Computer Analyses of Complex Kinetics Containing Equilibrium Processes. Example of Application for Unusual Atropisomerization of a Tetraphenylporphyrin Derivative

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Kinetic behavior of atropisomerization of tetraphenylporphyrin derivative containing equilibrium processes of dimer formation were analyzed directly by a non-linear least square optimization method which uses numerical integration of kinetic differential equations. Analyses clearly indicate a kinetic model determined with one rate and two equilibrium constants as the most plausible mechanism.

Recently we found an interesting atropisomerization system of meso-tetrakis(2-carboxy-4-nonylphenyl)porphyrin **1** which gave αααα-atropisomer exclusively at the final equilibrium state.[1] It has been known that the usual atropisomerization process is well explainable by using kinetic model 1 shown in Figure 1 where each rate constant for the isomerization processes is given by a statistically weighted rotational rate of the benzene ring and the isomer ratio of αααα/ααββ/αααβ/αβαβ = 1/2/4/1 is expected at the final equilibrium state.[2] It is evident that this standard model can not explain present unusual atropisomerization where the αααα isomer is practically the sole product at the final state. The observation indicates that a new kinetic model is necessary for further analyses of this system. Since spectroscopic investigations suggest that the αααα isomer of **1** is effectively stabilized via dimer formation, kinetic models such as model 2 - 4 emerge as the plausible mechanism of the atropisomerization of **1**. We report here procedures and a new program which make it possible to analyze these complex kinetic systems containing equilibrium processes.

The differential equations describing reaction dynamics of model 2 - 4 do not give simple analytically integrated forms, in contrast to those for model 1.[3] To analyze these systems, we used a new program REDAP which executes a least square optimization procedure using numerical integration for generation of theoretical kinetic traces.[4] REDAP is able to treat not only kinetic processes described by a set of differential equations but also thermodynamic processes which reach equilibrium much rapidly than the kinetic processes and are described by equilibrium equations.[5] The numerical integration in REDAP was performed with the Runge-Kutta-Gill procedure[6] and the damping Gauss-Newton[7] or Marquardt[8] algorithm was employed as the non-linear least square optimization method. In each cycle of numerical integration, the concentrations of αααα and/or αααβ and their dimers were evaluated with their equilibrium equations. Among the models examined in this work, the model 2 is the most simple system which contains one equilibrium process of αααα dimer formation in addition to the model 1. The model 3 is schematically similar to the model 2 but defined with six different rate constants for each kinetic process. The model 4 is presented by the same kinetic system as the model 1 having one common rate constant but contain two dimer formation equilibrium processes for αααα and αααβ isomers. The kinetic and equilibrium equations which describe the systems are given as subroutines in REDAP and, for example, the following set of equations is used for the analysis of the model 4;

$d[\alpha\alpha\beta\beta]/dt = 2k([\alpha\alpha\alpha\beta]-2[\alpha\alpha\beta\beta])$

$d[\alpha\beta\alpha\beta]/dt = k([\alpha\alpha\alpha\beta]-4[\alpha\beta\alpha\beta])$

$d[\alpha\alpha\alpha\beta]/dt = 4k([\alpha\alpha\beta\beta]+[\alpha\beta\alpha\beta]+[\alpha\alpha\alpha\alpha]-[\alpha\alpha\alpha\beta])/(1+4K_2[\alpha\alpha\alpha\beta])$

$d[\alpha\alpha\alpha\alpha]/dt = k([\alpha\alpha\alpha\beta]-4[\alpha\alpha\alpha\alpha])/(1+4K_1[\alpha\alpha\alpha\alpha])$

$d[\alpha\alpha\alpha\beta]_T/dt = d([\alpha\alpha\alpha\beta]+2[(\alpha\alpha\alpha\beta)_2])/dt = (1+4K_2[\alpha\alpha\alpha\beta])\cdot d[\alpha\alpha\alpha\beta]/dt$

$d[\alpha\alpha\alpha\alpha]_T/dt = d([\alpha\alpha\alpha\alpha]+2[(\alpha\alpha\alpha\alpha)_2])/dt = (1+4K_1[\alpha\alpha\alpha\alpha])\cdot d[\alpha\alpha\alpha\alpha]/dt$

