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Kinetic Isotope Effect on Proton Tautomerism in Tetraarylporphyrins

S. S. Eaton*[1a] and G. R. Eaton*[1b]

Contribution from the Department of Chemistry, University of Colorado at Denver, Denver, Colorado 80202, and the Department of Chemistry, University of Denver, Denver, Colorado 80210.

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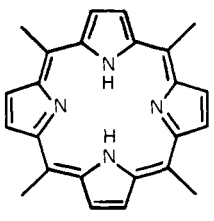
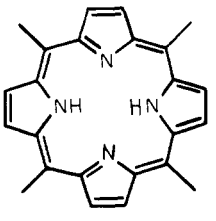
Abstract: Rates and activation parameters for proton and deuteron tautomerism in tetrakis(pentafluorophenyl)porphyrin, tetrakis(*p*-trifluoromethylphenyl)porphyrin, tetrakis(*p*-isopropylphenyl)porphyrin, and tetrakis(*p*-diethylaminophenyl)porphyrin have been obtained by variable-temperature proton NMR and total line shape analysis. Rates are independent of concentration, phenyl ring substituents, and solvent, consistent with a mechanism involving simultaneous movement of the two hydrogens through a symmetrical transition state. Based on six independent sets of data, the ratio of the rates for proton and deuteron tautomerism, k_H/k_D, at 298, 263, and 243 K is 19 ± 5, 32 ± 7, and 48 ± 14, respectively. The large values of k_H/k_D are attributed to simultaneous exchange of the two hydrogens.

Proton tautomerism in porphyrins was first demonstrated by Storm and Teklu using variable-temperature ^{1}H NMR.[2a] At slow exchange two pyrrole β-proton resonances were observed and were assigned to pyrrole rings with and without a proton on the pyrrole nitrogen. Tautomerism (I ⇌ II) averages



I



II

the two environments. The isotope effect on the rate of tautomerism, k_H/k_D, was first estimated to be 67 for tetraphenylporphyrin,[2b] but later a value of 12 was obtained by comparison of rates estimated from ^{1}H and ^{13}C NMR spectra at 35 °C.[3] Because of the widespread interest in porphyrins it appeared worthwhile to obtain more accurate estimates of the kinetic isotope effect by performing a total line shape analysis of the spectra over the full exchange region. It was also of interest to determine whether the isotope effect on proton tautomerism in porphyrins is a case in which the isotope effect relates to the exactly equivalent motion of two hydrogens.

Recent papers have shown that phenyl ring substituents in tetraarylporphyrins influence rates of copper ion incorporation,[4] equilibrium constants for piperidine binding to Ni^{2+}, Co^{2+}, and $(VO)^{2+}$ porphyrins,[5,6] equilibrium constants for pyridine coordination to Zn^{2+} and Co^{2+} porphyrins,[6,7] basicity of free porphyrins,[8] electronic spectra of free porphyrins,[8] and redox potentials of Ni^{2+} and Co^{2+} porphyrins and free porphyrins[6,9,10] in accordance with Hammett correlations. It was therefore of interest to determine whether similar effects would be observed for proton tautomerism.

