

The first volume profile for a host–guest interaction: a variable pressure kinetic study of an inclusion reaction with α -cyclodextrin

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The full volume and entropy profiles of the inclusion reaction between α -cyclodextrin and the guest molecule, mordant yellow 7, are constructed from variable pressure and temperature kinetic experiments, showing a two-step mechanism where both steps involve contracted transition states.

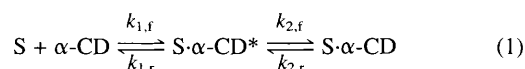
Inclusion reactions involving cyclodextrins as molecular hosts have shown that guest molecules of differing structures are able to be non-covalently bound in the hydrophobic host cavity. It has also been found that cyclodextrins show a degree of selectivity for guest molecules, which has been related to both electrostatic and steric effects which may vary with each particular guest.¹ The nature of the guest molecule also strongly influences the direction of insertion into the host cavity. Despite the wealth of interest in inclusion complexes of α -cyclodextrin (α -CD), there has been relatively few kinetic studies and of these none have involved high-pressure kinetic measurements.^{2–4}

Whereas temperature dependences can provide information about energy differences and activation energies, the investigation of pressure dependence gives information about volume differences and activation volumes. In the field of inorganic chemistry, kinetic studies of substitution reactions at different pressures, for example, have been extensively applied and have enabled mechanistic discriminations of basic importance.⁵ Among other aspects, this success of high-pressure studies can be related to the fact that it is comparatively simple to interpret volume differences in molecular terms even in the case of complex chemical systems where it is often very difficult to interpret entropy differences on a similar level. Therefore in an effort to further elucidate the complex mechanisms involved in the inclusion reactions of α -CD, we describe here the first high-pressure kinetic study of α -CD reacting with the azo dye mordant yellow 7 (S, see Scheme 1). It has been shown previously that inclusion of the dye proceeds exclusively *via* the sulfonate end of the substrate due to the fact that the methylsalicylate group is too large to be incorporated into the α -CD cavity.³

Both the dye [(2.5–5) $\times 10^{-5}$ M] and uncharged α -CD [(0.3–4.9) $\times 10^{-3}$ M] were dissolved in doubly distilled water. No electrolyte was added so as to avoid the possible formation of inclusion complexes with electrolyte ions. With the pH of both solutions around 6.5, the dye exists predominately in the form where both the carboxylate and sulfonate groups are

deprotonated ($pK_{a1} = 2.46 \pm 0.02$, $pK_{a2} = 11.88 \pm 0.01$, determined by spectrophotometric titration). ¹H NMR experiments that we have performed provide evidence for the inclusion of the dye inside the α -CD cavity, as described previously for analogous systems.^{4c,6}

The kinetics of the inclusion reaction between the dye, S, and α -CD [eqn. (1)] has been investigated by the stopped-flow



technique under pseudo-first-order conditions in the presence of at least a ten-fold excess of α -CD. Two distinct rate constants were observed as can be seen from the typical measurement shown in Fig. 1. If the first step is very fast compared to that of the second step in eqn. (1), the observed rate constants, $k_{1,obs}$ and $k_{2,obs}$, can be expressed by eqns. (2) and (3), where $K_1 = k_{1,f}/k_{1,r}$.

$$k_{1,obs}(\text{fast}) = k_{1,r}C_{\alpha\text{-CD}} + k_{1,r} \quad (2)$$

$$k_{2,obs}(\text{slow}) = k_{2,r} \frac{K_1 C_{\alpha\text{-CD}}}{(1 + K_1 C_{\alpha\text{-CD}})} + k_{2,r} \quad (3)$$

