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Synthesis and Kinetic Investigation of the Atropisomerization of *meso*-Tetra(2-cyanophenyl)porphine

Keiichiro HATANO,* Kazunori ANZAI, Tadashi KUBO, and Shoko TAMAI

Department of Pharmaceutical Sciences, Nagoya City University, Mizuho-ku, Nagoya 467

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Tetra(2-cyanophenyl)porphine (ToCNPP) has been synthesized and isolated into the four respective atropisomers. The rotation of a cyanophenyl ring about the bond to the methine carbon of the porphyrin leads to interconversion reactions among the isomers. The isomerization reactions have been studied kinetically by the separation and quantitative measurement of each isomer on thin layer chromatography plates. The results show that the free energy of activation for the hindered rotation is an average of $\Delta G^{*}=110$ kJ/mol at 50 °C. This is the highest barrier ever measured in similar porphyrin atropisomers. The apparent interaction between adjacent cyano groups is observed. The energy of interaction is estimated to be about 2.0 kJ per mole unit of interaction.

Rotational isomerism of some tetraarylporphyrins and their metal derivatives have been investigated by several groups of workers.$^{1-5)}$ The principal features of the atropisomerism, *i.e.*, tautomerism and statistical distribution of isomers, have been known since the resolution and isomerization of tetra(2-hydroxyphenyl)porphine (ToOHPP) was communicated twelve years ago.$^{1)}$ Many nuclear magnetic resonance (NMR) studies have also ratified the features.$^{2-4)}$

On the other hand, the isolation of a particular $\alpha,\alpha,\alpha,\alpha$ atropisomer of tetra(2-aminophenyl)porphine (ToNH$_2$PP) brought great advances in studies of synthetic models of the hemeproteins, such as the "picket fence" porphyrins.$^{6-8)}$ We are interested in the steric control of ligand coordination and redox reactions of the central metal ions of metalloporphyrins$^{9)}$ in connection with the catalytic selectivity and activity of various heme enzymes. Tetra(2-cyanophenyl)porphine (ToCNPP) is expected to be a good and new source for the synthetic models as well as ToNH$_2$PP.

In the course of our study to synthesize and isolate the desired isomer, $\alpha,\alpha,\alpha,\alpha$-isomer, of ToCNPP, we have found a new, but unfavorable for this isomer, effect of the cyano substituents on the atropisomerism. There is a steric repulsion between the CN groups through the space above the porphyrin plane, that disturbs the statistical distribution of isomers, especially, low yields of the $\alpha,\alpha,\alpha,\alpha$-isomer. This is the first report describing the kinetic analysis of the steric interaction as well as the synthesis and rotational isomerization of ToCNPP.

Experimental

Materials. A typical procedure to synthesize ToCNPP is as follows: 2-Cyanobenzaldehyde (10 g, 76 mmol) and pyrrole (5.3 ml, 76 mmol) in a mixture of acetic acid and pyridine (4:1 in volume, total 400 ml) were refluxed for 2 h. After the reaction mixture was cooled down to room temperature, twice the volume of methanol was added and the solution was allowed to stand for at least 2 d. Crystalline products precipitated in the solution were separated by filtration, washed with methanol, and dried in an oven at 50 to 70 °C. It was further purified by chloroform extraction using a Soxhlet extractor. The resulting purple crystals in the solution were collected by filtration (yield: *ca.* 0.4 g, 3%). Found: C, 80.22; H, 3.25; N, 15.11%. Calcd for $C_{48}H_{26}N_8$: C, 80.66; H, 3.67; N, 15.68%. IR (KBr) cm^{-1}: $\nu_{C\equiv N}$ 2230. UV (CHCl$_3$) λ_{max} nm ($\varepsilon\times10^{-4}$): 419 (37.4), 512 (2.12), 544 (0.72), 587 (1.04), 644 (0.57). Mp >300 °C.