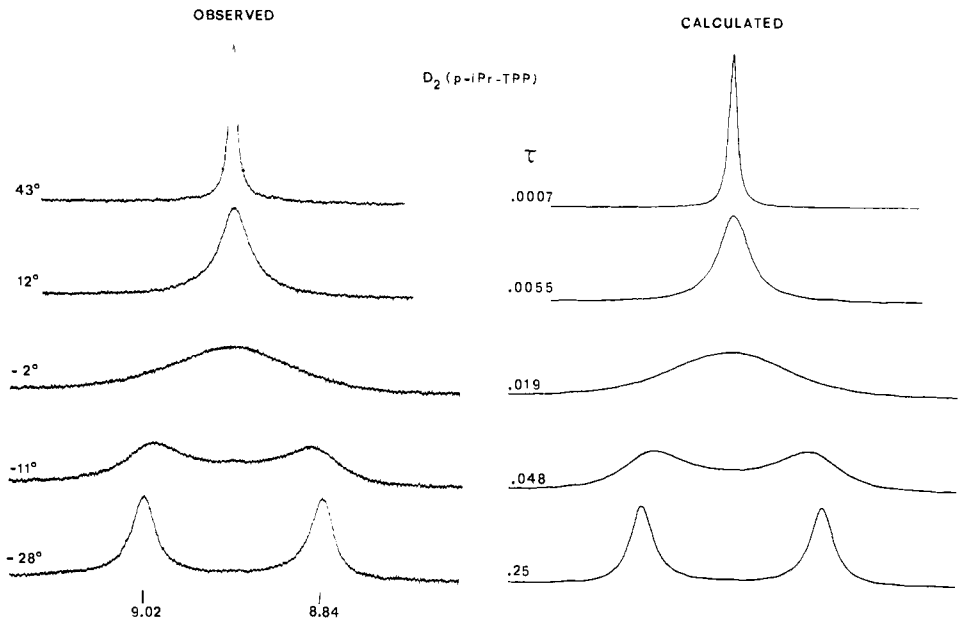


Figure 1. 100 MHz ^{1}H NMR spectra of the pyrrole protons in D_2(*p*-*i*-PrTPP) at various temperatures compared with spectra calculated by line shape analysis. Slow exchange chemical shifts are in ppm downfield of tetramethylsilane. τ values are in seconds.

Experimental Section

Porphyrins were prepared and characterized by literature methods: $H_2(F_5TPP)$,[11,12] H_2(*p*-CF_3TPP),[13] H_2(*p*-*i*-PrTPP),[14] and H_2(*p*-Et_2NTPP).[15] 1,1,2,2-Tetrachloroethane was distilled from P_2O_5 and stored under nitrogen. Dichloromethane and 1,1,2-trichloroethylene were purified by passage through alumina columns and stored under nitrogen. Methanol-d_1 was prepared by the method of Bunnett and Reinheimer[16] and found to be ca. 98% deuterated by NMR.

NMR spectra were run on freshly prepared samples. N-deuterated porphyrins were made in situ by addition of methanol-d_1 to the NMR samples. To make solutions for study of proton and deuteron tautomerism as similar as possible, methanol was added to the proton samples at the same concentration as methanol-d_1 was added to prepare the deuteron samples.

Proton NMR spectra were obtained on an HA-100 spectrometer equipped with a variable-temperature probe and operated at power levels well below saturation. Temperatures were calibrated after each set of data using a methanol standard and the temperature dependent shifts of Van Geet.[17] Temperatures are considered accurate to ±1.5 °C. Temperature calibrations were reproducible to ±0.5 °C. Chemical shifts in 1:2 C_2HCl_3:$C_2H_2Cl_4$ were measured with respect to $C_2H_2Cl_4$ and corrected to Me_4Si using 5.96 ppm as the chemical shift of $C_2H_2Cl_4$ at room temperature.

Room temperature chemical shifts in ppm from Me_4Si for the porphyrins in 1:2 C_2HCl_3:$C_2H_2Cl_4$ solution are: $H_2(F_5TPP)$; pyrrole-H, 8.93; N-H, −3.29; H_2(*p*-CF_3TPP); pyrrole-H, 8.82; *o*-H, 8.36; *m*-H, 8.04; N-H, −2.83; H_2(*p*-*i*-PrTPP); pyrrole-H, 8.92; *o*-H, 8.18; *m*-H, 7.63; CH, 3.23; CH_3, 1.53; N-H, −2.81; H_2(*p*-Et_2NTPP); pyrrole-H, 8.96; *o*-H, 8.07; *m*-H, 7.07; CH_2, 3.59; CH_3, 1.39; N-H, −2.58. Spectra for the deuterated analogues are identical except for the absence of the N-H signal. Chemical shift differences between nonequivalent pyrrole resonances at −60 °C were $H_2(F_5TPP)$, 23.6 Hz; H_2(*p*-CF_3TPP), 20.1 Hz; H_2(*p*-*i*-PrTPP), 18.5 Hz; and H_2(*p*-Et_2NTPP), 22.0 Hz. The same chemical shifts differences were observed in all cases for the proton and deuteron forms of the porphyrin.