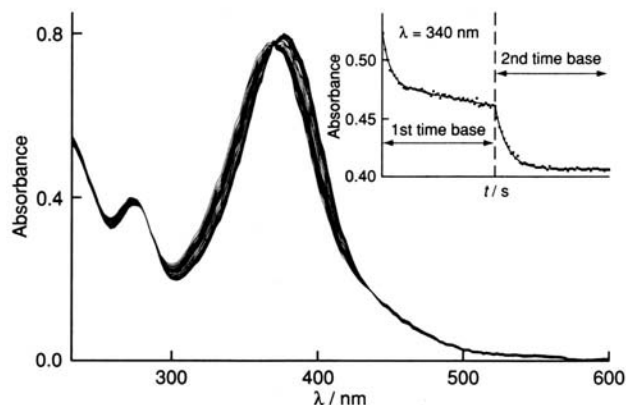
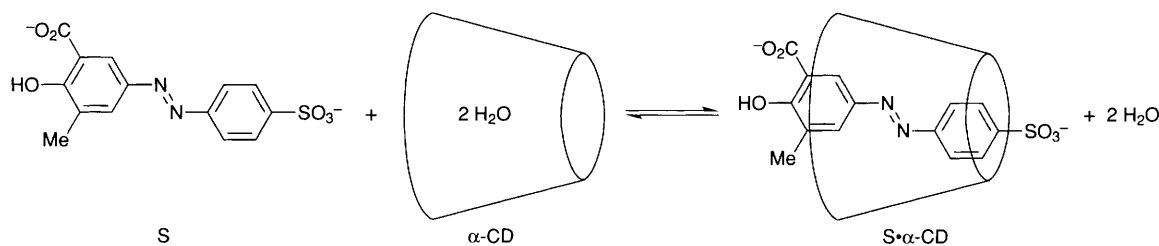


Fig. 1 Time-dependent spectra, at 200 MPa, of the inclusion reaction between mordant yellow 7 and α -CD at 288 K. The insert shows a single trace at 340 nm, showing 100 measurements over a split time base (acquisition time = 3 ms per spectrum, total first time base = 0.153 s, total second time base = 4.647 s). $C_{\alpha\text{-CD}} = 8 \times 10^{-4}$ M $C_S = 5 \times 10^{-5}$ M, I (ionic strength) = 0 M.



Scheme 1

The activation parameters ΔH^\ddagger and ΔS^\ddagger were obtained by measuring the reaction rates over the temperature range 278–318 K.‡ The volume of activation, ΔV^\ddagger , was measured with our high-pressure stopped-flow spectrometer⁷ at 288 K (Fig. 2).§,¶ The entropy and volume reaction profiles are presented in Fig. 3.

The rate at which the sulfonate group enters the α -CD cavity ($k_{1,t}$) is comparable with those observed previously with analogous azo dyes.^{3,4} The release rate of the dye (as measured by $k_{1,r}$) is more dependent on the structure of the whole dye molecule.^{3,4} This implies that for the intermediate, S- α -CD*,