Since ToCNPP is a mixture of four atropisomers, each component was separated by column chromatography using silica gel 100 (70—230 mesh, Merck) and dry chloroform. The chloroform solution of each isomer was evaporated *in vacuo* immediately after elution from the column. Before kinetic experiments, the atropisomers were purified further by preparative thin layer chromatography (TLC) (silica gel 60, 0.5 mm thick, Merck).

All reagents and solvents of reagent grade were used without further purification except chloroform which was washed with water, dried over CaH$_2$, and distilled.

Measurement of the Isomerization Rates. A chloroform solution of each atropisomer (*ca.* 5 mg/20 ml) in a flask was placed in a water bath kept at 50 or 60 °C. A few microliters of the solution was sampled with a glass capillary at appropriate intervals, and spotted on a TLC plate (silica gel 60, 0.25 mm thick, Merck). The rotational isomerization reaction of an isomer to the additional three components was monitored by measurements of the quantity of respective isomers which were separated with 98:2 chloroform–acetone on a TLC plate. The quantity was measured by spectrometry after the extraction of each isomer from the TLC plate with chloroform. The mole fractions of minor components determined by this method have relatively larger errors than the fraction of major ones. Under the present reaction conditions, no product other than the isomers was detected by TLC even after the reaction for 3 d.

Processing of the Data. The digital integration of the differential rate equations,

$$d[A_i]/dt = \sum_{j}\sum_{l} k_j[A_l],$$

where k_j is the first-order rate constant for the j th reaction concerning the A_i species, was performed at small increments of time by a local Fortran program using the Runge-Kutta approximation.$^{10)}$ An initial set of inputs, *i.e.*, rate constants and concentrations of isomers, was the experimental data obtained by the usual graphic method adapted to the initial stage of the reactions. The rate constants were refined by trial and error to fit the computed values to the experimental values of all isomers for the entire time course of the reaction.

The general structural parameters of the porphyrin skeleton$^{11)}$ and atomic coordinates of cyano(*meso*-tetraphenylporphinato)manganese(III)$^{12)}$ in the crystal were tentatively used for calculating the distances between atoms and for drawing.$^{13)}$ The positions of the CN substituents were determined by assuming that the carbon and nitrogen atoms were on the linear extension from the center of phenyl ring to the ortho carbon with distances of C_{ortho}–C=1.5 Å and

C–N = 1.15 Å. All calculations were carried out at the computing center of this university using a NEAC system 700S computer.

Results and Discussion

The Synthesis of ToCNPP. Two solvent systems have been proposed for the general syntheses of *meso*-tetraarylporphyrins in solution[14,15] besides Rothemund's original method and its applications.[16–18] Utilization of propionic acid, as proposed by Adler *et al.*,[14] to make ToCNPP has resulted in a large amount of tarry and black by-products which hamper the purification of the porphyrin in gram-quantities. On the other hand, Treib's procedure,[15] using 1:2 pyridine–acetic acid, for this porphyrin gave no precipitate even though the reaction mixture was allowed to stand for 2 d in a refrigerator.

The precipitation of crystalline products of reasonable purity and high yield from a simple reaction batch is considered to be the most important merit of the preparative procedure. We have determined the optimal conditions for preparing ToCNPP by varing the ratio of pyridine to acetic acid and by following the time course of the formation. The product yields obtained *in situ* by spectrometric methods increase from 4 to 8% by increasing the pyridine ratio from 10 to 33 v/v%. ToCNPP is found to be appreciably soluble in pyridine but much less soluble than the by-products, while ToCNPP is insoluble in acetic acid. Thus, the purest porphyrin products and highest isolated yield of a batch process have been obtained in 20% pyridine as described in Experimental. The total spectrometric yield reaches 7 to 8% level, but the complete isolation of the porphyrin is very difficult. The formation of ToCNPP in the boiling solution seems finished within 30 min and longer reaction time do not improve the yield.