Results

To determine optimum conditions for measurements, several initial experiments were performed on D_2(*p*-CF_3TPP). Variation of porphyrin concentration by a factor of 4 (2.1×10^{-2}, 1.0×10^{-2}, 5.0×10^{-3} M) caused no detectable changes in rate. Concentrations of 7.0×10^{-3} to 2.8×10^{-2} M (limited by solubility and signal-to-noise ratio) were used in subsequent studies. Identical rates were obtained whether MeOD or D_2O was added to the NMR sample to obtain the deuterated porphyrin. MeOD was used in all subsequent studies since it is miscible with the solvents used. When MeOH is added to a NMR sample of H_2(*p*-CF_3TPP), separate signals are observed at room temperature for porphyrin N-H and methanol O-H. Therefore under fast exchange conditions for proton tautomerism there is no evidence of exchange on the NMR timescale between porphyrin protons and methanol protons. Thus this process does not interfere with kinetic measurements.

Tautomerism was studied for $D_2(F_5TPP)$, D_2(*p*-CF_3TPP), D_2(*p*-*i*-PrTPP), D_2(*p*-Et_2NTPP), $H_2(F_5TPP)$, H_2(*p*-CF_3TPP), H_2(*p*-*i*-PrTPP), and H_2(*p*-Et_2NTPP) solutions in 1:2 1,1,2-trichloroethylene:1,1,2,2-tetrachloroethane over the full temperature range from slow to fast exchange. A typical set of pyrrole proton spectra for a porphyrin undergoing deuteron tautomerism is given in Figure 1. Similar line shape changes are observed about 40 °C lower for proton tautomerism. Calculated line shapes were obtained from the Lisle-Krieger-Whitesides program EXCNMR.[18] Chemical shifts were extrapolated from slow exchange values. Nonexchanging line widths were interpolated between slow and fast exchange limits. τ (s) is the mean preexchange lifetime of a pyrrole proton in a chemical shift environment. Thus $k = 1/\tau$ (s^{-1}) is the rate of exchange between pyrrole environments due to proton (or deuteron) tautomerism. τ values were determined by visual comparison of calculated and observed spectra and are considered accurate within 5 to 10% except near the slow and fast exchange limits where uncertainties are about 20%.

Activation parameters were obtained from weighted least-squares fits to Arrhenius ($\ln 1/\tau$ vs. $1/T$) and Eyring ($\ln h/kT\tau$ vs. $1/T$) equations with ten to twelve data points over a ca. 60 °C temperature range for each porphyrin. Values are presented in Table I. Uncertainties in parameters are ±3 standard deviations from the weighted least-squares lines. To check the reproducibility of the activation parameters, data for $D_2(F_5TPP)$ and D_2(*p*-Et_2NTPP) were each taken on two different samples on different days. The sets of data were analyzed independently and yielded parameters which agreed well within the stated uncertainties. For the two sets of data for $D_2(F_5TPP)$: $\Delta G^{\ddagger}_{298}$ = 13.8, 13.9; $\Delta H^{\ddagger}$ = 13.5, 12.9; $\Delta S^{\ddagger}$ = −1.0, −3.4; E_a = 14.1, 13.4; and for D_2(*p*-Et_2NTPP): $\Delta G^{\ddagger}_{298}$ = 13.9, 13.9; $\Delta H^{\ddagger}$ = 10.6, 11.0; $\Delta S^{\ddagger}$ = −10.9, −9.8; E_a = 11.2, 11.5 with units as in Table I. Values in Table I for these two compounds are based on a weighted least-squares

