Kinetic HH/HD/DH/DD Isotope Effects on Nondegenerate Stepwise Reversible Double Proton Transfer Reactions. NMR Study of the Tautomerism of meso-Tetraphenylchlorin

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Abstract: The tautomerism of meso-tetraphenylchlorin-15N4 (TPC) has been studied by dynamic 1H NMR spectroscopy. Only two degenerate tautomers of TPC, AC and CA, are observed whose structure corresponds to 5,10,15,20-tetraphenyl-7,8-dihydroporphyrin. Thus, the IUPAC name 5,10,15,20-tetraphenyl-2,3-dihydroporphyrin proposed for TPC is incorrect. Both tautomers interconvert via a mutual proton exchange process along two different routes. The rate constants of the tautomerism are given by k_{AC-CA}^{HH} = 10^{11.4\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{DD} = 10^{11.5\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{HH} = 10^{11.4\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{DD} = 10^{11.5\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{HH} = 10^{11.4\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{DD} = 10^{11.5\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{HH} = 10^{11.4\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{DD} = 10^{11.5\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{HH} = 10^{11.4\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{DD} = 10^{11.5\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{HH} = 10^{11.4\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{DD} = 10^{11.5\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{HH} = 10^{11.4\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{DD} = 10^{11.5\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{HH} = 10^{11.4\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{DD} = 10^{11.5\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{HH} = 10^{11.4\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{DD} = 10^{11.5\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{HH} = 10^{11.4\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{DD} = 10^{11.5\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{HH} = 10^{11.4\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{DD} = 10^{11.5\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{HH} = 10^{11.4\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{DD} = 10^{11.5\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{HH} = 10^{11.4\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{DD} = 10^{11.5\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{HH} = 10^{11.4\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{DD} = 10^{11.5\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{HH} = 10^{11.4\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{DD} = 10^{11.5\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{HH} = 10^{11.4\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{DD} = 10^{11.5\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{HH} = 10^{11.4\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{DD} = 10^{11.5\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{HH} = 10^{11.4\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{DD} = 10^{11.5\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{HH} = 10^{11.4\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{DD} = 10^{11.5\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{HH} = 10^{11.4\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{DD} = 10^{11.5\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{HH} = 10^{11.4\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{DD} = 10^{11.5\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{HH} = 10^{11.4\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{DD} = 10^{11.5\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{HH} = 10^{11.4\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{DD} = 10^{11.5\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{HH} = 10^{11.4\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{DD} = 10^{11.5\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{HH} = 10^{11.4\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{DD} = 10^{11.5\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{HH} = 10^{11.4\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{DD} = 10^{11.5\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{HH} = 10^{11.4\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{DD} = 10^{11.5\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{HH} = 10^{11.4\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{DD} = 10^{11.5\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{HH} = 10^{11.4\pm0.2} \text{ s}^{-1}, k_{AC-CA}^{DD} = 10^{11.5\plus
or C. In each elementary step the proton in flight contributes a primary kinetic isotope effect by observing strong kinetic solvent effects in one case where the double proton transfer was further corroborated independently in the case of the intermolecular reactions studied.24 Each of the deviations from the RGM were larger since it was found that

\[ k^{HH} \gg k^{HD} = k^{DH} \approx 2k^{DD} \]  

(2)

By use of formal kinetics this result could be modeled in terms of a stepwise proton motion as shown in Figure 2 where the reactant A and the product D interconvert via two consecutive single proton transfer steps involving an intermediate, either B or C. In each elementary step the proton in flight contributes a primary kinetic isotope effect \( P \) and the bound proton a secondary kinetic isotope effect \( S \) to the reaction rates. Depending on the type of reaction studied, \( P \) was found to be enhanced by proton tunneling.24 This interpretation of stepwise intramolecular double proton transfer was further corroborated independently by observing strong kinetic solvent effects in one case where the intermediate was expected to have a zwitterionic structure.6

The result of eq 2 applies, however, only to the case where the reactant A and the product D as well as the two intermediates B and C are degenerate. In this study we explore, therefore, theoretically and experimentally the more general problem of multiple kinetic hydrogen/deuterium isotope effects in stepwise double proton transfer reactions in the case where the equilibrium constant of the reaction studied is no longer unity. \( k^{HD} \) and \( k^{DH} \) are then no longer equivalent as in the degenerate case. Non-degenerate double proton transfer reactions play an important role in a number of organic and biochemical reactions systems.8–12 A theory of kinetic isotope effects of such reactions has been developed by Albery et al.10,11 in a form convenient for use in kinetic studies of irreversible reactions. We will adapt here the theory for use in dynamic NMR spectroscopy of reversible reactions. The theory will be applied to evaluate the kinetic isotope effects of the tautomerism of the inner protons in 5,10,15,20-tetraphenyl chlorin (TPC) according to Figure 3. Evidence for this process was found recently by NMR line-shape analysis of the inner proton signal of \(^{15}N\)-labeled TPC dissolved in organic solvents.17 Note that chlorins are also subject to phototautomerism in the solid state.18 The full proton transfer pathways of the chlorin tautomerism are shown in Figure 4. This reaction