The pyridine–acetic acid solvent system is also found to improve the isolation of crystalline tetra(2-nitrophenyl)- and tetra(2,6-dichlorophenyl)porphines from the single batch compared to the literature methods.[6,19]

Separation and Identification of the Atropisomers. The TLC of the reaction products show three distinct spots with R_f values of 0.47, 0.41, and 0.23 together with several minor spots at 0 to 0.2 when it is developed with 98:2 chloroform–acetone. The three materials extracted from the main spots display identical electronic absorption spectra with characteristic porphyrin maxima[19] and a common IR spectrum with a single C≡N stretching band. Each of the three compounds mutually interconverts in chloroform solution, and a new species at R_f=0.04 on TLC is generated in the interconversion. Thus the four spots on TLC correspond to the four atropisomers of ToCNPP. The distribution of the four isomers, equilibrated at 50 °C for 3 d, is 39 (±4), 24 (±3), 35 (±3), and 2 (±1)%, in the order of decreasing R_f values.

The compound with the smallest R_f value and mole fraction is easily assigned to α,α,α,α-isomer (iv) by consideration of the molecular polarity seen on TLC and the steric hindrance to assembling four cyano groups on the same side of the porphyrin plane. The kinetic studies mentioned below distinguish the α,α,α,β-isomer (iii) from the others as it is the only primary product of the isomerization of every isomer. We have tentatively identified the first and second eluents of chromatography to the α,β,α,β- (i) and α,α,β,β- (ii) isomers, respectively, based on the polarity on TLC. This assignment of the four atropisomers is consistent concerning the order of R_f values on TLC with that of ToNH$_2$PP reported by Collman *et al.*[6] The crystal structure of ii may be analysed for a definitive assignment elsewhere.

The proton NMR spectra of the isomers have been poorly characterized owing to the complex multiplicity of the phenyl protons and low solubility in NMR solvents at room temperature.

The Kinetic Studies of the Isomerization. Rotation of any one of the four phenyl rings of ToCNPP about the bond to the porphyrin skeleton leads to the stereochemical isomerizations as shown in Fig. 1. Two or more rings can rotate simultaneously, but this can be ignored in the kinetic analysis as a secondary perturbation of small statistical probability. Intramolecular isomerization reactions are generally first-order reactions. The present case is also found to be first-order from the analysis. The designation of the rate constants for the six isomerization reactions is displayed in Fig. 1.

The equilibrium constants defined by $K_m = k_j/k_{j+1}$ are conveniently determined by the distribution of four isomers at 50 °C mentioned above, and the values obtained at 40 and 60 °C are invariant within experimental error. Each of the purified isomers were subjected to the rate determinations.

The refined rate constants are listed in Table 1 and the computer simulations of them are reasonable matches for all experiments at 50 and 60 °C. Two examples are displayed in Figs. 2a) and 2b). The solid lines in the figures are the computer simulations. The rate constants are also consistent with the equilibrium constants obtained experimentally.

The activation energies determined by the Arrhenius equation are found to spread over 84 to 94 kJ/mol for the six reactions, hence, they are averaged into an E_a which is reported in Table 2.

The Rotational and Steric Effects of the Cyano Substituent. The free energy of activation (ΔG^*) is considered to reflect the height of the rotational barrier principally generated by the friction between an ortho substituent and a pyrrole proton of the porphyrin. Our result, a weighted average value ΔG^* = 110 kJ/mol given by the Eyring equation at 50 °C, can be compared with the published kinetic data[1–4] for ortho substituted tetraphenylporphyrins. The comparison of ΔG^* should be done at the same temperature. However, since the entropy of activation or the substitute for it is unavailable, we must adapt our data to the extensions of temperatures by assuming that the activation energy (E_a) is employable over the temperature range of 23 to 180 °C. This assumption is plausible because of the intrinsic independence of E_a with temperature. The ΔG^* values of the present isomerization, calculated at appropriate temperatures, are summarized in Table 2, and compared with the bar-