Table I. Activation Parameters for Tautomerism

Porphyrin	$\Delta G^{\ddagger}_{298}$, kcal/mole	$\Delta H^{\ddagger}$, kcal/mole	$\Delta S^{\ddagger}$, eu	E_a, kcal/mole
$H_2(F_5TPP)^a$	12.1 ± 1.4	10.0 ± 0.7	−7.1 ± 3.6	10.5 ± 0.9
$H_2(p\text{-}CF_3TPP)^a$	12.0 ± 1.5	10.1 ± 0.8	−6.4 ± 3.4	10.6 ± 0.8
$H_2(p\text{-}CF_3TPP)^b$	12.5 ± 1.0	9.1 ± 0.6	−11.4 ± 2.6	9.6 ± 0.6
$H_2(p\text{-}CF_3TPP)^c$	12.3 ± 1.0	10.0 ± 0.7	−8.0 ± 2.7	10.4 ± 0.7
$H_2(p\text{-}i\text{-}PrTPP)^a$	12.1 ± 1.0	9.4 ± 0.6	−8.9 ± 2.6	9.9 ± 0.6
$H_2(p\text{-}Et_2NTPP)^a$	12.0 ± 1.0	9.7 ± 0.6	−8.0 ± 2.7	10.1 ± 0.6
$D_2(F_5TPP)^{a,d}$	13.8 ± 1.0	13.2 ± 0.7	−2.1 ± 2.5	13.8 ± 0.7
$D_2(p\text{-}CF_3TPP)^a$	13.9 ± 1.0	11.8 ± 0.7	−6.9 ± 2.4	12.4 ± 0.7
$D_2(p\text{-}CF_3TPP)^b$	13.9 ± 1.2	12.2 ± 0.8	−6.0 ± 3.0	12.7 ± 0.7
$D_2(p\text{-}CF_3TPP)^c$	13.9 ± 0.8	12.2 ± 0.6	−5.6 ± 2.0	12.7 ± 0.6
$D_2(p\text{-}i\text{-}PrTPP)^a$	13.8 ± 1.5	12.9 ± 1.0	−2.8 ± 3.6	13.4 ± 1.0
$D_2(p\text{-}Et_2NTPP)^{a,d}$	13.9 ± 0.8	10.8 ± 0.7	−10.3 ± 2.0	11.4 ± 0.7

[a] In 1:2 1,1,2-trichloroethylene:1,1,2,2-tetrachloroethane solution. [b] In dichloromethane solution. [c] In methyl ethyl ketone solution. [d] Least-squares fit for two independent sets of data combined.

fit for two sets of data combined. Typical Arrhenius plots for proton and deuteron tautomerism are given in Figure 2 for $D_2(F_5TPP)$ and $H_2(F_5TPP)$. The close agreement between the two sets of data for $D_2(F_5TPP)$ is indicated.

Despite the large range in electron-donating and -withdrawing properties of the aryl substituents, the $\Delta G^{\ddagger}$ values are independent of substituent, in marked contrast to the results for other porphyrin processes[4-10] (vide infra).

To determine the effect of solvent on the rate of tautomerism, variable-temperature spectra were examined for $D_2(p\text{-}CF_3TPP)$ and $H_2(p\text{-}CF_3TPP)$ in dichloromethane and methyl ethyl ketone. Activation parameters (Table I) are unchanged, within experimental error, by the changes in solvent. Although the slight solubility of $D_2(p\text{-}CF_3TPP)$ in CS_2 precluded a full set of data, rates at several temperatures between 5 and 32 °C were within experimental uncertainty (10%) of those obtained with other solvents. Thus there appears to be no significant solvent effects on tautomerism in the diverse solvents examined.