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network includes all possible intermediates of the reaction. The different tautomers in Figure 4 are characterized by the type of pyrrole unit to which they are attached. Because of the chemical perturbation, the tautomers BD (DB) and the tautomers AC (CA) are no longer equivalent, in contrast to the symmetrically substituted porphyrins. As mentioned above eq 2 was found to be valid for the latter, indicating a stepwise proton transfer mechanism. It was now interesting for us to see how the kinetic isotope effects are influenced by chemical perturbation.

This paper is organized as follows. First we describe the theory of kinetic HH/HD/DH/DD isotope effects of the general stepwise double proton transfer reaction shown in Figure 2. Then we show that for the evaluation of the kinetic isotope effects the complex reaction network of chlorin shown in Figure 4 can be reduced to the simpler network of Figure 2. We then describe the experimental details of the synthesis of iN-labeled TPC and of the dynamic NMR experiments. After the Experimental Section the results on TPC are presented and discussed.

Theoretical Section

In the first part of this section we derive expressions for the kinetic HH/HD/DD/DD isotope effects of the reaction network in Figure 2, where B and C are intermediates of the reaction from A to D. We consider the case of a reversible reaction with an equilibrium constant $K_{AD} \neq 1$. In previous studies either the symmetric case with $K_{AD} = 1$ or the irreversible case with $K_{AD} \rightarrow \infty$ was treated. In the second part we consider a more complicated reaction network, which applied to the case of TPC. Note that all results are based on formal kinetics; thus, no reference is made to a particular kinetic theory such as transition state or tunneling theories, although we will use the former in order to illustrate some results. As a consequence, the equations derived are valid both for reactions over the barrier and for the case of tunneling.

Kinetic HH/HD/DD/DD Isotope Effects in the Case of a Double Proton Transfer Involving Two Stable and Two Metastable Tautomeric States. Using the usual steady-state approximation for the intermediates, one can easily derive the following expression for rate constants of the overall reaction A to D in Figure 2:

$$k_{L_{1}L_{2}} = \frac{k_{L_{1}L_{2}}}{k_{L_{1}L_{2}}} + \frac{k_{L_{1}L_{2}}}{k_{L_{1}L_{2}}} \cdot k_{L_{1}L_{2}}$$

Note that $k_{L_{1}L_{2}}$ is a double proton transfer rate constant where $L_{1}$ is the isotope transferred in site a of the molecule (e.g., between X and U in Figure 2) and $L_{2}$ is the isotope transferred in site b (e.g., between X and Y in Figure 2). By contrast, all kinetic quantities on the right-hand side of eq 3 are single hydrogen transfer rate constants. Then, $L_{1}$ is the proton in flight and $L_{2}$ the bound hydrogen isotope, the nonreactive mobile proton site.

Let us define the primary and secondary kinetic isotope effects $p_{L_{1}L_{2}}$ and $S_{L_{1}L_{2}}$:

$$p_{L_{1}L_{2}} = \frac{k_{L_{1}L_{2}}}{k_{L_{1}L_{2}}}, \quad S_{L_{1}L_{2}} = \frac{k_{L_{1}L_{2}}}{k_{L_{1}L_{2}}}$$

Note that in the absence of isotopic fractionation between all reactants and intermediates, i.e., in the absence of equilibrium isotope effects between the latter, the following relations hold:

$$p_{H_{1}H_{2}} = p_{D_{1}D_{2}} = p_{H_{1}D_{2}} = p_{D_{1}H_{2}}, \quad S_{H_{1}H_{2}} = S_{D_{1}D_{2}} = S_{D_{1}H_{2}} = S_{H_{1}D_{2}}$$

It is convenient to define according to Albery splitting factors of the type:

$$k_{1} = k_{A_{1}A_{2}}/k_{A_{1}A_{2}}, \quad k_{2} = k_{A_{1}A_{2}}/k_{A_{1}A_{2}}, \quad k_{3} = k_{A_{1}A_{2}}/k_{A_{1}A_{2}}, \quad k_{4} = k_{A_{1}A_{2}}/k_{A_{1}A_{2}}$$

By introducing eqs 4 and 6 into eq 3 one can obtain expressions for $k_{L_{1}L_{2}}$, listed as eqs A7–A11 in the Appendix. In order to discuss eq A7–A11, it is useful to have a look at some special cases.

