7.2, 2.0 Hz, 1 H, H-11), 7.69 (d, J = 7.8 Hz, H-12); ^{13}C NMR Table I; MS m/e 342 (M^+), 295, 180, 167, 166, 82, 74, 59 (base), 41.

Methyl 20-Deethyl-2,16-didehydrotubifolidine-1-carboxylate (14). To a solution of **5** (H-6β apimer) (75 mg, 0.2 mmol) in absolute EtOH (5 mL) was added freshly prepared Raney Ni (W-2, 2 spatulas), and the mixture was refluxed for 4 h. The solids were removed by filtration and washed with EtOH. Removal of the solvent and purification of the residue by flash chromatography (95:5 Et_2O–DEA) gave **14** (23 mg, 41%): IR (KBr) 1718 cm^{-1}; ^{1}H NMR δ 1.42 (dm, J = 12.6 Hz, 1 H, H-14R), 1.65 (dd, J = 11.3, 7.2 Hz, 1 H, H-6α), 1.65–1.90 (m, 2 H, H-20), 1.96 (dt, J = 12.6, 2.6 Hz, 1 H, H-14S), 2.55 (m, 1 H, H-15α), 2.57 (td, J = 12.4, 5.1 Hz, 1 H, H-21β), 2.75–3.10 (m, 3 H, H-5 and H-6β), 2.92 (dm, J = 12.4 Hz, 1 H, H-21α), 3.80 (br s, 1 H, H-3α), 3.92 (s, 3 H, CH_3O), 6.07 (d, J = 8.1 Hz, 1 H, H-16), 7.04 (td, J = 7.4, 1.2 Hz, 1 H, H-10), 7.10–7.22 (m, 2 H, H-9 and H-11), 7.60 (d, J = 8.0 Hz, 1 H, H-12); ^{13}C NMR Table I; MS m/e 296 (M^+), 255, 240, 225, 194, 180, 167, 166, 95, 71 (base), 58; HRMS calcd for $C_{18}H_{20}N_2O_2$ 296.1525, found 296.1518.

Operating as above, from **5** (H-6α epimer) (20 mg, 0.05 mmol) in EtOH (2 mL) and Raney Ni (W-2, 1 spatula), pentacycle **14** (5 mg, 34%) was obtained.

Operating as for **5**, from **13** (17 mg, 0.05 mmol) in EtOH (2 mL) and Raney Ni (W-2, 1 spatula), the pentacyclic compound **14** (4 mg, 27%) was obtained.

Acknowledgment. This work was supported by the DGICYT (project PB88-0316), Spain.

Registry No. (±)-**3a-1** (isomer 1), 143370-85-8; (±)-**3a-1** (isomer 2), 143370-97-2; (±)-**3a-2** (isomer 1), 143370-95-0; (±)-**3a-2** (isomer 2), 143370-98-3; (±)-**4**, 101481-16-7; (±)-6α-**5**, 143370-86-9; (±)-6β-**5**, 143370-94-9; (±)-**5**, 99552-97-3; (±)-**7**, 143370-87-0; (±)-**7**·HCl, 143370-99-4; (±)-**8**, 143370-88-1; (±)-**8**·HCl, 143370-96-1; (±)-**9**, 143370-89-2; (±)-**10**, 143370-90-5; (±)-**12**, 143370-91-6; (±)-**13**, 143370-92-7; (±)-**14**, 143370-93-8; $C_6H_5S(CH_2)_2Br$, 4837-01-8.

