

Stoichiometry-dependent Photodimerization of Tranilast in a γ -Cyclodextrin Inclusion Complex

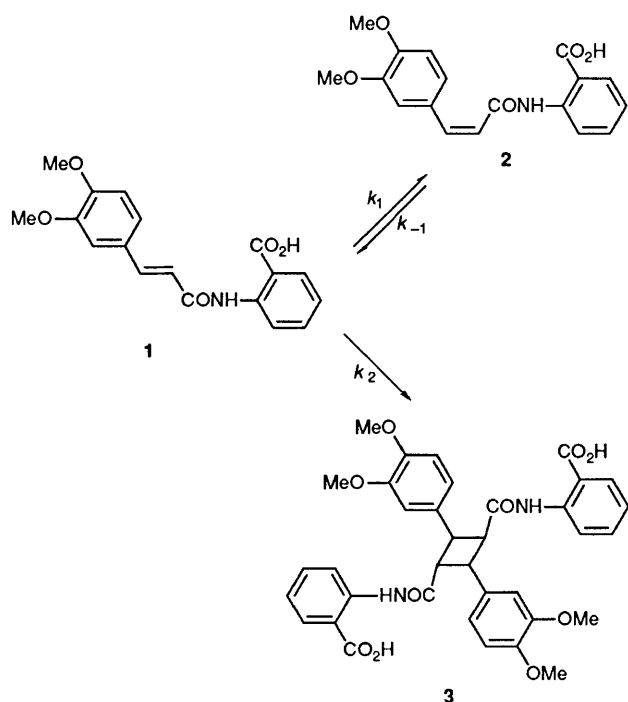
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The photodimerization of tranilast is markedly accelerated by the 2 : 1 (guest : host) complexation with γ -cyclodextrin, but decelerated by the 1 : 1 and 1 : 2 complexations.

γ -Cyclodextrin (γ -CD) is a cyclic oligosaccharide made up of eight glucose monomers, and exhibits the unique property of including two guest molecules in its large cavity.¹ Ternary complexations with γ -CD have mostly been studied by using various spectroscopic techniques.² As yet, however, kinetic evidence on the ternary complexation has been rather scarce, except for a few reports where bimolecular reactions such as Diels–Alder cycloadditions³ and dimerizations of anthracene⁴ have been assisted by β -CD or γ -CD. Now, we report clear kinetic evidence that γ -CD forms inclusion complexes with different stoichiometry, affecting the photodimerization rate of an antiallergic drug tranilast **1**, *N*-(3,4-dimethoxycinnamoyl)anthranilic acid.⁵

An aqueous solution of **1** (phosphate buffer, pH 7.0 and μ 0.2 mol dm⁻³) was irradiated at 25 °C with a UV-A lamp (Toshiba FL20SE-30, Tokyo) which emits between 320 to 400 nm with a maximum at 365 nm. Concentrations of **1** and its photoproducts, (*Z*)-isomer **2** and dimer **3**, were measured by high performance liquid chromatography.† The isomerization and dimerization rate constants (Scheme 1) were determined by analysing the concentration–time curves of the three species, according to parallel first- and second-order kinetics, respectively, using a least-squares method.



Scheme 1 Photoreaction pathway of **1**

† Under the experimental conditions, no products other than **2** and **3** were obtained (mass balance greater than 98%), and the reaction pathway of Scheme 1 was not changed by the addition of γ -CD. The structure of **3** was determined to be the anti-head-to-tail dimer resulted from **1**, not from **2** or **1** and **2**, by comparison of the ¹H NMR spectroscopy data with the literature.⁶

Fig. 1 shows the changes in the photodimerization rate constant (k_2) of **1**, as a function of concentration of γ -CD or **1**. The dimerization of **1** was accelerated with increasing concentration of γ -CD up to about 3.0×10^{-5} mol dm⁻³, but decelerated with further increase of γ -CD concentration. At a constant concentration of γ -CD [Fig. 1(b)], however, k_2 decreased initially and then increased with increasing concentration of **1**. The isomerization rates (k_1 and k_{-1}) were simply decreased over the γ -CD concentration range employed. These results suggest that the dimerization rate of **1** is controlled by the stoichiometry of the complex.