In these expressions, the observed concentrations of the αααα and αααβ isomers, $[\alpha\alpha\alpha\alpha]_T$ and $[\alpha\alpha\alpha\beta]_T$, are presented as $[\alpha\alpha\alpha\alpha]+2[(\alpha\alpha\alpha\alpha)_2]$ and $[\alpha\alpha\alpha\beta]+2[(\alpha\alpha\alpha\beta)_2]$ respectively, because, due to their rapid equilibrium, these monomer and dimer species are not observed separately by HPLC which employed as the analytical method in this work. Following equations derived from the equilibrium conditions were also used as the relationship between the concentrations of these monomer and dimer species.

$d[(\alpha\alpha\alpha\alpha)_2]/dt = 2K_1 d[\alpha\alpha\alpha\alpha]/dt$, $d[(\alpha\alpha\alpha\beta)_2]/dt = 2K_2 d[\alpha\alpha\alpha\beta]/dt$

Similar sets of differential equations are also easily written for the model 2 and 3. In the calculations, all these rate and equilibrium constants were used as optimization parameters. The results of fitting by use of these kinetic models are summarized in Figure 2 and Table 1.

Although the model 2 roughly reproduces the trend of exclusive production of the αααα isomer at the final state, this

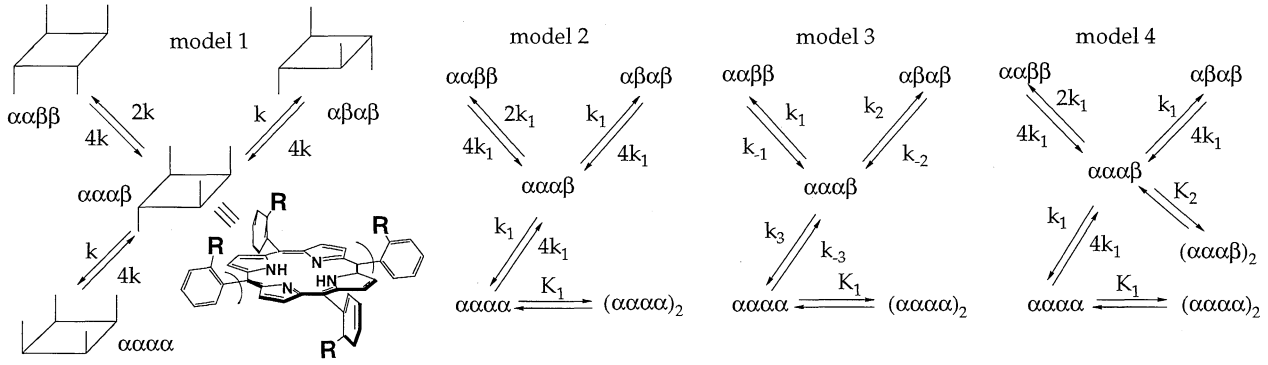

Figure 1. Four different kinetic models for atropisomerization of tetraphenylporphyrin derivatives.