Double-Sided Degenerate Stepwise Double Proton Transfer. If A and D as well as B and C are degenerate it follows that:

$$k_{1} = k_{2} = k_{3} = k_{4} = 1$$

Assuming the validity of eq 5, eqs A7–A11 simplify then to the following expressions derived previously:

$$k_{H_{1}H_{1}D_{D}} = k_{H_{1}H_{1}D_{D}}$$

$$k_{H_{1}H_{1}D_{D}} = k_{H_{1}H_{1}D_{D}} = \frac{2}{P + S}, \quad k_{A_{1}A_{2}} = \frac{2}{P + S}$$

$$k_{A_{1}A_{2}} = \frac{(PS)^{-1}}{k_{A_{1}A_{2}}}, \quad (PS)^{-1} = k_{A_{1}A_{2}}$$

For the case where $P \gg 1$ and $S \equiv 1$, eq 2 follows directly from eqs 8–10. Equations 8–10 can be visualized in the free energy diagram shown in Figure 5. In all isotopic processes there are two equivalent pathways via either intermediate B or C. The initial and final states A and D as well as the two intermediates B and C have two bound hydrogen isotopes, leading to three isotopic states of different energy, containing either mobile HH, HD, or DD isotopes. By contrast, the states where one hydrogen isotope in flight are characterized by only two isotopic states of different energy because there is only one bound hydrogen isotope. Note that the term "state with a hydrogen isotope in flight" can be either a conventional transition state or a state where the isotope tunnels from a thermally activated state through the reaction energy barrier. Let us first compare the HH and the DD reaction profiles in Figure 5. Both profiles are symmetric. Therefore, a problem of internal return arises in the sense that the intermediate reacts to D only with a probability of $1/2$ and returns with the same probability to A. The factor of $1/2$ entering the expression for $k_{A_{1}A_{2}}$ and $k_{A_{1}A_{2}}$ is, however, canceled in eqs 8 and 10 because there are two equivalent pathways via B and via C for all isotopic reactions. The DD reaction is slower than the HH reaction because of the loss of zero point energy of the XH/XD stretching vibration in the transition states. By contrast, the reaction profile of the HD
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process is asymmetric and the transition states E and G (and F and H) are now no more equivalent. Therefore, the problem of internal return is absent. If one neglects secondary kinetic isotope effects, the energy necessary to reach the H transition states is similar to that in the HH process and the energy necessary to reach the D transition states is similar to that in the DD case. The D transfer step constitutes, therefore, the rate-limiting step of the reaction. The HD reaction has then the same free energy of activation as the DD reaction; however, since in the HD reaction all molecules that have passed the transition state react to products by contrast to the DD reaction, it follows that

$$k_{D}^{D} = k_{D}^{D} = k_{D}^{D}$$

(19)

Let us first discuss the case where A and D are degenerate, i.e., where \( \kappa = 1 \). The results are similar to eqs 8-10, with the difference that the right-hand sides of eqs 8-10 are multiplied by a factor of \( \sqrt{A_{k_b}} \). This result means that, in practice, a single- and a double-sided degenerate proton transfer cannot be distinguished experimentally.

Let us now discuss another limiting case of eqs 12-15 where \( \kappa \gg 1 \). Then

$$k_{D}^{D} = k_{D}^{D} / \kappa = k_{D}^{D} / \kappa = k_{D}^{D}$$

(16)

$$k_{D}^{D} = k_{D}^{D} / \kappa = k_{D}^{D} / \kappa = k_{D}^{D}$$

(17)

$$k_{D}^{D} = k_{D}^{D} / \kappa = k_{D}^{D} / \kappa = k_{D}^{D}$$

(18)

$$k_{D}^{D} = k_{D}^{D} / \kappa = k_{D}^{D} / \kappa = k_{D}^{D}$$

(19)

These results can again be visualized in a free energy diagram as shown in Figure 6. Let us first consider the HH reaction. Since the transition state H is higher in energy than G, the pathway characterized by the broken line does not contribute to the reaction rates. For the sake of simplicity, this pathway is, therefore, no longer discussed in the other isotopic reactions; only the favored pathway characterized by the solid line that involves the transition states E and G is considered further. Since \( \kappa \gg 1 \), transition state E does not influence the reaction rates but only the equilibrium \( A = B \). The true transition state of the reaction in all isotopic reactions is G. The DD reaction is slower than the HH reaction because in the DD case one needs one more XH/XD zero point energy difference in order to reach G than in the HH case. Thus, neglecting secondary kinetic isotope effects, the DH reaction is as fast as the HH reaction. By contrast, in the HD reaction the D isotope is transferred in the rate-limiting step. Therefore, the HD reaction is as slow as the DD reaction.