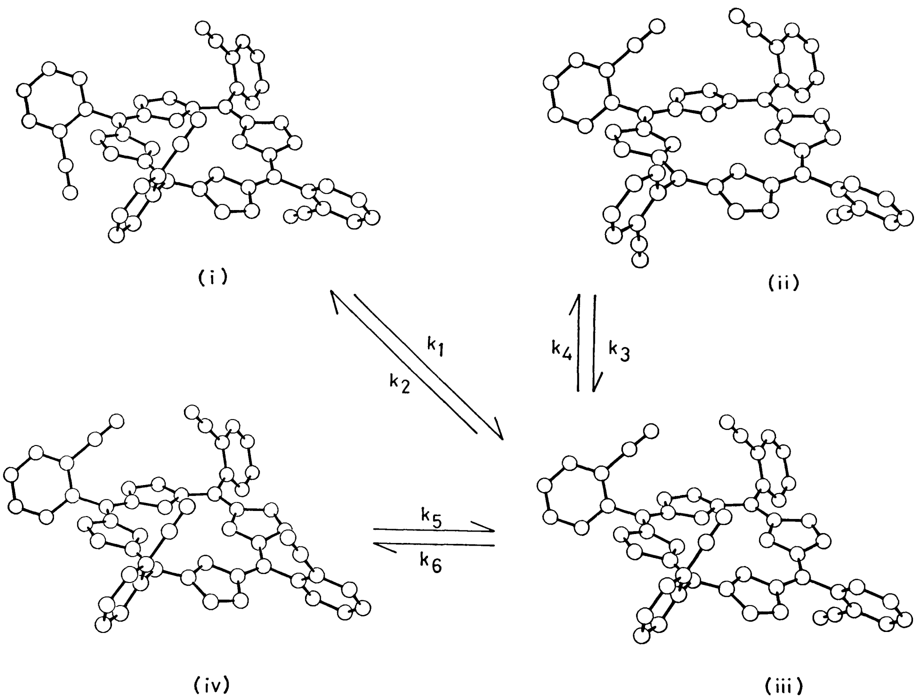

Fig. 1. Schematic representation of the rotational isomerizations of ToCNPP. The k_i denote the first-order rate constant of the reaction.
(i) α,β,α,β-, (ii) α,α,β,β-, (iii) α,α,α,β-, (iv) α,α,α,α-, conformations.

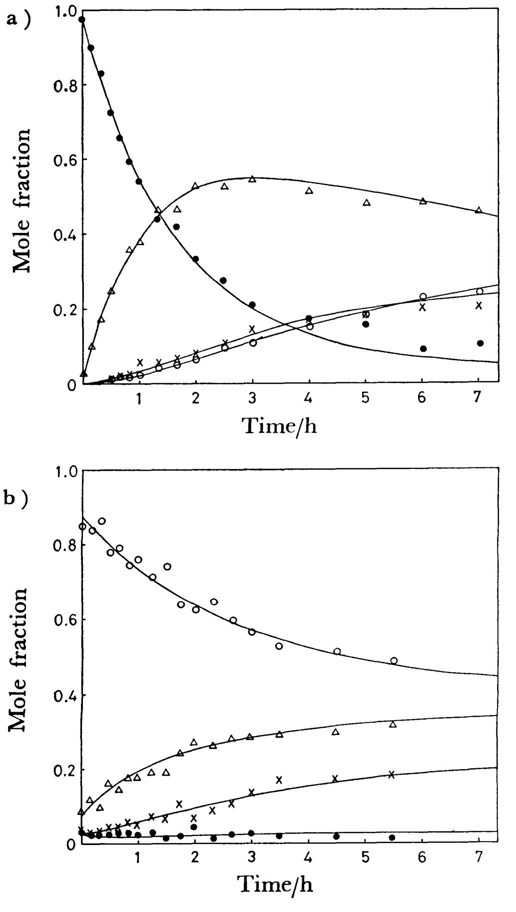

Fig. 2. Time course of isomerization reactions starting from (a) iv at 50 °C and (b) i at 60 °C.
(○) i; (×) ii; (△) iii; (●) iv. The solid lines represent the computer simulations.