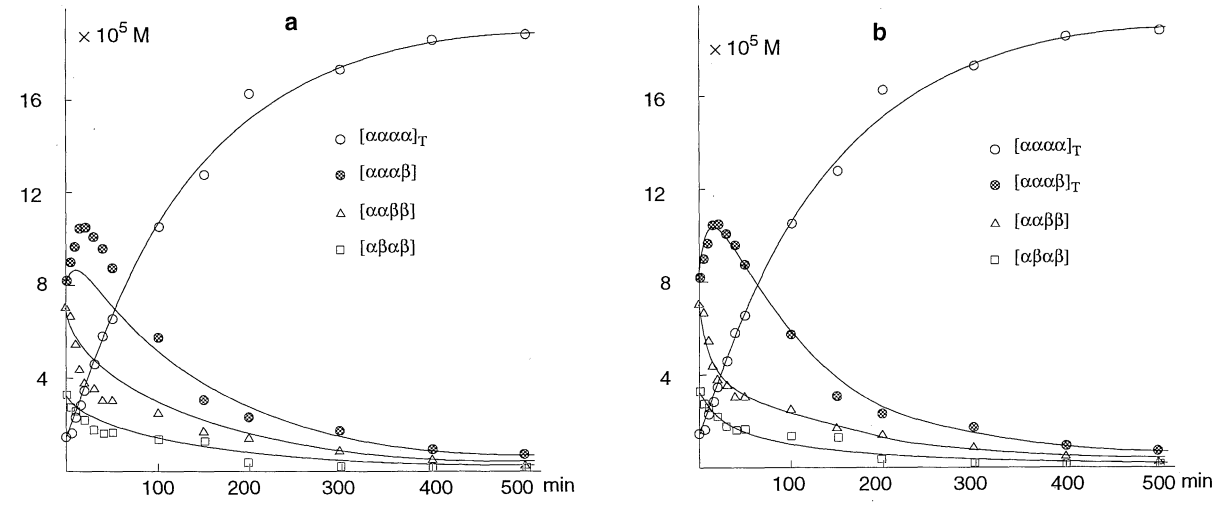

Figure 2. Fitting results for (a) model 2 and (b) model 4. The solid lines show the theortical curves generated by REDAP using parameters shown in Table 1. Fitting results for model 3 are very similar to those for model 4.

model results in the significant deviations from the observed kinetic traces for other isomers as shown in Figure 2a. The model 3 does not give a normal stable parameter set under the usual convergent conditions.[9] The parameters obtained under the more milder conditions, however, shows good fitting with the experimental data as indicated by the smaller residual square sum value, ss (the calculated curves are not shown in Figure 2 but apparently almost same with those of Figure 2b). Finally, optimization for the model 4 results in normal convergence and shows excellent agreement with all kinetic traces as shown in Figure 2b. It should be noted that the model 4 gives better fitting (smaller ss) than the model 3, even though the former is defined with much fewer parameters than the latter. Since there is no rational reason for assuming six different rate constants for rotation of each benzene ring of **1** at the present stage, the results strongly indicate that the model 4 is the most plausible mechanism of atropisomerization of **1** not only from viewpoint of statistics but also from viewpoint of Ockham's razor.[10] Thus, the present results demonstrate that the combination of non-linear least square optimization and numerical integration may be utilized as a powerful tool for analyses of complex kinetic models containing equilibrium processes.

Table 1. Optimized parameters for kinetic models of atropisomerization of **1** [a]

model	$k_{\pm1}$	$k_{\pm2}$	$k_{\pm3}$	K_1	K_2	ss [b]
		$\times 10^2$ min^{-1}		$\times 10^{-5}$ M^{-1}		$\times 10^{10}$
2	1.3 (0.1)	—	—	1000 (3000)	—	32.6
3 [c]	1.7	5.9	0.85	530	—	7.93
	5.6	1.1	2.1			
4	1.7 (0.1)	—	—	740 (340)	0.045 (0.005)	5.50

[a]The experimental conditions ; $[\mathbf{1}]_{Total} = 2 \times 10^{-4}$ M, at 80 °C in $CHCl_2CHCl_2$. Standard deviations are given in parentheses. [b]Residual suquare sum. [c]Standard deviations are not given, because optimization gives no convergent parameter.

The main source code and examples of test applications of REDAP are available from the author on request.

References and Notes

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3 The model 1 gives analytically integrated rate expressions.
4 REDAP (**Re**action **D**ynamics **A**nalysis **P**rogram) is written in C language, runs on NEC PC9800 series computers and includes a graphic routine for presentation of results.
5 A similar program was reported as OPKINE. The program treats equilibrium processes based on microscopic reversibility of kinetic processes, see J. J. Baeza Baeza, G. R.Ramis Romos, F. Perez Pla, R. Valero Mokina, *Analyst*, **115**, 721 (1990), F. Perez Pla, J. J. Baeza Baeza, G. Ramis Ramos, J. Palou, *J. Comp. Chem.*, **12**, 283 (1991).
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9 REDAP stops the optimization procedures when change rates of the residual square sum and the all parameters are less than 0.001% and 0.01%, respectively.
10 The present results do not exclude the possible perticipation of a hetero-dimer such as αααα•αααβ. At the present stage, we should consider the K_1 and K_2 values as a kind of avaraged values affected by existence of the hetero-dimer. The formation constants of such hetero-dimers, however, are reasonably expected to be as small as K_2 compared with K_1.