Double Hydrogen Transfer Including Mutual Proton Exchange. In this section we expand the reaction network of Figure 2 and allow the mutual exchange of the two jumping protons according to Figure 7. This case is relevant for the tautomerism of asymmetrically substituted porphyrins13-15 and of chlorin.16,17 We will

Figure 6. Free energy diagram for a nondegenerate stepwise double hydrogen transfer reaction according to Figure 2 and eqs 16-19. The secondary kinetic isotope effect \( S \) was set to unity.
show that in the presence of molecular symmetry the network of Figure 7 can be reduced to the network of Figure 2 as far as the evaluation of kinetic isotope effects is concerned.

In order to define the different processes in Figure 7 we have to expand our notation. It has been shown useful in the case of evaluation of kinetic isotope effects.

Figure 7. Extended double proton transfer reaction with four stable and eight metastable states. \( L_a = HH, HD, DH, DD \).

Furthermore, in the case of \( LL = HH, DD \)

Thus, the overall quadrupole proton transfer rate constants \( k_{AC}^{HH} = k_{AC}^{DD} \) can be reduced to the double proton transfer rate constants \( k_{AC}^{HH} - DB, LL = HH, HD, DD, DD \) with the intermediates AB and DC. By use of the transcription \( A = AC, B = DC, C = AB, D = DB \), the equations of the previous paragraph can be adapted for the evaluation of the kinetic isotope effects.

The splitting factors (eq 6) are then given by

\[
\begin{align*}
\kappa_1 &= \frac{k_{AC}^{HH} - DB}{k_{AC}^{AB}} \\
\kappa_2 &= \frac{k_{AC}^{HH} - DD}{k_{AC}^{AB}} \\
\kappa_3 &= \frac{k_{AC}^{HH} - DB}{k_{AC}^{AB}} \\
\kappa_4 &= \frac{k_{AC}^{HH} - DB}{k_{AC}^{AB}}
\end{align*}
\]

For the case where the cis tautomers with a hydrogen isotope bound on site B, i.e., AB, BC, CB, and BA are considerably raised in energy as compared to the other cis tautomers, i.e., when

\[
\kappa_1 = \frac{k_{AC}^{HH} - DC}{k_{AC}^{AB}} \gg 1
\]

it follows from eq 12-15 that

\[
\begin{align*}
k_{AC}^{HH} - DB &= \frac{1}{1 + \kappa} k_{AC}^{HH} - DC \\
k_{AC}^{HH} - DB &= \frac{1}{S + P} k_{AC}^{HH} - DC \\
k_{AC}^{HH} - DB &= \frac{1}{P + S} k_{AC}^{HH} - DC \\
k_{AC}^{HH} - DB &= \frac{1}{1 + \kappa} P S k_{AC}^{HH} - DC
\end{align*}
\]

These equations will be used to evaluate the experimental kinetic isotope effects of the tautomism of TPC.

Experimental Section

Synthesis of \(^ {1}H\)-Labeled meso-Tetraphenylchlorin (TPC). For the preparation of hydroxyporphyrines, different methods have been proposed.\(^ {19,20}\) Since we wanted to study all reduction products of meso-tetraphenylporphyrin, i.e., \(^ {1}H\)-meso-tetraphenylchlorin, we used the reduction of porphyrin (TPP) with diimide described by Whitlock et al.\(^ {19}\) with toluenesulfonic hydrazide as diimide precursor,
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with a subsequent chromatographic separation of all reaction products. The starting compound meso-tetraphenyldoporphin-15N4 (TPP) was synthesized according to Adler et al.11 using 15N-labeled pyrrole (95% 15N; Fa. Hempel, Düsseldorf, Germany) as reactant. We then proceeded as follows.

In a double-necked round-bottom flask with reflux, drop funnel, and nitrogen stream, 53 mg of TPP was dissolved in 5 mL of dried and nitrogen-saturated pyridine. Then, 450 mg of dried K2CO3 was added. The mixture was stirred with a magnet bar and heated to 105 °C. From the funnel 500 mg of toluenesulfonic hydrazide dissolved in 25 mL of dried pyridine was added dropwise over 6 h. The reaction mixture was poured into a mixture of 100 mL of water and 200 mL of toluene and stirred on a water bath for about 1 h. The toluene phase was separated under a nitrogen stream and after cooling to room temperature it was washed with (i) 3 N ice-cold HCl, (ii) with water, (iii) with a bicarbonate solution, and (iv) twice with water. The yield was 20 mg of TPC (~40% of theory).

In order to separate the chlorin from remaining porphyrin and from bacteriochlorin, extraction with phosphoric acid19 was found not to be practicable. The reaction products were, therefore, separated by medium-pressure liquid chromatography (MPLC) with silica (LiChroprep Si 60; Merck) as stationary phase and cyclohexane/dichloromethane as liquid phase. Since silica tends to decompose porphyrins and hydroprophyrins because of its acidity, we added 1% pyridine to the solvent in order to deactivate the solid phase.

