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D. BETHELL

The Robert Robinson Laboratories
Department of Chemistry
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Preface

With ever increasing specialization among chemists, there is a continuing need to ensure that research in one area is not hampered by lack of awareness of developments in contiguous areas, expressed in language that is understood by both groups of specialists. Over the thirty years of its existence, such bridge-building has been a consistent aim of *Advances in Physical Organic Chemistry* in relation to the physical and organic chemical communities, and a considerable debt is owed to the many contributors who have striven to present their material in an attractive and comprehensible way. More recently the series has sought to reflect the relevance of the physical organic approach to developments in the field of new materials and, in an as yet small but it is hoped increasing way, in the burgeoning realm of bio-organic research. The Editor and his Advisory Board continue to encourage comments on the series, suggestions of topics that are worthy of coverage in future volumes, and, perhaps best of all, offers to contribute articles on any aspect of the quantitative study of organic compounds and their reactions.

D. BETHELL

Contributors to Volume 29

Anthony J. Kirby University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK

Jay K. Kochi Department of Chemistry, University of Houston, Houston, TX 77204-5641, USA

Henry A. Kurtz Department of Chemistry, Memphis State University, Memphis, TN 38152, USA

Oswald S. Tee Department of Chemistry and Biochemistry, Concordia University, Montreal, Quebec H3G 1M8, Canada

Richard V. Williams Department of Chemistry, University of Idaho, Moscow, ID 83844-2343, USA

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The Stabilization of Transition States by Cyclodextrins and other Catalysts

OSWALD S. TEE

Department of Chemistry and Biochemistry, Concordia University, Montreal, Canada

1 Introduction

Enzymes fascinate (and exasperate) chemists because they can catalyse reactions at ambient temperatures and at modest pH, often with high substrate selectivity, regioselectivity, and enantioselectivity. Moreover, they do all this at rates that are 10^6–10^{17} times faster than the uncatalysed reaction. The origins of these impressive feats almost certainly lie in supramolecular behaviour (Lehn, 1985, 1988) since enzymes invariably form

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enzyme·substrate complexes from which the catalysed reactions ensue. Many static and dynamic studies of enzyme behaviour have provided ample evidence of such complexes and great progress has been made in elucidating many of the mechanisms by which enzymes transform their substrates into products (Walsh, 1979; Fersht, 1985; Page and Williams, 1987; Liebman and Greenberg, 1988; Dugas, 1989). At the same time, there have been significant advances in understanding the factors underlying the catalytic abilities of enzymes (Jencks, 1969, 1975; Bender, 1971; Lienhard, 1973; Gandour and Schowen, 1978; Page, 1984; Fersht, 1985), although at times it has seemed as though there were too many theories of enzymatic catalysis, based on the multiplicity of ideas about the efficiency of intramolecular processes (Page, 1984, 1987; Menger, 1985; Page and Jencks, 1987)!

The underlying principle of enzyme catalysis was expounded many years ago by Haldane (1930) and Pauling (1946). According to them, catalysis results from stabilization by the enzyme of the reaction transition state, relative to that of the initial state. This view was developed by Kurz (1963) into a quantitative approach to transition state binding, and hence of transition state stabilization, albeit in the context of catalysis by acids and bases (Kurz, 1963, 1972). His approach was taken up and used by enzymologists (Wolfenden, 1972; Lienhard, 1973; Jencks, 1975; Schowen, 1978; Fersht, 1985; Kraut, 1988), so much so that it is now implicit in many modern studies of enzyme action (see, for example: Fersht *et al.*, 1986, 1987; Leatherbarrow and Fersht, 1987). Of particular note, Kurz's innovation helped to develop the use of "transition state analogues" (Jencks, 1969) as efficient enzyme inhibitors, either for the purposes of mechanistic studies or for possible pharmaceutical use (Wolfenden, 1972; Wolfenden and Frick, 1987; Wolfenden and Kati, 1991). In turn, the availability of transition state analogues as haptens has been critical to the recent development of "catalytic antibodies" (Schultz, 1988, 1989a,b).

