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Guest–host interactions in the cleavage of phenylphenyl acetates by β-cyclodextrin in alkaline medium

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Abstract. Kinetics of cleavage of phenylphenyl acetates (PPA) and several *para*-substituted PPAs in basic aqueous sodium carbonate–bicarbonate buffer containing β-cyclodextrin (CD) have been studied. The reaction exhibits saturation type kinetics and CD accelerates the rate of cleavage by the formation of 1G : 1H inclusion complex. The kinetic results indicate that aryloxy moiety of PPA is included in the hydrophobic cavity of CD. The overall rate constants for the cleavage of the [CD–ester] complex correlate with the Hammett σ-constants and Hansch hydrophobicity parameters π. At higher concentrations of CD, there is an additional catalysis due to the formation of weak 1G : 2H complex.

Keywords. Phenylphenyl acetate; β-cyclodextrin; hydrophobic interactions; guest–host complexes.

1. Introduction

Cyclodextrins (CD) are typical 'host' molecules and form inclusion complexes with a wide variety of molecules in which the guest molecule is held by non-covalent interactions.[1,2] The main factors affecting the stability of the inclusion complexes are:[3] Vander walls interaction; hydrogen bonding between guest and hydroxyl groups of CD; hydrophobic interactions; solvent surface tension. The stoichiometry of the inclusion complex is generally 1G : 1H.[4–7] But evidences are reported for 2G : 1H and 1G : 2H complexes[8,9] in some cases (G = Guest; H = Host). The rates of chemical reactions are often modified by complexation with CD and this characteristic has led to their utilization as enzyme models. Both CDs and enzyme bind substrates in non-covalent manner. The CDs recognize the size and shape of the guest molecules basically by hydrophobic interaction. Extensive studies have been reported on the rates and mechanisms of chemical reactions catalysed by CDs.[10–13]

In basic aqueous solution CDs cleave phenyl acetates via CD–ester complex in which the phenyl group of the ester resides in the hydrophobic cavity of CD.[14–16] In the cleavage of *p*-nitrophenyl alkanoates by CD, for longer acyl chains (>C6), the alkyl group occupies the CD cavity.[17] But in case of *m*-nitrophenyl alkanoates, the aryloxy moiety is present in the CD cavity.[18] In the cleavage of *para*-carboxyalkanoates[19] by CD, if the ester function is made increasingly hydrophobic, there is an increase in the inhibition on the hydrolysis rate. This is attributed to the inclusion of the alkyl part of the ester in the CD cavity. In phenylphenyl acetate (PPA) both side of the ester group is flanked by aryl groups. Therefore it was thought of interest to investigate the cleavage of PPA catalysed by β-cyclodextrin (CD).

2. Experimental

All the esters were prepared by literature method.[20] Phenyl acetic acid was converted into corresponding acid chloride by refluxing with thionyl chloride. Excess of thionyl chloride was removed by distillation and the acid chlorides were distilled under reduced pressure.

Phenylacetyl chloride (1·32 ml, 0·01 M) was refluxed with phenol (0·94 g, 0·01 M) in chloroform (110 ml) and pyridine (1 ml) for 4 h in a water bath. The resulting solution was extracted with ether and washed with dilute hydrochloric acid. The crude sample was recrystallised from suitable solvents.

Doubly distilled water was used for all the kinetic measurements. All the kinetic measurements were

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made in carbonate–bicarbonate buffer of pH 10·6 at 30°C containing 5% (v/v) acetonitrile. The reaction was monitored by measuring the appearance of phenol at the corresponding λ_{max} with a Hitachi 200-20 UV-Vis. spectrophotometer equipped with a thermostatic cell holder. The pseudo-first order rate constants k_{obs} of the reaction were evaluated from the slope of the plot of $\log(A_\infty - A_t)$ versus time where A_t and A_∞ are the absorbances of the phenol released at time t and after the completion of the reaction respectively.