Sample Preparation. Sealed NMR samples with a diameter of 5 mm were prepared on a vacuum line as described previously.14 Both toluene-d8, dried over potassium/sodium alloy, and tetrachloroethane-d2 were used as solvents. The deuterium fraction in the mobile proton sites was either D = 0 or D = 0.85. The deuteration was carried out using a mixture of the CH3OD, dried over molecular sieve, and the organic solvent.

NMR Measurements. The 1H NMR spectra were measured with the pulse FT NMR spectrometers, Bruker CXP 100 working at 90.02 MHz and Bruker MSL 300 working at 300.13 MHz. The sample temperatures were calibrated before and after the NMR measurements with a PT 100 resistance thermometer (Degussa), imbedded in an NMR tube, and are estimated to be accurate to about 0.5 °C. The spectra were transferred from the Bruker Aspect 2000 and 3000 minicomputers to a PC and then to a mainframe UNIVAC 1108/12 computer of the Rechenzentrum der Universität Freiburg. Kinetic parameters were obtained by simulation of the spectra, as described previously6 for the 1H-15N signals of 15N-labeled azophenine.

The initial experiments at D = 0 were performed with tetrachloroethane-d2 as solvent. However, in these experiments it was found that this solvent decomposes slowly at higher temperatures. The experiments were, therefore, repeated with toluene-d8 as solvent. No kinetic solvent effect on the reaction rates could be observed. Therefore, samples with D = 0.85 were prepared only with the latter solvent. Samples with D = 0 were measured with tetrachloroethane-d2 and toluene-d8 as solvents.

Results

In the first stage of this study we tried to obtain information on the tautomerism of TPC by carefully studying the NMR signals of the nonmobile protons of TPC, which should be modulated when a two-proton jump occurs in this molecule. However, these signals did not show significant changes with temperature. The β-pyrrole protons 17 and 18 (for the atom numbering see Figure 3) give rise to a singlet at δ = 8.34 ppm. The hydrogen atoms 2 and 3 (as well as 12 and 13) form with the corresponding 15N atoms an AA'XM'Y spin system, with 1J(2,15N) = 8.15 ppm, 1J(3,15N) = 8.52 ppm, 1J(AA') = 3.8 Hz, and 1J(XM') = 3.7 Hz. Since these signals do not show signs of a tautomerism of the inner protons, it follows that the tautomers BD and DB in Figure 4 are not directly observable by 1H NMR spectroscopy.

The line-shape analysis of the signal of the inner protons, measured at 90.02 MHz, was more successful, as shown in Figure 8. Because of the aromatic ring current this signal appears at high field, i.e., between -1 and -1.5 ppm, depending on the solvent. At room temperature the signal is split into a doublet by scalar coupling with one 15N spin. Note that only one single 1H-15N signal is observed, which indicates that both inner hydrogen atoms of TPC have the same chemical shifts. This result is only consistent with the structures AC and CA in Figure 4. In the tautomerism BD and DB as well as in all cis tautomers the inner hydrogen atoms would experience different chemical shifts. As the temperature is raised, a doublet-triplet interconversion occurs, with an exchange-broadened central triplet line. This phenomenon arises from a fast intramolecular exchange of the two inner protons. The triplet arises because in this regime, within the NMR time scale, each proton is coupled to the 15N spins of the rings A and C. No scalar coupling to the 15N atoms in rings B and D is observed, indicating that the tautomers BD and DB are not populated to an observable extent, in agreement with the observations of the signals of the nonmobile protons. A small population of the latter tautomers should lead to an additional splitting of the triplet lines, as was previously found for acetylporphyrin.15 Therefore, one can say that the inner proton signal of TPC is sensitive to the four-proton transfer AC → CA (see Figure 4), described by the rate constants kAC-CA. By the line-shape theory described previously1-5 these constants could be determined by simulation of the spectra at D = 0, as shown in Figure 8. Line-shape analysis is facilitated here by the fact that the outer lines of the triplet are not affected by the exchange; they provide, therefore, both the line width \( W/2 \) in the absence of exchange and the coupling constant \( J_{1H,15N} \) needed in order to extract the kinetic information from the center line.5 In the top of Figure 8 it may be noted that there is a line broadening at high temperature when tetrachloroethane-d2 is used as solvent; this broadening is ascribed to intermolecular proton exchange due to acid impurities formed by thermal composition of the solvent; this extra line broadening is absent when using toluene-d8 as solvent. Nevertheless, the intramolecular proton transfer rates obtained by simulation are not affected by the intermolecular exchange in the spectra of Figure 8. No kinetic solvent effect was observed within the margin of error of our experiments.