Supplementary Material Available: ^{1}H NMR spectra for compounds **3a-2** and **13** and ^{13}C NMR spectra for compounds **5** (both epimers), **12**, and **14** (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Variable-Temperature Dynamic ^{1}H NMR N–H Line-Shape Analysis for Meso-Monosubstituted Octaethylporphyrins: An Indication of Remarkably Slow N–H Tautomerism

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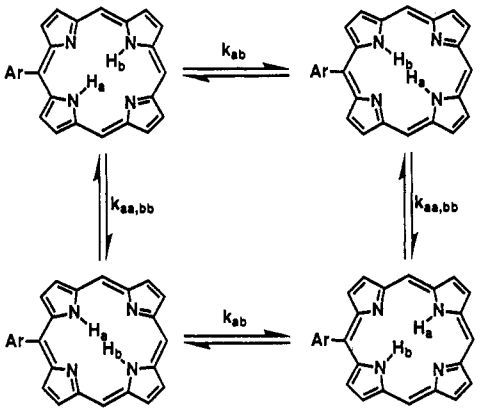
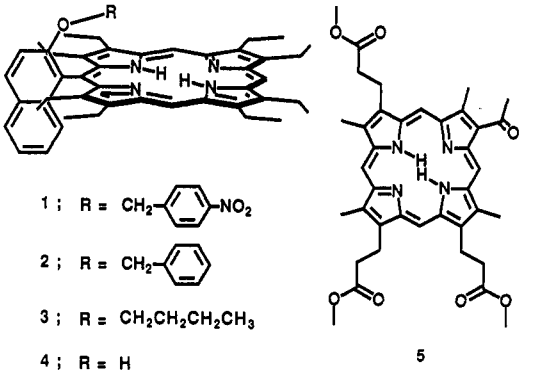
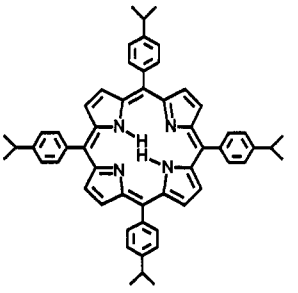
Tautomerism is an intramolecular proton transfer process coupled with migration of double bonds. The N–H tautomerism in porphyrins (Scheme I) involves a shift of highly conjugated double bond systems.[2-8] The exchange between two tautomers is usually so fast that they can be distinguished spectroscopically only at very low temperatures. The present work is concerned with meso-monosubstituted octaethylporphyrins (OEP's). We report here that the tautomerism rate constants evaluated by variable-temperature dynamic ^{1}H NMR N–H line-shape analysis for these compounds are surprisingly small.

Scheme I







Three OEP derivatives **1**–**3** having a 2-alkoxy-1-naphthyl group on a meso position were prepared by alkylating the parent 2-hydroxy-1-naphthyl compound **4** with an appropriate alkyl bromide. The ^{1}H NMR spectrum for the 4-nitrobenzyl (**1**), benzyl (**2**), or n-butyl derivative (**3**) in

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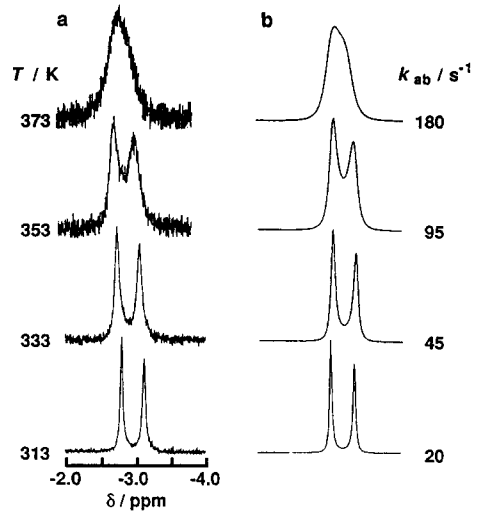

Figure 1. Observed (a) and computer-simulated (b) ^{1}H NMR spectra for the nitrogen-bonded inner protons of compound **2** in $Cl_2DCCDCl_2$ as a function of temperature.