The fascination of chemists with enzymes has led, in recent years, to many attempts to model or mimic their action (e.g. Bender, 1971, 1987; Breslow, 1982, 1986a,b; Page, 1984; Tagaki and Ogino, 1985; Kirby, 1987; Stoddart, 1987; Schultz, 1988, 1989a,b; Dugas, 1989; Chin, 1991). The object of such studies has been to understand enzyme action and, in a broader sense, catalysis better, and possibly to learn how to synthesize catalysts ("artificial enzymes") for specific purposes (Breslow, 1982; Schultz, 1988). Many such studies have employed model systems based on the binding and catalytic properties of cyclodextrins (CDs) or their derivatives (Bender and Komiyama, 1978; Breslow, 1980, 1982, 1986a,b; Tabushi, 1982; Komiyama and Bender, 1984; Bender, 1987; D'Souza and Bender, 1987; Tee, 1989). At the same time, CDs have commanded another, more practical and populous audience due to their many potential applications in the food, pharmaceutical, and cosmetic industries (Szejtli, 1982; Pagington, 1987). These differing interests in the chemistry of CDs have led to an explosion in the literature

concerning these molecules in recent years, especially now that they are produced commercially and are available relatively cheaply.

The present review deals with a particular aspect of the chemistry of cyclodextrins: the effects that they can have on organic reactions by virtue of their abilities to bind to many organic and inorganic species (Bender and Komiyama, 1978; Saenger, 1980; Szejtli, 1982). It is a considerable expansion of an earlier work (Tee, 1989) which first showed how the Kurz approach to transition state stabilization can be employed profitably in discussing reactions mediated by cyclodextrins. Most of the large amount of data that are analysed is collected in tables in the Appendix so as to avoid breaking up the discussion in the main text too frequently.

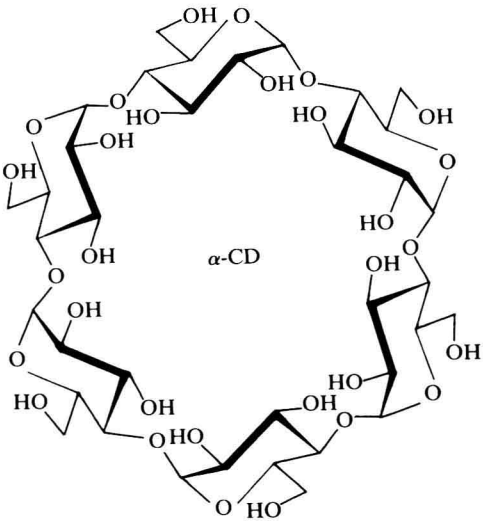
While the main emphasis of this review is on catalysis, since this is of greater interest, the Kurz method can also be applied to retardation. In fact, for some of the systems discussed later, the smooth transition from retardation, through inactivity, to full catalysis can be quantified and analysed in relation to the structure of the species concerned.

At the end of the review there are some examples involving catalysis by acids and bases, metal ions, micelles, amylose, catalytic antibodies, and enzymes to give the reader a feeling for how Kurz's approach may be usefully applied to other catalysts. Very few of these examples, or those involving cyclodextrins, were discussed in the original literature in the same terms. It is hoped that the present treatment will stimulate further use and exploration of the Kurz approach to analysing transition state stabilization.

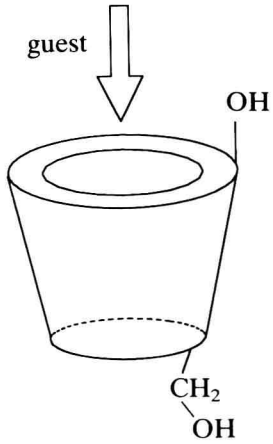
2 Cyclodextrins

These water-soluble molecules are cyclic oligomers of α-D-glucose formed by the action of certain bacterial amylases on starches (Bender and Komiyama, 1978; Saenger, 1980; Szejtli, 1982). α-Cyclodextrin (cyclohexaamylose) has six glucose units joined $\alpha(1,4)$ in a torus [1], whereas β-cyclodextrin (cycloheptaamylose) and γ-cyclodextrin (cyclooctaamylose) have seven and eight units, respectively.