3. Results and discussion

3.1 *Hammett relationship*

The hydrolysis of PPA and several substituted PPAs was studied in carbonate–bicarbonate buffer of pH 10·6 by measuring the pseudo-first order rate constants, k_{obs}, spectrophotometrically first in the absence of cyclodextrin. The reaction rates vary in the manner expected from the electronic character of the substituents i.e. electron releasing substituents decrease the rate whereas electron-attracting substituents increase the rate with respect to the unsubstituted compound. Rate data give a fairly good fit to Hammett relationship with ρ value of 1·13 ($r = 0{\cdot}980$).

3.2 *Mechanism and rate law*

Addition of β-CD increases the rate of hydrolysis (table 1). Figure 1 shows the variation of k_{obs} with [CD] for p-NO_2 PPA. At low concentrations of CD, the plot shows saturation type kinetics indicating the formation of an inclusion complex (1G : 1H) of the ester with CD. But at higher concentrations of CD there is an additional catalysis involving another molecule of CD. One can envisage the following scheme 1 for the catalytic cleavage of PPA by CD.

The rate law[9] for the scheme 1 is

$$k_{obs} = \frac{k_u K_D + k_{c1}[CD] + K_{c2}[CD]^2}{(K_D + [CD])}, \qquad (1)$$

where K_D is the dissociation constant of CD–ester complex, k_{c1} is the first order rate constant for the dissociation of CD–ester complex (1G : 1H), k_{c2} is the second order rate constant for the cleavage of ester by 2 CD molecules and k_u is the rate constant for uncatalysed pathway.

By appropriate fitting of the kinetic data into equation (1) the rate constants and complex dissociation constants were evaluated for various substituted PPAs (table 2).

3.3 *Mode of insertion in 1G : 1H complex*

In CD catalysed reactions, generally the rate acceleration is measured by k_c/k_u. For all the esters, the rate is accelerated approximately 5–7 fold and the rate of acceleration is not related to the electronic effect of the substituents. The substrate binding constants ($1/K_D$) are also not related to the substituent constants.

In PPA both the groups (aryloxy and aryl) flanking the ester function are hydrophobic. Therefore, either aryloxy or aryl group may occupy the hydrophobic cavity of CD in the 1G : 1H complex (figure 2a, 2b).

It has been shown that in the hydrolysis of phenyl acetates[14] (PA) in the presence of CD, the aryloxy group is included in the CD cavity. The plot of $\log k_c$ of PA (data from reference 14) with $\log k_{c1}$ of PPA is linear with slope nearly equal to unity. Further, the value of K_D for [PPA-CD] complex is sensitive to the nature of the substituents in the aryloxy moiety. These factors indicate that in PPA also the aryloxy

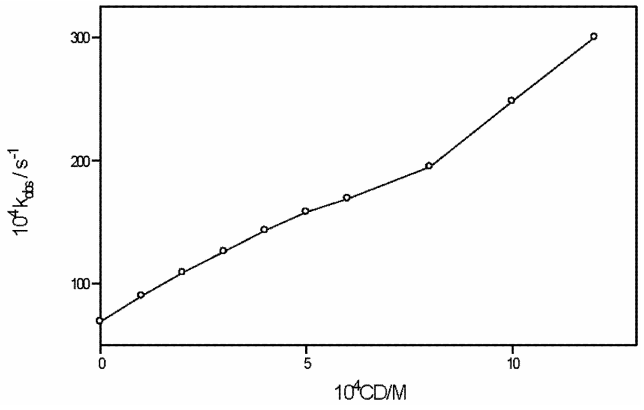

Figure 1. Variation of k_{obs} with [CD] for p-NO_2 PPA.

$$S \xrightarrow{k_u} P$$

$$S + CD \underset{}{\overset{K_D}{\rightleftharpoons}} [S.CD] \xrightarrow{k_{c1}} P$$

$$[S.CD] + CD \xrightarrow{k_{c2}} P$$

Scheme 1.

Table 1. Effect of β-CD on the alkaline hydrolysis of substituted PPA.

	$10^4 k_{obs}/s^{-1}$						
	10^4CD/M						
Sub	0	2	4	6	8	10	12
p-CH_3	6·4	9·4	11·8	13·9	15·9	18·8	21·8
p-H	7·4	10·8	13·6	16·4	18·4	23·6	28·8
p-Cl	11·5	25·4	34·2	45·6	48·0	57·0	66·0
p-Br	12·3	–	39	43·5	47·4	50·8	54·2
p-NO_2	69	109	143	169	195	248	300

Table 2. Rate and equilibrium constants for the catalytic cleavage of PPA by CD.