Table I. Rate Constants (k, s^{-1}) for the N-H Tautomerism in Porphyrins[a,b]

	compound				
T/K	**1**	**2**	**3**	**5**[c]	**6**[d]
373	190	180			
353	85	95	180		
333	40	45	150	42 000[e]	54 000[e]
313		20	115		
298			90		

[a] Errors in k's for compounds 1–3 are ±10%. [b] Solvents are DCl_2CCDCl_2 for 1–3, CD_2Cl_2 for 5, and a 1:2 mixture of Cl_2CCDCl and DCl_2CCDCl_2 for 6. [c] Reference 7d. [d] Reference 3. [e] Extrapolated values.

deuteriated 1,1,2,2-tetrachloroethane showed two distinct singlets of equal intensities but with slightly different line widths for the N–H groups at δ −3.11 and −2.75 for **1**, −3.10 and −2.77 for **2**, and −2.42 and −2.18 for **3** at 313 K. These results can be interpreted as suggesting that the presence of a naphthyl substituent with either an aromatic or aliphatic pendant renders the two nitrogen-bonded inner protons magnetically nonequivalent[9] and their exchange (Scheme I, ab process) is slow as compared with NMR time scale at room temperature.

There was a slight temperature dependence of the chemical shifts for the two N–*H* resonances. At higher temperatures they coalesced. The actual spectra for compound **2** at various temperatures are shown in Figure 1. If it is assumed that only exchange is responsible for the temperature-dependent line shapes, then the rate constants for exchange (k_{ab}, Scheme I) can be determined, as indicated in Figure 1, so as to simulate the observed spectra.[10] The rate constants thus obtained are summarized in Table I together with those for the corresponding processes for two typical porphyrins **5**[7d] and **6**.[3] Plots of ln k vs $1/T$ according to the Arrhenius equation, $\ln k = \ln A - E_a/RT$, gave a straight line with E_a (kcal/mol) = 9.6 for compound **1** or 8.5 for **2**,[11] as compared with E_a = 10.0 for **5**[7d] or 9.9 for **6**.[3]

For the present tautomerism, only the k_{ab} process (Scheme I) affects the N–H line shapes. On the other hand, the rate constants of tautomerism in compounds **5**[12] and **6**[13] were analyzed on the basis of what was affected by both of the two rate processes corresponding to the ab and (aa, bb) steps (Scheme I). If it is assumed that $k_{ab} = k_{aa,bb}$, then the rate constants for **5** and **6** must be divided by 2 in order to be compared with those (k_{ab}) for **1–3**. Such a minor statistical correction being made, there is still a remarkable difference (by a factor of 140–675) in k's for **1–3** and **5–6** at 333 K. In fact, the coalescence temperatures for the former are much higher than the room temperature, while those for the latter and other usual porphyrins are much lower than it,[2-8] e.g. −40 °C for tetraphenylporphyrin.[14] Nevertheless, the activation energy (~9 kcal/mol) for such a slow process for compound **1** or **2** is unusually low.

To summarize, variable-temperature dynamic ^{1}H NMR N–H line-shape analysis for meso-monosubstituted octaethylporphyrins suggests that the N–H tautomerism therein is surprisingly slow. A significant steric hindrance between the naphthalene ring and the two adjacent ethyl groups[15] at the transition state of proton transfer might be responsible for the remarkably slow tautomerism in compounds **1–3**. Alternatively, the proton-transfer reaction may be directly affected by substituent R on the naphthalene ring. However, the activation parameters are unusual and not easily understood. Something seems to be amiss with the temperature dependence of the NMR spectra.[10] There might also be some unknown factor associated with the present tautomerism.

An interest in tautomeric systems lies in their potential application to memory-storage molecular devices.[16,17] Porphyrin tautomers have in fact been applied to photochemical hole burning.[18] The present study suggests that the rate of tautomerism in an octaethylporphyrin free base can be remarkably lowered by suitable modification at the meso position, i.e., the kinetic stability of each tautomer can be significantly enhanced thereby. The mechanism of the present substituent effects remain to be elucidated. Further work is now under way along these lines.

Experimental Section

^{1}H NMR spectra were taken with a JEOL JNM-GX 270 spectrometer for solutions in $Cl_2DCCDCl_2$, unless otherwise indicated, which was pretreated with basic alumina (Woelm, activity I). Line-shape analysis was performed by a standard procedure.[19] The rate constants (with errors of ±10%) were determined on the basis of visual fitting of the observed and simulated spectra.