In order to obtain information on the kinetic HH/HD isotope effects on the reaction rates, a line-shape analysis of the inner proton signals of TPC was carried out at D = 0.85 using toluene-d8 as solvent. Since the deuteration strongly decreased the signal to noise ratio, the experiments had to be performed at 300 MHz. The results are shown in Figure 9. Note that the use of a higher magnetic field strength does not influence the exchange-broadened

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outer signal components are sharp at all temperatures, indicating species were taken into account in the simulations. Note that the spectra stem from a toluene-d8 with deuterium fraction; W,, determined from the nonexchanging components of the IH-15N signal. *Calculated according to eq 39.

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*Solvent: Tol, toluene-d8; TCE, tetrachloroethane-d2. Method: NH, I'H NMR line-shape analysis of the 15N-I'H signals. Δν = Δν_{IH-15N} = k_{LL_{IC-CA}} - k_{HH_{IC-CA}}. LL = HH and HD; D, deuterium fraction; W., determined from the nonexchanging components of the I'H-15N signal. *Calculated according to eq 39.

Figure 9. Superposed experimental and calculated 300-MHz I'H NMR spectra of the inner protons of HD tetraphenylchlorin-15N4 as a function of temperature. The spectra stem from a ~10 mmol/L solution in toluene-d8 with D = 0.85. Acquisition parameters as in Figure 8.

line shape since the line broadening is due to a modulation of the scalar I'H-15N coupling and not to chemical shifts by the exchange. From the simulation of the line shapes, the rate constants k_{HD_{AC-CA}} were obtained. The known contributions of the undeuterated species were taken into account in the simulations. Note that the outer signal components are sharp at all temperatures, indicating that possible intermolecular proton exchange processes are slow within the NMR time scale.

Unfortunately, it was not possible to obtain information on the rate constants k_{HD_{AC-CA}} by I'H NMR spectroscopy because of line broadening due to fast transverse I'H relaxation and the small value of J_{HR-15N}. Since the chemical shifts of the remote I'H, I'C, and 15N spins are not modulated by the exchange AC→CA and since there were no signs of the formation of the tautomers BD and DB, no attempts were made to obtain further kinetic information by I'C and 15N NMR spectroscopy during this study.

All kinetic results are listed in Table 1 from which the Arrhenius curves of the HH and the HD migration in TPC were constructed, as shown in Figure 10. A nonlinear least-squares fit of the data leads to the expressions

\[ k_{HH_{AC-CA}} = 10^{1.14±0.2} \exp(58.4±1.4 \text{ KJ mol}^{-1}/RT), \quad 298 \text{ K} \leq T \leq 406 \text{ K}, \quad k_{HH_{AC-CA}(298)} = 15 \text{ s}^{-1} \quad (39) \]

\[ k_{HD_{AC-CA}} = 10^{1.58±0.2} \exp(-61±2 \text{ KJ mol}^{-1}/RT), \quad 329 \text{ K} \leq T \leq 411 \text{ K}, \quad k_{HD_{AC-CA}(298)} = 5.8 \text{ s}^{-1} \quad (40) \]

The error margins given in eqs 39 and 40 are purely statistical and do not include any systematic errors. We calculate the following kinetic isotope effect k_{AC-CA}/k_{HH-CA} ≈ 2.6 at 298 K.

**Discussion**

In the theoretical section we have described a formal theory of kinetic hydrogen/deuterium isotope effects for nondegenerate double proton transfer networks that involve composite single proton transfer steps according to Figures 2 and 7. In this discussion we will apply this theory to the tautomeration of 5,10,15,20-tetraphenylchlorin-15N4 (TPC, Figures 3 and 4), which was studied in the previous section by dynamic I'H NMR spec-
Isotope Effects on Proton Transfer Reactions

TPC forms in liquid solution only the degenerate tautomers AC and CA in Figure 4. Therefore, the name 5,10,15,20-tetraphenyl-15N]-7,8-dihydroporphyrin for TPC in the IUPAC recommendations is not consistent with these findings. The correct name of TPC should read 5,10,15,20-tetraphenyl-15N]-7,8-dihydroporphyrin. At room temperature the tautomers AC and CA were found to interconvert slowly and at 380 K rapidly on the NMR time scale. The tautomers BD and DB are intermediates of this rearrangement and were not directly observable. The rate constants $k_{AC-CA}$ and $k_{AC-CA} = k_{AC-CA}$ were measured as a function of temperature. Besides the preliminary communication neither rate constants for the proton nor for the deuteron migration in chlorines have been measured before. The kinetic HH/HD isotope effect of 2.6 at 298 K is unexpectedly small when compared to values obtained previously for other intramolecular degenerate double proton transfer reactions.4-6

In the following we will explain this finding in terms of a stepwise proton transfer mechanism.