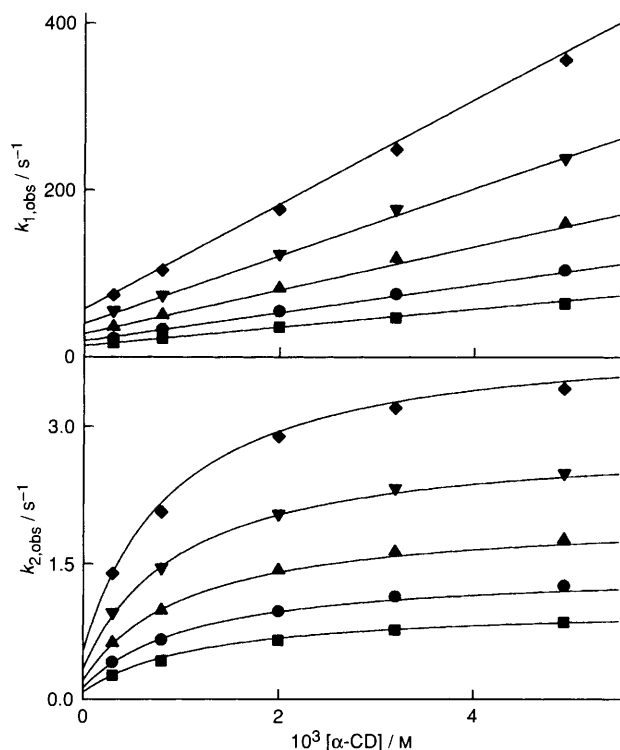


Fig. 2 Pressure dependence for both $k_{1,obs}$ and $k_{2,obs}$ for the inclusion reaction of mordant yellow 7 with α -CD; $C_S = 2.5\text{--}5 \times 10^{-5}$ M, $I = 0$ M, $T = 288$ K, $P = 2$ (■), 50 (●), 100 (▲), 150 (▼), 200 MPa (◆), $[k_{1,r}^{298} = (1.52 \pm 0.03) \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$, $k_{1,r}^{298} = 25.4 \pm 0.5 \text{ s}^{-1}$, $K_1^{298} = 598 \pm 24 \text{ M}^{-1}$, $k_{2,r}^{298} = 1.83 \pm 0.04 \text{ s}^{-1}$, $k_{2,r}^{298} = 0.17 \pm 0.02 \text{ s}^{-1}$, $K_2^{298} = 10.5 \pm 1.1]$

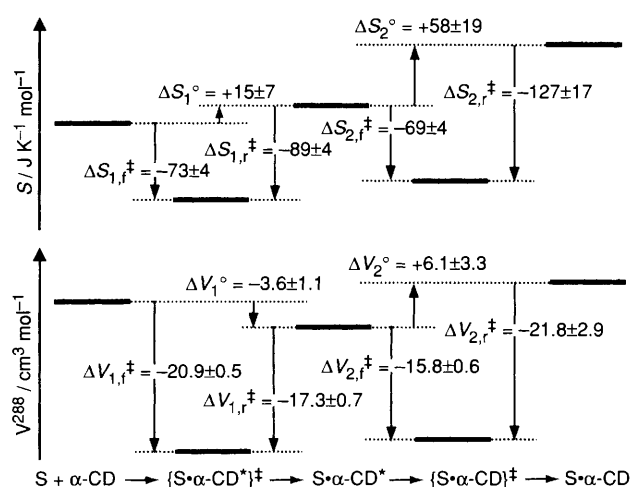


Fig. 3 Entropy and volume reaction profiles for the inclusion formation and dissociation reactions between mordant yellow 7 and α -CD, in aqueous solution

the dye is most probably completely inserted inside the α -CD cavity, and close to the final equilibrium position S- α -CD. The first step requires the desolvation of the sulfonate group when the guest is initially included in the cavity. At the first transition state, strong interactions can exist between the sulfonate group and the two not fully coordinated 'activated' water molecules which are included in the cavity.² This interaction should be the principle contribution to the significant contraction at the transition state, as shown by the large negative value of $\Delta V_{1,t}^\ddagger$. In the intermediate state, the sulfonate group is resolvated from the bulk water, as it was initially, resulting in a slowing of the reverse step and also hindering further access to the cavity. The two 'activated' water molecules have left the cavity, thus enabling full hydrogen bonding with the water molecules from the bulk. This explains the small negative volume of reaction ΔV_1° for the first step.

The second step is assumed to be a subsequent intramolecular rearrangement of the intermediate complex which is in equilibrium with a more stable final inclusion complex of relatively similar volume (ΔV_2°). This slow process is anticipated owing to the intramolecular motion in the small α -CD unit. The very negative $\Delta V_{2,r}^\ddagger$ value may be explained by the formation of hydrogen bonds between the hydroxy and carboxylate groups of the dye and α -CD. It has been suggested that an 'empty' α -CD in water exists in a distorted conformation, which arises as a result of the rotation of one or more D-glucose rings around glycoside linkages. For better overlap between α -CD and the dye, this distorted conformation is relieved to have a relaxed conformation of the α -CD in the final product.² The entropy profile displays the same trends as the volume profile (Fig. 3).

We have shown that, as in inorganic chemistry, high-pressure techniques are a powerful tool in the elucidation of inclusion reaction mechanisms, as they provide valuable information at the molecular level.

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Footnotes

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‡ Temperature-dependent kinetic studies were carried out on a Applied Photophysics SX.18MV stopped-flow spectrometer using the multiple shot facility.

§ Pressure-dependent kinetic measurements were carried out using a J&M TIDAS diode array spectrometer (Fig. 1).

¶ The observed rate constants were calculated from the multiwavelength data sets via global analysis software. Simultaneous analysis of the k_{obs} values yielded the activation parameters values, which are listed in Fig. 3.

|| $K_2 = k_{2,t}/k_{2,r}$.

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