5-(2-Hydroxy-1-naphthyl)octaethylporphyrin (**4**) was obtained as the main product in the aldehyde-promoted cyclization reaction of tripyrrole and monopyrrole derivatives to give an α,β-disubstituted porphyrin.[20] Thus, a degassed mixture of

(9) The corresponding resonance for compound **4** was not well resolved.

(10) Actually, there is a possible temperature-dependent contribution from ^{14}N quadropole-induced relaxation to the line widths, thus the assumption that only exchange is responsible for the line broadening would give the upper limits for the exchange rate constants.

(11) The ln A values obtained are 18.2 and 16.7 for compounds **1** and **2**, respectively, as compared with ln A = 25.7 (for **5**) and 25.8 (for **6**).

(12) From line-shape analysis of the N–*H* resonance for the triply ^{15}N-labeled compound.

(13) From line-shape analysis of the pyrrolic β-proton resonance.

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2,3,7,8,12,13-hexaethyltripyrrane (92 mg), 3,4-diethylpyrrole (30 mg), and 2-hydroxy-1-naphthaldehyde (80 mg), zinc acetate (80 mg), and *p*-toluenesulfonic acid (100 mg) in methanol (40 mL) was stirred at 25 °C for 20 min. To the resulting dark reddish solution was added a THF solution (40 mL) of chloranil (100 mg), and the mixture was stirred for 1 h. Workup and chromatography on silica gel (Wakogel C-200) with chloroform as eluant gave the Zn^{II} complex of 4. Demetalation with HCl followed by recrystallization from chloroform–hexane afforded compound 4 (33 mg, 20%): δ ($CDCl_3$, at 298 K) −3.00 (br, 2 H, NH), 0.91, 1.84, 1.92 (each t, 3 H, 3 H, 6 H, CH_3), 2.56, 2.82, 4.00, 4.12 (each m, 2 H, 2 H, 4 H, 8 H, CH_2CH_3), 5.27 (br, 1 H, OH), 6.81–8.27 (m, 6 H, naphthyl H), 10.01, 10.22 (each s, 1 H, 2 H, meso H); λ_{max} ($CHCl_3$) 411, 509, 541, 576, 626 nm.

Alkylation of compound 4 was carried out as typically shown below for the preparation of 5-(2-(4-nitrobenzyl)-1-naphthyl)-octaethylporphyrin (1). A mixture of compound 4 (200 mg), potassium carbonate (20 mg), and 4-nitrobenzyl bromide (100 mg) in dry acetone (20 mL) was stirred under reflux for 1 h. Workup involving chromatography on silica gel (Wakogel C-200) with dichloromethane as eluant and recrystallization from dichloromethane–hexane gave compound 1 (216 mg, 90%): δ (at 313 K) −3.11, −2.78 (each s, each 1 H, NH), 0.71, 1.80, 1.93, 1.95 (each t, each 6 H, CH_3), 2.57, 3.94, 4.09 (each m, 4 H, 4 H, 8 H, CH_2CH_3), 5.11 (s, 2 H, OCH_2), 6.54, 7.31 (each d, each 2 H, phenyl H), 7.00–8.38 (m, 6 H, naphthyl H), 9.99, 10.17 (each s, 1 H, 2 H, meso H); λ_{max} ($CHCl_3$) 409, 506, 539, 574, 625 nm. Anal. Calcd for $C_{53}H_{58}N_5O_3$: C, 78.29; H, 7.19; N, 8.61. Found: C, 78.35; H, 7.03; N, 8.48. Compound 2: δ (at 313 K) −3.10, −2.77 (each s, each 1 H, NH), 0.70, 1.83, 1.94 (each t, 6 H, 6 H, 12 H, CH_3), 2.60, 3.96, 4.09 (each m, 4 H, 8 H, CH_2CH_3), 5.07 (s, 2 H, OCH_2), 6.71–6.90 (m, 5 H, phenyl H), 6.70–8.37 (m, 6 H, naphthyl H), 10.03, 10.22 (each s, 1 H, 2 H, meso H); λ_{max} ($CHCl_3$) 409, 506, 538, 574, 625 nm. Anal. Calcd for $C_{53}H_{59}N_4O$: C, 82.88; H, 7.74; N, 7.29. Found: C, 82.86; H, 7.72; N, 7.11. Compound 3: δ (at 313 K) −2.42, −2.18 (each s, each 1 H, NH), 0.42 (t, 3 H, $CH_2CH_2CH_2CH_3$), 0.72 (q, 2 H, $CH_2CH_2CH_2CH_3$), 1.00 (m, 2 H, $CH_2CH_2CH_2CH_3$), 1.15 (t, 2 H, $CH_2CH_2CH_2CH_3$), 0.85, 1.92, 2.03, 2.05 (each t, each 6 H, CH_3), 2.62, 2.80, 4.08, 4.15 (each m, 2 H, 2 H, 4 H, CH_2CH_3), 6.82–8.43 (m, 6 H, naphthyl H), 10.03, 10.22 (each s, 1 H, 2 H, meso H); λ_{max} ($CHCl_3$) 409, 505, 536, 574, 626 nm. Anal. Calcd for $C_{53}H_{58}N_5O_3$: C, 81.81; H, 8.38; N, 7.63. Found: C, 81.98; H, 8.45; N, 7.37.