The form of cyclodextrins (CDs) is variously described as being "conical", "toroidal", "bucket shaped", or "doughnut shaped" [2]. Regardless of the adjective used and the finer details of their structure, the most important feature of CDs is the cavity, because this enables them to form inclusion complexes in solution and in the solid state. By virtue of their cavities, CDs possess the requisite amount of preorganization and the convergent surfaces (Cram, 1983, 1988) necessary for them to function as hosts for small molecular guests of an appropriate size, shape, and polarity. The depths of CD cavities are all the same (approximately 7.5 Å), being determined by the width of a glucose molecule, but the sizes of their cavities differ in diameter (α-CD about 5.0, β-CD about 7.0 and γ-CD about 9.0 Å) (Bender and



[1]



[2]

Komiyama, 1978; Szejtli, 1982), giving rise to a gradation in binding affinity.

The geometrical features of CDs, plus their relative rigidity, obviously impose constraints on their ability to form guest–host (inclusion) complexes with organic and inorganic species (Bender and Komiyama, 1978; Saenger, 1980; Szejtli, 1982; Atwood *et al.*, 1984). Nevertheless, CDs have been labelled "promiscuous" for their propensity to act as hosts to a wide variety of small- to medium-sized guests (Stoddart and Zarzycki, 1988). It is the ability of CDs to form complexes that enables them to influence chemical reactions through supramolecular effects (Sirlin, 1984; Lehn, 1985, 1988). In what follows, some of the basic aspects of CD binding, relevant to the reactions discussed later, are presented. More detailed discussions of CD inclusion complexes can be found in the references already cited.

Broadly speaking, the cavity sizes of α-, β-, and γ-CD are appropriate for binding simple derivatives of benzene, naphthalene, and anthracene, respectively (Sanemasa and Akamine, 1987; Fujiki *et al.*, 1988; Sanemasa *et al.*, 1989). Many studies of the inclusion of aromatics, particularly of dyes and other molecules with strong chromophores, have been reported, and these have been useful in delineating the main features of CD binding (Bender and Komiyama, 1978; Saenger, 1980; Szejtli, 1982; Atwood *et al.*, 1984; Stoddart and Zarzycki, 1988). In contrast, the affinity of small to medium aliphatic molecules for CDs have been less well studied, most

probably for practical reasons. Nevertheless, there have been studies with various surfactants (Ono *et al.*, 1979; Satake *et al.*, 1985, 1986; Diaz *et al.*, 1988; Palepu and Reinsborough, 1988; Palepu *et al.*, 1989), alkanes (Sanemasa *et al.*, 1990), and a particularly interesting study of the binding of many alcohols to both α- and β-CD (Matsui and Mochida, 1979; see also, Matsui *et al.*, 1985; Fujiwara *et al.*, 1987).

For the most part, CDs form simple 1 : 1 host–guest complexes with suitable guests. But it is important to note that 2 : 1 binding can be significant with longer aliphatics (Palepu and Reinsborough, 1988; Palepu *et al.*, 1989; Sanemasa *et al.*, 1990), aromatics (Sanemasa and Akamine, 1987; Fujiki *et al.*, 1988), azo dyes (Bender and Komiyama, 1978; Szejtli, 1982), and aryl-alkyl guests (Tee and Du, 1988, 1992), and this can influence reactivity. Also, there is now evidence of 1 : 1 : 1 binding of CD + two guests (Hamai, 1989a,b) which has been implicated in some reactions (Ramamurthy, 1986; Tee and Bozzi, 1990).

The ability of a CD to form inclusion complexes in aqueous solution results from its cavity, the interior of which is less polar than water and hydrophobic. The apparent polarity of the CD cavity seems to depend on the probe used. Some studies have suggested a similarity to dioxane (Bender and Komiyama, 1978; Hamai, 1982), while others favour ethanol (Cox *et al.*, 1984; Heredia *et al.*, 1985). No doubt the particular observations are affected by the presence or absence of specific interactions, such as hydrogen bonding, between the guest and the CD host, as well as by the depth of penetration of the guest/probe. Decarboxylation studies, to be discussed more fully later, suggest an environment like 50% aqueous 2-propanol (Straub and Bender, 1972a,b).

Various other factors have been cited (Bender and Komiyama, 1978; Szejtli, 1982) as contributing to the binding ability of CDs. However, the principal factors seem to be the hydrophobicity of the guest and the appropriateness of its size and shape in relation to that of the CD cavity (Tabushi, 1982). These factors are evident in the binding of alcohols to CDs (Matsui *et al.*, 1985) and of other guests with alkyl groups (Tee, 1989; Tee *et al.*, 1990b). For illustrative purposes, and because of its relevance to a later section, the binding of alcohols will be discussed in some detail.