Table 1. The first-order rate constants for the rotational isomerization of ToCNPP

Temp	Rate constants/h^{-1}					
°C	k_1	k_2	k_3	k_4	k_5	k_6
50	0.089	0.100	0.220	0.135	0.609	0.052
60	0.228	0.256	0.583	0.361	1.730	0.148

riers reported in literature.1–4)

The order $CN > CH_3 \approx CH_3O \approx OH$ is seen in the barriers. The cyano substituent on the ortho position of a phenyl ring has a higher rotational barrier, as expected by the bulk of the constituted atoms, than OH or CH_3. Moreover, since the CN group is erected linearly from the phenyl ring while CH_3O is bent at the oxygen atom, the awkwardness of CN passing through the porphyrin plane may contribute some kJ/mol to the activation state as compared with the flexible methoxide. The calculated rate constant for the rotation about one cyanophenyl-porphyrin bond at 23 °C is of the order of 10^{-6} s^{-1}. This value allows direct comparison with the only explicit parameter reported for ToOHPP.1) That the rate in ToCNPP is about a tenth of that in ToOHPP indicates the reasonable substitution effect for CN.

The abundance ratio of the ToCNPP isomers deviates from the statistical expectation. This is the first reported example of the quantitative measurement for a nonstatistical distribution of porphyrin atropisomers. This can be interpreted as the non-bonded interactions of a CN substituent to CN substituent. The small mole fraction of iv indicates the interaction to be repulsive or maybe electrostatic. With consideration of the statistical ratios, the relative free

Table 2. Activation energy and free energy of activation for a phenyl ring rotation, and energy of steric interaction between neighboring substituent groups at ortho position of the phenyl ring in several porphyrins

Substituent group	E_a kJ mol^{-1}	ΔG^*/kJ mol^{-1} 296 K	433 K	453 K	E_{int}[c] kJ mol^{-1}	Ref.
CN	88.5[a]	108	118	120	2.0	This work
OH	—[b]	100	—	—	0	1
OCH_3	—[b]	—	108	—	0	4
CH_3[d]	—[b]	—	—	>109	0	2

a) Averaged value. b) The data were not shown. c) See text. d) Ni complex.

energy differences of any one of the isomers can be determined by the relationship $\Delta G^\circ = -RT \ln K$. The energy levels of ii, iii, and iv lie at 3.2, 4.0, and 7.9 kJ/mol above the level of i, respectively, based on the experimental data observed at 50 °C. The repulsive forces are thought to be due to the nitrogen atom of CN, because no such effect is reported for OH, NH_2, or CH_3 substituents. The intramolecular atomic distances of the nitrogen to the adjacent or diagonal nitrogen are interesting parameters to evaluate the long range and weak non-bonded interactions. Supposing that the dihedral angles between the porhyrin plane and all phenyl rings are 90° in molecule iv, the distances are estimated to be 6.1 Å between the adjacent nitrogens and 8.6 Å between the diagonal ones. The latter does not seem to be responsible for the interaction as it must be further than the distance between the adjacent nitrogens of NH_2 in α,α,α,α-$ToNH_2PP$. This static model leads to the conclusion that the energy of an interaction between two nitrogens of CN 6.1 Å apart is 2.0 kJ per mole unit of interaction, since iv has four interactions. This value is also consistent with the interactions in iii. The smaller value seen in ii is perhaps the result of lessened contacts between adjacent cyano phenyl rings resulting from tilting a bit more away from each other, but without making any new closer contacts. However, we do not necessarily predict that the dihedral angles between the porphyrin plane and phenyl planes in the crystal of ii are as small as the smallest angles found in metallotetraphenylporphyrins.[20] There are many examples of intermolecular contacts shorter than 6.1 Å, a result of crystal packing effects. We do, however, claim that the long range (6.1 Å) and appreciable (2.0 kJ/mol·interaction) interaction between the CN groups is observed in the atropisomers of ToCNPP. The unfavorable effect on the isolation of α,α,α,α-isomer may be overcome by the utilization of the intermolecular interaction, *e.g.*, adsorbance,[5] selective crystalization and so on.

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