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Synthesis of (−)-Shikimate and (−)-Quinate 3-Phosphates by Differentiation of the Hydroxyl Functions of (−)-Shikimic and (−)-Quinic Acids

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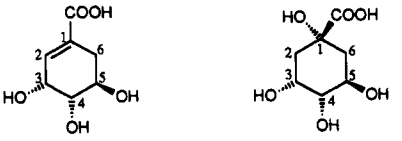
Shikimic acid **1a** is a central intermediate in the shikimate pathway along which the aromatic amino acids and a multitude of other aromatic and alicyclic compounds are biosynthesized in bacteria, fungi, and plants.[1,2] Shikimate 3-phosphate (**10a**) is the substrate for 5-enolpyruvoylshikimate 3-phosphate synthase (EPSPS) which is the target for the broad-spectrum herbicide *N*-(phosphonomethyl)glycine (glyphosate).[3]

Chart I

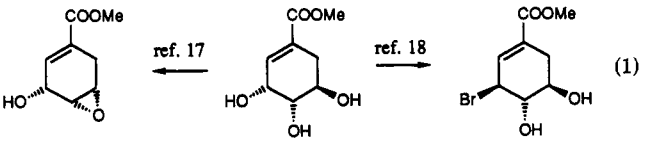


1a **1b**

The (−)-shikimate 3-phosphate has been obtained by enzymatic phosphorylation of shikimic acid using shikimate kinase and ATP.[4,5] Bartlett[6] has described a total synthesis of racemic shikimate 3-phosphate, but to our knowledge no report exists for the chemical synthesis of the natural (−)-derivative.

Quinic acid **1b** is involved only in plants, but it can constitute a source of carbon in bacteria.[7] Its presence can be related to a regulation of the shikimate pathway.[8] However, the presence of significant quantities of quinic acid (more than 5% of the weight of dried vegetal in some instances) suggests other possible metabolic activities and/or other relations with the shikimate pathway, for instance, through quinate 3-phosphate **10b**.[9]

We hereby report the first chemical synthesis of both (−)-shikimate and (−)-quinate 3-phosphates. It poses the problem of selective hydroxyl-group functionalization. A limited number of such processes of discrimination have been reported in these series. One strategy was based on acetal formation involving the cis 3,4-diol of **1a**[10-12] and of **1b**[13] or analogous carbonate[14] and borate[15] cyclic esters. Another approach[17] consisted of the reaction of methyl shikimate with triphenylphosphine–dialkyl azodicarboxylate (eq 1) leading to a *syn*-hydroxy epoxide.



(1)

Recently, Ganem's group[18] reported a selective modification of 3- and 4-hydroxyl groups using 2-acetoxyisobutyryl bromide (eq 1) giving a bromoacetate.

A method for versatile functionalization of the 3-hydroxyl group is applied in this work to the preparation of the title compounds. This methodology using the 3,4-*O*-stannylene derivatives rests upon the dimeric structure

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