Let us first recall the kinetic data obtained for the tautomerism of meso-tetraphenylporphyrin (TPP), which has been recently reinvestigated. Thus, it was found that $k_{AC-DA}(298) \approx 2725 \text{s}^{-1}$, $k_{AC-DB}(298) \approx 290 \text{s}^{-1}$, and $k_{AC-DB}(298) \approx 163 \text{s}^{-1}$, i.e., $k_{AC-DB}(298)/k_{AC-DB}(298) = 9.4$, $k_{AC-DB}(298)/k_{AC-DB}(298) = 1.8$ (41)

These results were interpreted in terms of eq 8-10, valid for a degenerate stepwise proton transfer according to Figure 11. These equations read as follows in the case of TPP: $k_{AC-DB}/k_{AC-DB} = PS$, $k_{AC-DB}/k_{AC-DB} = 2/(P^1 + S^1)$

$P$ is the primary and $S$ the secondary kinetic isotope effect associated with the formation of the intermediates from the initial states. The temperature dependence of these quantities is given in approximation $2A^2$4

$$P = 0.2 \exp(11 \text{kJ mol}^{-1}/RT), \ S = 1$$ (43)

Let us now compare the rate constants of the TPP tautomerism with those of the TPC tautomerism studied here. In the theoretical section it was shown that for the rate constants of the TPC tautomerism eqs 27 and 28 hold, i.e.,

$$k_{AC-CA} = 1/2k_{AC-DB} + 1/2k_{AC-DB} = k_{AC-DB} = k_{AC-DB}$$ (44)

where no assumption was made on whether the double proton transfers occur concerted or stepwise. Equation 44 shows that the rate constants of the HH migration in TPP (eq 41) and TPC (eq 43) can directly be compared. Thus, we find that the double proton transfer process AC $\rightarrow$ BD is much slower in TPC as compared to in TPP. This finding can be explained as follows. By contrast to symmetric porphyrinys TPC raises in energy when it reacts from AC to CA to BD or DB, because of the loss of the aromatic resonance energy. As a consequence, also the energy of the transition states for the tautomerism is raised. Extending this argument, it is straightforward that the nonaromatic cis tautomers AB and CB must have a higher energy than the aromatic cis tautomers DC and DA. Therefore, the stepwise reaction will preferentially take place via the routes (i) AC $\rightarrow$ DC $\rightarrow$ DA $\rightarrow$ DA to CA and (ii) AC $\rightarrow$ AD $\rightarrow$ BD $\rightarrow$ CD to CA. This circumstance is illustrated schematically in Figure 11 using parabolic potential curves. The rate-limiting steps of route i are the steps DC $\rightarrow$ DB and DB $\rightarrow$ DA, which involve the jump of the hydrogen isotope $L$ in Figure 4. By contrast, in the rate-limiting steps AD $\rightarrow$ BD and BD $\rightarrow$ CD of route ii the isotope $L$ is transferred.

In other words, eqs 34 is fulfilled, which states that $k_1 = k_{AC-DB}/k_{AC-DB} \gg 1$. Therefore, eqs 35-38 hold and can be introduced into eqs 30-32:

$$k_{AC-DB}/k_{AC-DB} = \frac{0.5(k_{AC-DB} + k_{AC-DB})}{0.5(k_{AC-DB} + k_{AC-DB})} = 0.5\left[\frac{1 + k}{S + P_k} + \frac{1 + k}{S + P_{k'}}\right]$$ (46)

$P$ and $S$ have the same meaning as in eq 42. $k_{AC-DB}$ is the rate constant along route i where the H isotope is transferred in the rate-limiting step. By constant, $k_{AC-DB} = k_{AC-DB}$ is the rate constant along route ii where the D isotope is transferred in the rate-limiting step. Therefore

$$k_{AC-DB} \gg k_{AC-DB}$$ (47)

Since $P \gg S \approx 1$ this means that $k \approx 1$ in eq 46. As a consequence, route i for the case $L = H$ and $L = D$ is almost as fast as in the HH case where $L = H$, $L = D$. Thus it follows that $k_{AC-DB} \approx k_{AC-DB}$, and with eqs 46 and 47 it follows that

$$k_{AC-DB} \approx \frac{1}{2k_{AC-DB}}$$ (48)

Equation 48 is already very close to the experimental finding of $k_{AC-DB}/k_{AC-DB} = 2.6$; thus, assuming a stepwise proton transfer mechanism, the unexpected kinetic HH/HD isotope effect of the TPC migration can easily be explained. A nonlinear least-square fit of the Arrhenius curves of the TPC migration to eqs 46 and 47 using eq 43 leads to a rough estimate of the splitting factor

$$k \approx 0.005 \exp(20.8 \text{kJ mol}^{-1}/RT), \ k \approx 22.1$$ (49)

This means that the second step of the reactions AC $\rightarrow$ DB and CA $\rightarrow$ DB in TPC is slower than the first as expected from Figure 11. The calculated Arrhenius curves are almost indistinguishable from the solid curves in Figure 10, obtained by linear least-squares fitting.

