Dynamic Molecular Recognition in a Multifunctional Porphyrin and a Ubiquinone Analogue

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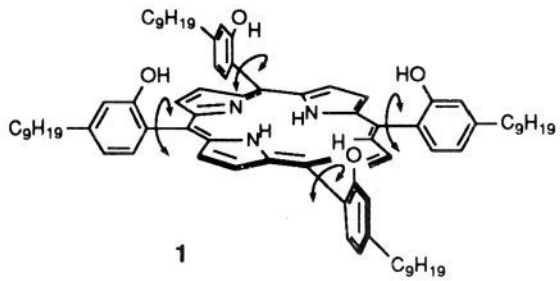
We have recently presented the effective intermolecular interaction between ubiquinone analogue and the porphyrin receptor $\alpha,\alpha,\alpha,\alpha$-*meso*-tetrakis(2-hydroxynaphthyl)porphyrin (**3**).[1] Particularly, **3** has four convergent 2-hydroxynaphthyl groups fixed upon the porphyrin ring to obtain good affinity for ubiquinone analogues.[2] In this communication, we report that the guest molecule tetramethoxy-*p*-benzoquinone (**2**) acts as a trigger of atropisomerization of *meso*-tetrakis(2-hydroxy-4-nonylphenyl)-porphyrin (**1**) to enrich the particular $\alpha,\alpha,\alpha,\alpha$-isomer (**1a**) with induced fitting interaction[3] as shown in Scheme I. This is the first example of the equilibrium of atropisomers shifting to the $\alpha,\alpha,\alpha,\alpha$-isomer in homogeneous solution.[4]



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Porphyrin **1** was prepared in 14% yield by condensation of pyrrole and 2-methoxy-4-nonylbenzaldehyde in propionic acid and treatment with BBr_3. Four alkyl groups were linked at the para positions of the *meso*-2-hydroxyphenyl groups to improve the solubility of the parent porphyrin in organic solvents.[5] HPLC analysis of resulting porphyrin **1** showed a mixture of the four atropisomers $\alpha,\alpha,\alpha,\alpha$ (**1a**), $\alpha,\alpha,\alpha,\beta$ (**1b**), $\alpha,\alpha,\beta,\beta$ (**1c**), and $\alpha,\beta,\alpha,\beta$ (**1d**) in the ratio 1.0:4.4:2.2:0.8, respectively. Silica gel column chromatography at ambient temperature could not separate the atropisomers of the mixture. The rate constant of rotation of one carbon–carbon bond of porphyrin–phenyl ring was determined to be $k = 1.7 \times 10^{-5}$ s^{-1} at 25 °C in $CHCl_3$ by HPLC analysis.

The **1a** and **1b** bind specifically to **2** forming a complex of 1:1 stoichiometry ($K_{1a} = 6.0 \times 10^3$ M^{-1}, and $K_{1b} = 3.0 \times 10^2$ M^{-1}, respectively, in $CHCl_3$ at 25 °C).[6] It is likely that **1a** selectively interacts with **2** via four efficient hydrogen bonds to maintain the cofacial porphyrin–quinone pair in the most stable form, and the subsequent atropisomerization is initiated to provide **1a** for complexation with **2**.[7]

Scheme I

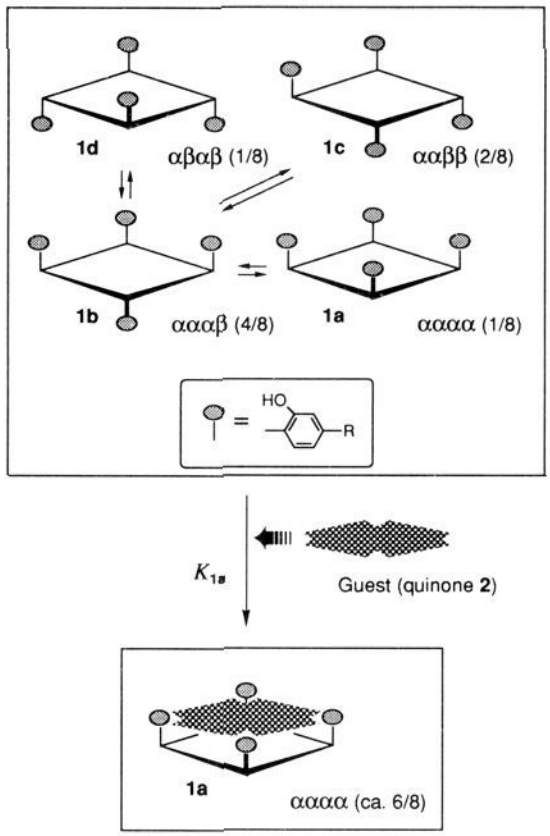

Table I. Relative Proportion of $\alpha,\alpha,\alpha,\alpha$-Isomer **1a** among Four Atropisomers of **1** in the Presence of **2** at Equilibrium in $CDCl_3$[a]