The continuous variation plot⁷ for **1**– γ -CD complex was made at a relatively low concentration, and was maximum at 0.33, as shown in Fig. 2, indicating the 2 : 1 (guest : host) stoichiometry. On the other hand, the solid complex with 1 : 2 (guest : host) stoichiometry precipitated at a higher γ -CD concentration (above 3.0×10^{-2} mol dm⁻³), which was identified by the solubility method,⁸ powder X-ray diffraction and chemical analysis of the isolated complex. Thus, the following equilibria and rate equation^{9,10} were considered

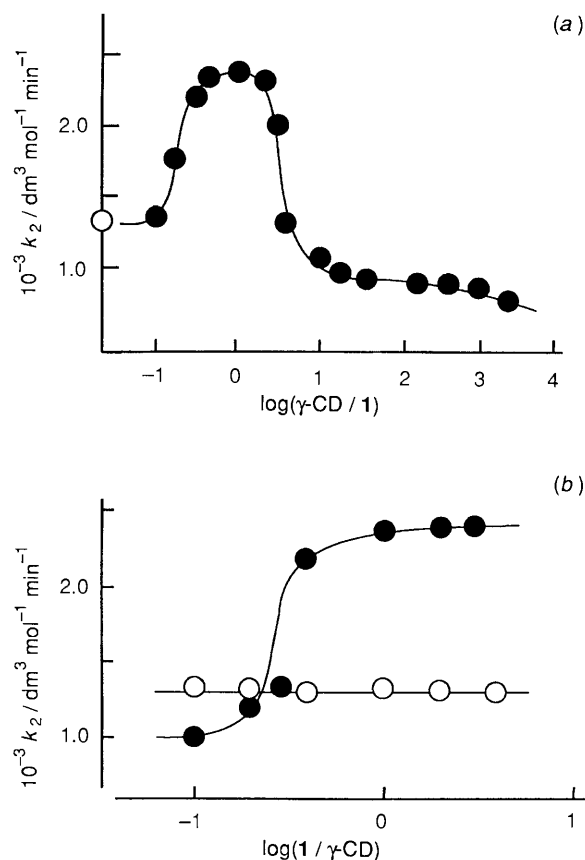


Fig. 1 Photodimerization rate constants k_2 of **1** vs. molar ratios of γ -CD and **1**: (a) concentration of γ -CD was varied, while that of **1** was constant (2.5×10^{-5} mol dm⁻³); (b) concentration of **1** was varied, while that of γ -CD was constant (2.5×10^{-5} mol dm⁻³): (○) in the absence of γ -CD; (●) in the presence of γ -CD. Solid curves show the theoretical k_2 calculated by using the rate constants and association constants in the text.

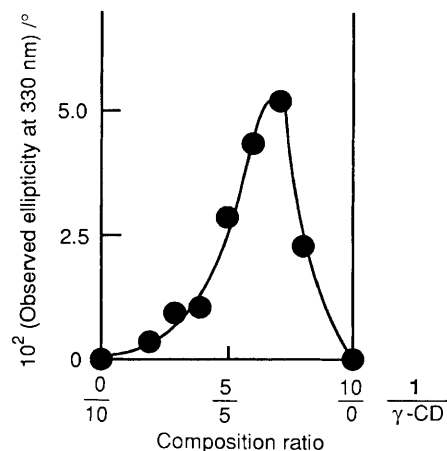
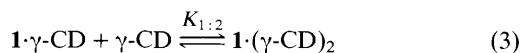
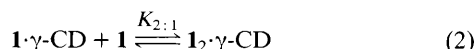


Fig. 2 Changes in ellipticity at 330 nm of **1**- γ -CD system in phosphate buffer (pH 7.0, μ 0.2 mol dm⁻³) at 25 °C, monitored by the continuous variation method. The total concentration of **1** and γ -CD was 5.0 \times 10⁻⁶ mol dm⁻³.