For linear, primary alcohols (n-alkanols) the strength of complexation with CDs, expressed by $pK_S = -\log K_S$, where K_S is the dissociation constant of the complex, correlates strongly with their coefficients for partition (P_e) between diethyl ether and water (Matsui and Mochida, 1979; Matsui *et al.*, 1985), with slopes close to 1 (1a and 1b). It has also been

$$\alpha\text{-CD:} \qquad pK_S = 0.91 \log P_e + 1.25; \qquad r = 0.994 \tag{1a}$$

$$\beta\text{-CD:} \qquad pK_S = 0.94 \log P_e + 0.58; \qquad r = 0.994 \tag{1b}$$

noted (Tee, 1989; Tee *et al.*, 1990b) that for these alcohols, and other linear

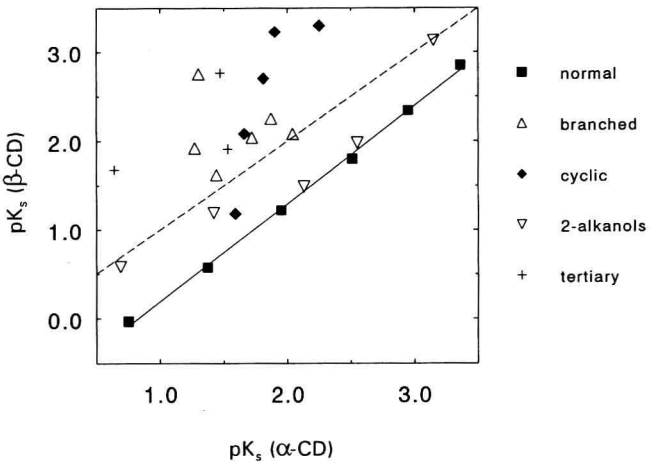


Fig. 1 Correlation between the binding of aliphatic alcohols to β-CD and to α-CD: (——) the least-squares line for n-alkanols; (– – – –) pK_S (β-CD) = pK_S (α-CD); above this line a given alcohol binds strongly to β-CD than to α-CD. Data from Matsui and Mochida (1979) and Matsui *et al.* (1985).

aliphatics, pK_S values vary linearly with N, the number of carbon atoms in the chain. These observations are reasonable since, as remarked above, the binding of guests to CDs is largely governed by their size and hydrophobicity (Tabushi, 1982). Obviously, the sizes of extended n-alkyl chains increase linearly with N, but so also do various measures of hydrophobicity, such as the logarithms of partition coefficients, critical micelle concentrations, solubilities (Hansch, 1971; Leo *et al.*, 1971; Hansch and Leo, 1979; Tanford, 1980; Menger and Venkataram, 1986).

Equations (1a) and (1b) represent two nearly parallel lines with a vertical difference of about 0.7, indicating that a given linear alcohol binds about five times more tightly to α-CD than to β-CD. This makes sense in terms of the sizes of the α- and β-CD cavities (about 5 and about 7 Å, respectively) in relation to the cross-section of methylene chains (about 4.5 Å) (Sanemasa *et al.*, 1990). With bulkier types of alcohols (secondary, tertiary, cyclic, and branched) there is a tendency towards stronger binding in the larger cavity of β-CD. This feature is clearly seen in Fig. 1 which plots values of pK_S for β-CD against those for α-CD. For the linear n-alkanols there is straight-line correlation (r = 0.9991) with a slope of 1.10. Other, bulkier alcohols deviate *above* this line, showing the tendency to a stronger affinity with β-CD. Points for the bulkiest alcohols (branched, tertiary, cyclic $>C_3$) lie above the dashed line corresponding to pK_S (β-CD) = pK_S (α-CD), since such alcohols are bound more strongly by β-CD (Fig. 1).

One other feature of CDs is relevant to later discussion: the acidity of their secondary hydroxyl groups, with pK_a values about 12.2 (VanEtten *et*

al., 1967b; Gelb *et al.*, 1980, 1982). The conjugate anions may function as nucleophiles or general bases and react with substrates included in the CD cavity (Bender and Komiyama, 1978; Komiyama and Inoue, 1980c; Daffe and Fastrez, 1983; Cheng *et al.*, 1985; Tee, 1989; Tee *et al.*, 1993a).