			proportion of **1a** ($\alpha,\alpha,\alpha,\alpha$)	
entry	quinone **2** (equiv)	temp (°C)	rel[b] (%)	simulated[c] (%)
1	1.0	25	58	50
2	1.0	43	39	
3	1.0	9	72	
4	0.5	25	36	34
5	2.0	25	69	64
6	3.0	25	78	71
7	5.0	25	80	76
8	10	25	80	80

[a] [**1**] = 2.4×10^{-3} M. [b] The relative proportion was determined by the intensity of the *ortho*-proton resonance by 400-MHz ^{1}H NMR. [c] A computational simulation of the relative proportion was calculated from the binding constants of **2** for **1a** and **1b** and the initial isomer ratios (**1a**:**1b**:**1c**:**1d** = 1:4:2:1).

Specific stabilization for the **1a**–**2** pair is observed by the proton resonances of **1** as shown in Figure 1. Although *meso*-phenyl proton signals in the ^{1}H NMR spectrum of **1** are not clearly distinguishable from each atropisomer (Figure 1a), the coexistence of **2** enables us to assign signals (Figure 1b). The ^{1}H NMR spectrum of a mixture of **1a** and **2** indicates exclusive existence

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(1) Hayashi, T.; Miyahara, T.; Hashizume, N.; Ogoshi, H. *J. Am. Chem. Soc.* **1993**, *115*, 2049.

(2) Atropisomerization of porphyrin **3** was not observed in toluene at 110 °C after 2 h.

(3) (a) Chen, C.-W.; Whitlock, H. W., Jr. *J. Am. Chem. Soc.* **1978**, *100*, 4921. (b) Rebek, J., Jr.; Askew, B.; Killoran, M.; Nemeth, D.; Lin, F.-T. *J. Am. Chem. Soc.* **1987**, *109*, 2426. (c) Adrian, J. C.; Wilcox, C. S. *J. Am. Chem. Soc.* **1989**, *111*, 8055. (d) Vicent, C.; Hirst, S. C.; Garcia-Tellado, F.; Hamilton, A. D. *J. Am. Chem. Soc.* **1991**, *113*, 5466. (e) Adrian, J. C., Jr.; Wilcox, C. S. *J. Am. Chem. Soc.* **1992**, *114*, 1398. (f) Güther, R.; Nieger, M.; Vögtle, F. *Angew. Chem.* **1993**, *105*, 647.

(4) Elliott and Lindsey have reported the isomerization on silica gel, which allows conversion of the mixture of atropisomers to the $\alpha,\alpha,\alpha,\alpha$-isomer in 60-70% yield. (a) Elliott, C. M. *Anal. Chem.* **1980**, *52*, 666. (b) Lindsey, J. *J. Org. Chem.* **1980**, *45*, 5215.

(5) Gottwald and Ullman have reported the atropisomerization of *meso*-tetrakis(2-hydroxyphenyl)porphyrin; however, this porphyrin is slightly soluble in nonpolar solvents. Gottwald, L. K.; Ullman, E. F. *Tetrahedron Lett.* **1969**, 3071.

(6) Face to face complexations between **1a** or **1b** and **2** were confirmed by the downfield shift of the hydrogen-bonded OH of **1a** or **1b** and upfield shift of the OCH_3 in the ^{1}H NMR spectra in a similar manner as in previous work.[1] These affinities were determined by titrimetric measurement of visible spectra with clear isosbestic points in the region 550–700 nm. The titration was manipulated in a short time at 25 °C after the isolation of each isomer. The isomerization of **1a** was carefully examined by HPLC after measurement, and isomerization of **1a** to the other three atropisomers was below 5%.

(7) Thermodynamic parameters of **1a**–**2**: $\Delta G° = -5.5$ kcal/mol, $\Delta H° = -11.6$ kcal/mol, and $T\Delta S° = -6.1$ kcal/mol, respectively, in $CHCl_3$ (without EtOH as a stabilizer) at 25 °C.