Substituent	$10^4 k_u/s^{-1}$	$10^3 K_D/mol^{-1}\ dm^3$	$10^4 k_{c1}/s^{-1}$	$10^4 k_{c2}/dm^{-3}\ mol^{-1}\ s^{-1}$	k_{c1}/k_u
p-NO_2	69·0	1·90	488	298	7·0
p-Br	12·3	0·32	58	57	4·7
p-Cl	11·5	0·88	79	60	6·9
p-H	7·4	0·23	50	9·8	6·7
p-CH_3	6·4	1·6	35	4·9	7·0

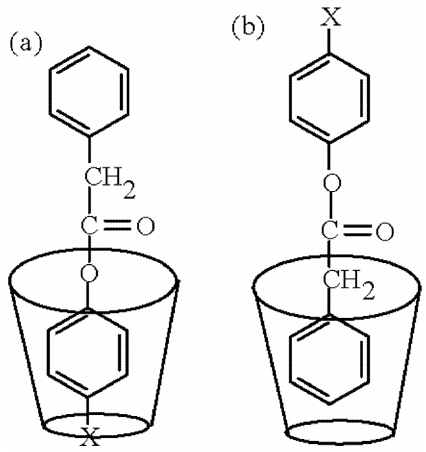

Figure 2. Inclusion complex of CD-PPA.

group is included in the CD cavity in the 1G : 1H complex (figure 2a).

3.4 *Quantitative analysis of hydrophobic interaction*

Generally, in discussion of catalysis by CDs less often the quantity $k_2 = k_c/K_D$ is discussed. It is the apparent second-order rate constant for S + CD → P and measure of the selectivity of CD for the substrate. The k_{c1} value is affected by electronic effect of the substituents; the substrate binding constants largely depend on the hydrophobicity. Therefore, it will be logical to correlate the quantity k_{c1}/K_D with the Hammett σ-constants and Hansch[21] hydrophobicity constants of the substituents.

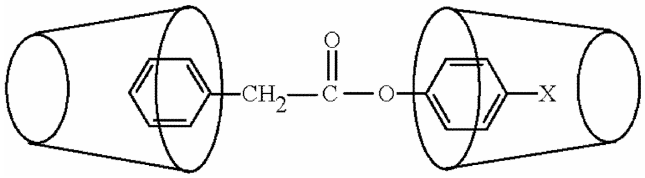

Figure 3. 1G : 2H complex.

For PPA, the quantity k_{c1}/K_D was correlated with σ and π values of substituents by multiple linear regression to give equation (2).

$$\log k_{c1}/K_D = 1{\cdot}40\sigma + 0{\cdot}50\pi + 0{\cdot}34 \quad (R = 0{\cdot}987). \tag{2}$$

These results clearly indicate that the overall reactivity of the CD–ester complex depends on both the electronic effect and hydrophobicity of the substituents present in the aryloxy ring.

3.5 *Formation of 1G : 2 H complex*

At higher concentrations of CD, there is an additional catalysis due to the formation of 1G : 2H complex (figure 3).

In this complex the aryloxy group of ester occupies the hydrophobic cavity of one CD molecule and the aryl ring occupies the cavity of another CD molecule (figure 3). Since the value of k_{obs} increases almost linearly with increase of CD at higher concentrations, the binding in 1G : 2H complex may be

very weak due to the less hydrophobicity of the aryl ring compared to that of aryloxy ring.

4. Conclusions

β-cyclodextrin catalyses the cleavage of phenyl-phenyl acetates by forming 1G : 1H complex at lower concentrations of CD. The overall reactivity of the CD–ester complex depends on the electronic effect and hydrophobicity of the substituents. In the 1G : 1H complex, aryloxy group is included in the hydrophobic cavity of CD. At higher concentrations of CD there is an additional catalysis due to the formation of weak 1G : 2H complex.

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