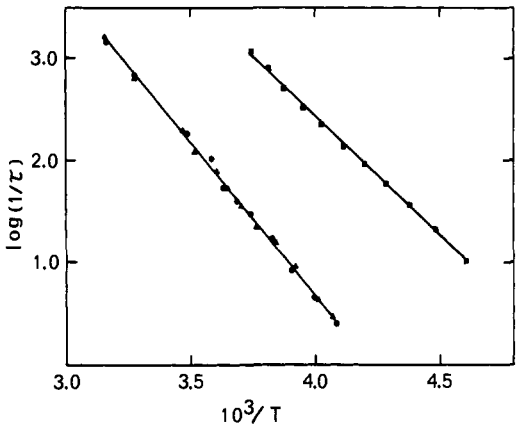
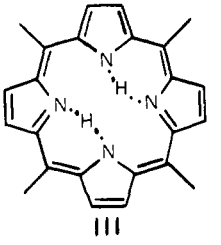


Figure 2. Arrhenius plots for proton and deuteron tautomerism; (■) $H_2(F_5TPP)$; (▲, ●) two independent sets of data for $D_2(F_5TPP)$.

Discussion

The rate of proton tautomerism in tetraarylporphyrins has been found to be independent of porphyrin concentration and independent of solvent. This evidence strongly suggests an intramolecular process with a nonpolar transition state. The absence of an effect by the aryl substituents on the rate of proton tautomerism is also significant. $\Delta G^{\ddagger}$ for copper incorporation into tetraarylporphyrins increases by about 1.5 kcal/mol from R = *p*-OMe to R = *p*-CN.[4] The acid dissociation constants for tetraarylporphyrins increase by about 2.5 pK units from R = *p*-CN to R = *p*-OH.[8] Thus the ring substituent effects are clearly transmitted to the porphyrin nitrogens. The differences in electron-donating and -withdrawing properties between $H_2(F_5TPP)$, $H_2(p\text{-}CF_3TPP)$, $H_2(p\text{-}i\text{-}PrTPP)$, and $H_2(p\text{-}Et_2NTPP)$ span a greater range of Hammett σ values than the two studies cited above, yet with no change in $\Delta G^{\ddagger}$ for proton or deuteron tautomerism. These observations suggest that in the transition state the protons (deuterons) are partially bonded to two nitrogens with the loss of bonding to one nitrogen compensated by bonding to the second nitrogen. All available evidence is consistent with simultaneous movement of the two hydrogens through a symmetrical transition state, III.

Since four porphyrins were studied and $H_2(p\text{-}CF_3TPP)$ and $D_2(p\text{-}CF_3TPP)$ were studied in three solvents, there are six independent measurements of k_H/k_D. The average of the six measurements of k_H/k_D is 19 at 298 K with a standard deviation of 5 and a range of 12 to 25. Since the data for proton tautomerism have to be extrapolated to obtain rates at 298 K,



III

the isotope effect was also evaluated at 263 and 243 K which are in the intermediate exchange region for both proton and deuteron tautomerism. At 263 and 243 K the ratio k_H/k_D is 32 ± 7 and 48 ± 14, respectively. Bell has calculated that the maximum semiclassical isotope effect, k_H/k_D, for breaking an N-H bond is 11, 15, and 20 at 298, 263, and 243 K, respectively.[19] Thus the isotope effect observed for proton tautomerism is consistently greater than the calculated values. As initially pointed out by Storm et al.,[2b] simultaneous movement of the two protons (deuterons) would contribute to an enhanced isotope effect. If two N-H vibrations are largely eliminated in the transition state, the isotope effect at 298 K could be 70-80.[19] According to Bell's semiclassical calculations, the ratio of the isotope effect for simultaneous exchange of the two protons to the isotope effect for breaking a single N-H bond increases with decreasing temperature.[19] The ratio of the experimental isotope effect for proton tautomerism to the isotope effect calculated for breaking a single N-H bond increases with decreasing temperature. Thus the temperature dependence of the isotope effect is qualitatively in agreement with

a mechanism involving simultaneous movement of the two hydrogens.