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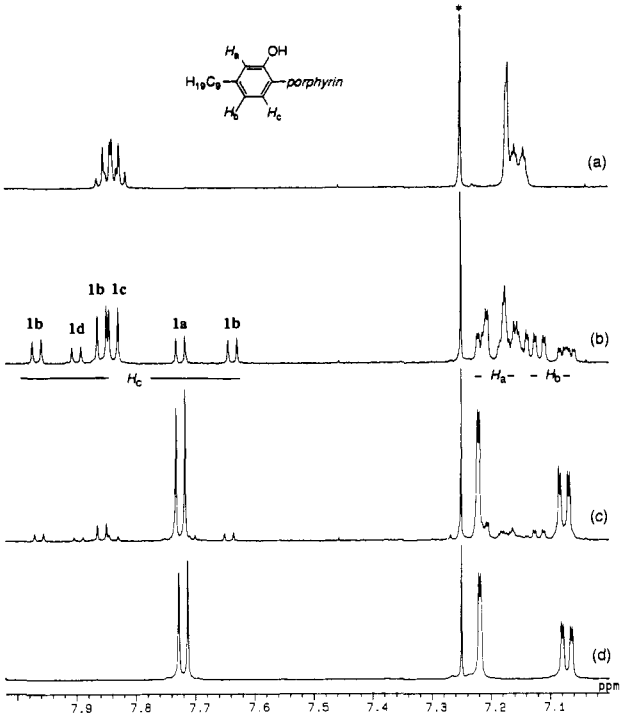

Figure 1. The 500-MHz ^{1}H NMR spectra of phenyl protons of **1** in $CDCl_3$ at 25 °C: (a) no quinone added; (b, c) after addition of **2** to a $CDCl_3$ solution of **1** ([**2**]/[**1**] = ca 3.0), (b) after 0.4 h, (c) after 479 h; (d) a mixture of isolated **1a** and **2**. The signal marked with an asterisk (*) is due to $CHCl_3$.

of a **1a–2** complex (~99%) in Figure 1d,[8] and the main peaks of Figure 1c are assignable to a **1a–2** complex. Thus, changes in the population of atropisomer–quinone pairs were monitored by the signal intensity of *meso*-phenyl protons (Figure 1b,c). For example, addition of 10 equiv of **2** to a $CDCl_3$ solution of **1** caused the relative proportion of **1a**, including the complex and free host,[9] to change from 12.5% to 80% after equilibrium was reached (500 h) at 25 °C, whereas the relative proportions of **1b**, **1c**, and **1d** decreased to 17%, 2%, and 1%, respectively. Table I summarizes the effect of temperature and concentration of quinone on the proportion of **1a** induced by complexation at equilibrium. (1) Atropisomerization to **1a** from the rest of isomers unambiguously increases as the temperature is lowered (entries 1–3). (2) The proportion of **1a** is largely influenced by the addition of **2** in the range 0.5–2.0 equiv (entries 1, 4, and 5), whereas the proportion of **1a** is almost saturated above 3.0 equiv of **2** (entries 6–8). Addition of 3 equiv of **2** results in the predominant existence of the **1a** isomer (78% of **1**) as a cofacial complex (more than 97% of **1a**). (3) Computational simulation of isomerization to **1a** initiated by molecular recognition was carried out by using two higher binding constants of **2** (K_{1a} and K_{1b}).[10] In addition, we have assumed that the initial isomers populate in the statistical ratio (**1a**:**1b**:**1c**:**1d** = 1:4:2:1) and atropisomerization among the free isomers proceeds at the same rate. The calculated percentage of the $\alpha,\alpha,\alpha,\alpha$-isomer for the complex **1a–2** and free host **1a** shows good agreement with the observed value at a higher concentration of **2**.

The unique system presented here may provide an example of the induced fitting type of molecular recognition, where specific intermolecular interaction between host and guest causes structural change in the host molecule to form a more stable complex. Elucidation of such *dynamic* molecular recognition is required to gain a fresh insight into the functions of enzymes and receptors. Further work on the kinetic property of present porphyrin–quinone adducts is in progress, and details on these will appear in future publications.

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Supplementary Material Available: Scheme for the synthesis of compound **1**, experimental procedures, and the details of the calculation of the relative proportion of **1a** at equilibrium (5 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.

(8) The **1a** isomer isolated at 4 °C maintains its conformation for a time in the presence of **2** due to retardation of isomerization, since **1a** interacts very strongly with quinone to form the stable complex.

(9) Signals of **1a** and **1a–2** could not be discriminated in the NMR time scale at room temperature due to fast exchange of free and bound quinone.

(10) The binding affinities of **1c** and **1d** with **2** seem to be neglected compared with those of **1a** and **1b**.