the transition state is symmetrical in the sense that the partial bonds holding the atom being transferred are equal, $\delta(\text{ZPE})^{\ddagger}$ will have a minimum value, $\Delta(\text{ZPE})^{\ddagger}_{\text{min}}$. As dissymmetry is introduced in the form of reactant-like or product-like character, $\delta(\text{ZPE})^{\ddagger}$ will increase from this minimum value, and, in the limit of a completely reactant-like transition state, it will be equal to the isotopic zero-point energy

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[1] Marcus, R. A. *J. Phys. Chem.* **1968**, *72*, 891-9.

[2] (a) Cohen, A. O.; Marcus, R. A. *J. Phys. Chem.* **1968**, *72*, 4249-56. (b) Kresge, A. J. *Chem. Soc. Rev.* **1973**, *2*, 475-503.

[3] Kresge, A. J. *Acc. Chem. Res.* **1975**, *8*, 354-60.

[4] Kresge, A. J. In "Isotope Effects on Enzyme-Catalyzed Reactions"; Cleland, W. W., O'Leary, M. H., Northrup, D. B., Eds.; University Park Press: Baltimore, Md., 1977; Chapter 2. Kreevoy, M. M.; Oh, S.-W. *J. Am. Chem. Soc.* **1973**, *95*, 4805-10.

[5] (a) Bell, R. P. *Chem. Soc. Rev.* **1974**, *3*, 513-44. (b) More O'Ferrall, R. A. In "Proton Transfer Reactions"; Caldin, E. F., Gold, V., Eds.; Chapman and Hall: London; Chapter 8.

[6] See, e.g.; Melander, L.; Saunders, W. H. "Reaction Rates of Isotopic Molecules"; Wiley-Interscience: New York, 1980; p 7.

[7] Melander, L. "Isotope Effects on Reaction Rates"; Ronald Press: New York, 1960; pp 24-32. Westheimer, F. H. *Chem. Rev.* **1961**, *61*, 265-73.

0002-7863/80/1502-7797$01.00/0