In other words, the unexpectedly small kinetic HH/HD isotope effect of the TPC tautomerism AC $\rightarrow$ CA is not the result of a small intrinsic kinetic hydrogen/deuterium isotope effect but of the following circumstance. In the HH reaction there are two independent equivalent routes, AC $\rightarrow$ DC $\rightarrow$ DB $\rightarrow$ DA $\rightarrow$ CA and (ii) AC $\rightarrow$ AD $\rightarrow$ BD $\rightarrow$ CD to CA. This circumstance is illustrated schematically in Figure 11 using parabolic potential curves. The rate-limiting steps of route i are the steps DC $\rightarrow$ DB and DB $\rightarrow$ DA, which involve the jump of the hydrogen isotope $L$ in Figure 4. By contrast, in the rate-limiting steps AD $\rightarrow$ BD and BD $\rightarrow$ CD of route ii the isotope $L$ is transferred. Therefore, the rate of the HD reaction is approximately half of the rate of the HH reaction.
Routes involving the nonaromatic intermediates AB, CB, BC, and BA do not contribute to the reaction rates.

Conclusions

A theory of kinetic HH/HD/DH/DD isotope effects on non-degenerate stepwise double proton transfer reactions has been adapted and applied to the tautomerization of 5,10,15,20-tetraphenylchlorin, for which rate constants including kinetic HH/HD isotope effects have been measured by dynamic NMR spectroscopy. It is expected that this theory is able to accommodate the kinetic HH/HD/DD isotope effects of tautomerism in asymmetrically substituted porphyrins and related compounds.

Acknowledgment. We thank the Deutsche Forschungsgemeinschaft, Bonn-Bad Godesberg, and the Fonds der Chemischen Industrie, Frankfurt, for financial support.

Appendix

For the equilibrium constants of the reaction network in Figure 2 the following reactions hold:

\[ K_{AD} = K_{AB}K_{BD} = K_{AC}K_{CD} = \frac{k_{HH}^{AB}k_{HH}^{BD}}{k_{HH}^{AB}k_{HH}^{BD}} \]  

It follows then from eq 6 that

\[ k_1k_2 = k_3k_4 \text{ and } k_3 = \frac{k_1k_2}{k_4} \]  

By inserting eqs 6 and A5 into eqs A1–A4 the overall rate constants \( k_{A-B}^{HH} \) can be expressed by the single rate constants \( k_{A-B}^{HH} \) or \( k_{A-C}^{HH} \):

\[ k_{A-B}^{HH} = \left[ \frac{k_1}{1 + k_3} + \frac{k_4}{1 + k_4} \right] k_{A-C}^{HH} \]  

\[ k_{A-B}^{HH} = \left[ \frac{1}{1 + k_3} + \frac{k_4/k_1}{1 + k_4} \right] k_{A-B}^{HH} \]  

\[ k_{A-D}^{HH} = \left[ \frac{S_{A-B}^{HH}p_{A-B}^{HH} + S_{B-A}^{HH}p_{B-A}^{HH}}{S_{B-A}^{HH} + p_{B-A}^{HH}} \right] k_{A-C}^{HH} \]  

\[ k_{A-D}^{HH} = \left[ \frac{S_{B-A}^{HH}p_{B-A}^{HH} + S_{A-B}^{HH}p_{A-B}^{HH}}{S_{A-B}^{HH} + p_{A-B}^{HH}} \right] k_{A-B}^{HH} \]  

By combining eqs 4 and 3 it follows with \((P^k)^{-1} = P^k\) and \((S^k)^{-1} = S^k\) that

\[ k_{A-D}^{HH} = \frac{k_{A-B}^{HH}k_{B-D}^{HH}}{k_{A-B}^{HH} + k_{B-D}^{HH}} + \frac{k_{A-C}^{HH}k_{C-D}^{HH}}{k_{A-C}^{HH} + k_{C-D}^{HH}} \]  

\[ k_{A-D}^{HH} = \frac{k_{A-C}^{HH}k_{C-D}^{HH}}{k_{A-C}^{HH} + k_{C-D}^{HH}} + \frac{k_{A-B}^{HH}k_{B-D}^{HH}}{k_{A-B}^{HH} + k_{B-D}^{HH}} \]  

\[ k_{A-D}^{HH} = \frac{k_{A-B}^{HH}k_{B-D}^{HH}}{k_{A-B}^{HH} + k_{B-D}^{HH}} + \frac{k_{A-C}^{HH}k_{C-D}^{HH}}{k_{A-C}^{HH} + k_{C-D}^{HH}} \]  

\[ k_{A-D}^{HH} = \frac{k_{A-B}^{HH}k_{B-D}^{HH}}{k_{A-B}^{HH} + k_{B-D}^{HH}} + \frac{k_{A-C}^{HH}k_{C-D}^{HH}}{k_{A-C}^{HH} + k_{C-D}^{HH}} \]