The possibility that the large isotope effect is primarily due to quantum mechanical tunneling appears less likely for several reasons. (1) The Arrhenius plots are not curved. (2) The preexponential factors and values of $\Delta S^{\ddagger}$ are not significantly different for proton and deuteron tautomerism. (3) If the two protons move simultaneously, then the mass for tunneling would be 2 amu (rather than 1 amu as in single proton transfers), substantially decreasing the tunneling contribution to the rate of proton tautomerism relative to the case of movement of one proton.

Thus the porphyrin proton tautomerism rate data are consistent with a mechanism involving simultaneous movement of two hydrogens via a symmetrical transition state and do not compel interpretation in terms of a tunneling process. The porphyrins are believed to be the only class of compounds in which the exactly equivalent motion of two hydrogens has been observed to give a kinetic isotope effect.

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Synthesis and Reactions of the Highly Mutagenic 7,8-Diol 9,10-Epoxides of the Carcinogen Benzo[*a*]pyrene

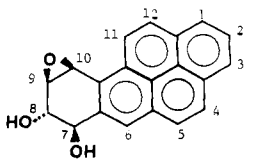
H. Yagi, D. R. Thakker, O. Hernandez, M. Koreeda,[1] and D. M. Jerina*

Contribution from the Laboratory of Chemistry, National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health, Bethesda, Maryland 20014. *Received July 6, 1976*

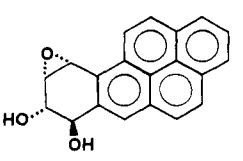
Abstract: Stereoselective syntheses are described for the preparation of the two possible diastereoisomeric epoxides at the 3,4-position of *trans*-1,2-dihydroxy-1,2-dihydronaphthalene and at the 9,10-position of *trans*-7,8-dihydroxy-7,8-dihydrobenzo[*a*]-pyrene. Both of the highly mutagenic diol epoxides from benzo[*a*]pyrene undergo trans addition at C-10 of the epoxide ring with methoxide, *p*-nitrothiophenolate, or aniline as nucleophiles. On solvolysis in water, the diol epoxide from benzo[*a*]pyrene, in which the benzylic hydroxy group is cis to the oxirane ring, undergoes mainly cis addition of water at C-10 to produce tetraols, while the other isomer, which cannot form an intramolecular hydrogen bond between the benzylic hydroxy group and the oxirane oxygen, suffers mainly trans hydration. The structures of the four tetraols were assigned by the NMR spectra of their acetates and by direct synthesis in some cases. The remarkable reactivity of the two diol epoxides from benzo[*a*]pyrene is emphasized by their ability to alkylate aqueous inorganic phosphate at pH 7.

In a recent preliminary report,[2] we have described the synthesis and stereochemical assignment of the two isomeric 9,10-epoxides of (±)-*trans*-7,8-dihydroxy-7,8-dihydrobenzo[*a*]pyrene, which are known metabolites[3] of the environmental carcinogen benzo[*a*]pyrene. These two stereoisomers, (±)-7β,8α-dihydroxy-9β,10β-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene (diol epoxide **1**) and (±)-7β,8α-dihydroxy-9α,10α-7,8,9,10-trahydrobenzo[*a*]pyrene (diol epoxide **2**), are of substantial chemical and biological interest.

These isomers are chemically interesting in that the benzylic hydroxy group at C-7 can intramolecularly hydrogen bond to the oxygen of the oxirane ring in diol epoxide **1**, whereas such an intramolecular hydrogen bond is not possible for diol epoxide **2**.[2,4,5] In structurally related epoxysterols[6,7] and the antileukemic agent triptolide,[8] intramolecular hydrogen bonding of this type causes as much as a 20-fold acceleration in rate for the attack of nucleophiles on the oxirane ring due to anchimeric assistance by a proximate *cis*-hydroxy group.



diol epoxide 1



diol epoxide 2