to interpret the γ -CD concentration-dependence of the dimerization rate [see eqns. (1)–(4)]; where $K_{1:1}$, $K_{2:1}$ and $K_{1:2}$ are association constants of the 1:1, 2:1 and 1:2 complexes, respectively. In eqn. (4), I_t is the total concentration of **1**, and k_0 , $k_{1:1}$, $k_{2:1}$ and $k_{1:2}$ are dimerization rate constants of **1**, **1**· γ -CD with **1**, **1**₂· γ -CD, and **1**·(γ -CD)₂ with **1**,



$$k_2[I_t]^2 = k_0[\mathbf{1}]^2 + k_{1:1}[\mathbf{1} \cdot \gamma\text{-CD}][\mathbf{1}] + k_{2:1}[\mathbf{1}_2 \cdot \gamma\text{-CD}] + k_{1:2}[\mathbf{1} \cdot (\gamma\text{-CD})_2][\mathbf{1}] \quad (4)$$

respectively. The association constants and rate constants of the complexes were determined by analysing the curve of Fig. 1(a) using a least-squares method. The results were as follows; $K_{1:1} = 250 \pm 10$, $K_{2:1} = 2240 \pm 110$ and $K_{1:2} = 1050 \pm 70$ dm³ mol⁻¹, and $k_0 = 1330 \pm 5$, $k_{1:1} = 930 \pm 20$, $k_{1:2} = (5.23 \pm 1.2) \times 10^{-2}$ dm³ mol⁻¹ min⁻¹ and $k_{2:1} = 3240 \pm 50$ min⁻¹. The γ -CD induced rate changes become more apparent when the rate constant is compared in second-order dimension. For example, the dimerization rate in **1**₂· γ -CD complex is faster by about 7800 times than that in **1**· γ -CD complex ($k_{2:1} \times K_{2:1} = 7.26 \times 10^6$ dm³ mol⁻¹ min⁻¹ and $k_{1:1} = 930$ dm³ mol⁻¹ min⁻¹), whereas that in **1**·(γ -CD)₂ complex is suppressed about 17 800 times. Fig. 3 shows inclusion modes of the three complexes estimated from the above kinetic results, together with space-filling molecular models. At higher **1**: γ -CD molar ratios, two of **1** are included in the γ -CD cavity in a head-to-tail mode favourable for the photodimerization, leading to the marked acceleration. With increasing γ -CD concentration, one of **1** is withdrawn from the 2:1 complex and forms the 1:1 complex, which retains the residual dimerization-reactivity because of the partial inclusion. At lower **1**: γ -CD molar ratios, however, **1** is completely included by two γ -CDs and its photoreactivity is lost because of the inaccessibility of one more **1** to the 1:2 complex. Thus, the present results indicate clearly that the stoichiometric change of the γ -CD complex affects the photodimerization of **1**, and guest: host molar ratios may have to be optimized to achieve maximal acceleration or deceleration for other

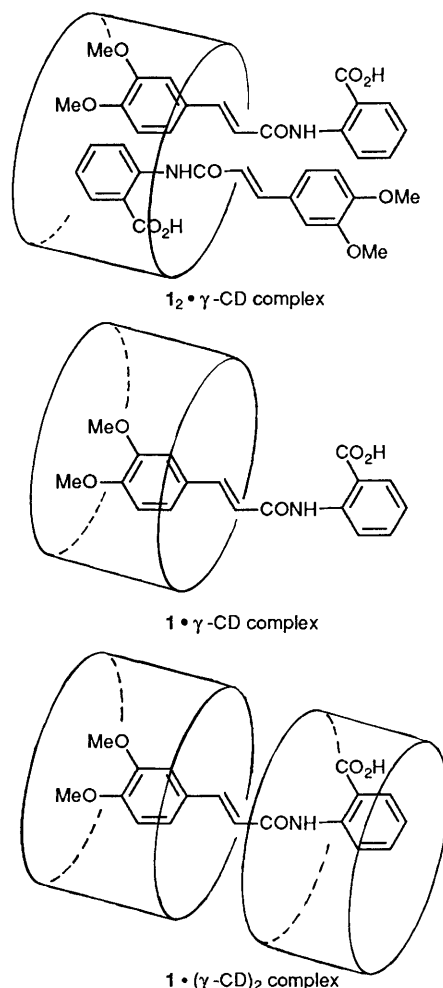


Fig. 3 Proposed inclusion modes of **1**- γ -CD complexes

dimerizing systems of CD complexes. Further studies are now under way to elucidate the detailed inclusion structure and the rate-perturbing mechanism.

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