By virtue of their complexing ability, CDs may influence the course of chemical reactions in respect of rates and/or product selectivity. In consequence, there is a large body of data in the literature on the effect of CDs on many types of reactions (Fendler and Fendler, 1975; Bender and Komiyama, 1978; Szejtli, 1982; Tabushi, 1982; Sirlin, 1984; Ramamurthy, 1986; Ramamurthy and Eaton, 1988). The present review concentrates on reactions for which sufficient kinetic data are available to allow quantification of the effects of CDs on transition state stability, in an attempt to understand how cyclodextrins influence reactivity in either a positive or negative sense.

EFFECTS ON REACTIVITY

The kinetics of reactions which are influenced in a simple way by CDs may be viewed in the following manner (Bender and Komiyama, 1978; Szejtli, 1982; Tee and Takasaki, 1985). For a substrate S that undergoes an "uncatalysed" reaction (2) in a given medium and a "catalysed" reaction through a 1:1 substrate/CD complex (3), the expected variation of the observed rate constant with [CD] is given by (4).

$$S \xrightarrow{k_u} P \tag{2}$$

$$S + CD \underset{K_S}{\rightleftharpoons} S \cdot CD \xrightarrow{k_c} P + CD \tag{3}$$

$$k^{obsd} = \frac{(k_u \cdot K_S + k_c[CD])}{(K_S + [CD])} \tag{4}$$

Equation (4) corresponds to saturation-type (Michaelis–Menten) kinetics and rate constants obtained over a suitable range of [CD], sufficient to reflect the hyperbolic curvature, can be analysed to provide the limiting rate constant, k_c, and the dissociation constant, K_S (VanEtten *et al.*, 1967a; Bender and Komiyama, 1978; Szejtli, 1982; Sirlin, 1984; Tee and Takasaki, 1985). The rate constant k_u is normally determined directly (at zero [CD]), and sometimes K_S can be corroborated by other means (Connors, 1987).

Traditionally, data corresponding to (4) are analysed by using a Lineweaver–Burk approach, but an Eadie–Hofstee treatment is preferable for statistical reasons (Dowd and Riggs, 1965; VanEtten *et al.*, 1967a; Bender and Komiyama, 1978). With the present, widespread availability of

cheap microcomputers and appropriate software, it is now feasible to analyse data more directly in terms of (4), using non-linear least-squares fitting techniques (Bevington, 1969; Leatherbarrow, 1990; Duggleby, 1991). In our own work, we have settled on this last approach, usually keeping k_u fixed at the measured value, and treating k_c and K_S as the constants to be fitted (Tee and Takasaki, 1985). Using such non-linear fitting gives a more consistent approach to data analysis, particularly when one has to use expressions more complex than (4), because of additional processes such as non-productive 2:1 binding or reactions with a second CD molecule (Tee and Du, 1988, 1992).

Generally speaking, discussions of the effects of CDs on reaction rates are given in terms of k_c/k_u, K_S, and, sometimes, k_c/K_S. Most often, the ratio k_c/k_u is emphasized since this quantity measures the maximal rate acceleration (or retardation) due to binding to the CD. Obviously, K_S measures the strength of binding of S to CD, but it conveys no information whatsoever about the mediation of the reaction by the CD or the mode of binding in the transition state which may be very different from that of the substrate (Tee, 1989; Tee *et al.*, 1990b). Sometimes use is made of the apparent second order rate constant for the reaction of the substrate with the CD (5), where

$$S + CD \xrightarrow{k_2} P \qquad (5)$$

$k_2 = k_c/K_S$ (3), since this rate constant measures the selectivity of the CD for different substrates. This usage is analogous to the use of k_{cat}/K_M for measuring the "specificity" of enzymes (Fersht, 1985). In cases of catalysis where saturation kinetics are not observed, because binding of the substrate to the CD is weak and K_S is relatively large, k_2 may be obtainable from the linear increase of k^{obsd} with [CD].

Provided due attention is paid to the potential deprotonation of the substrate, and of the cyclodextrins (VanEtten *et al.*, 1967a,b; Gelb *et al.*, 1980, 1982; Tee and Takasaki, 1985), the value of K_S should not be pH dependent. However, for many reactions, such as the widely studied ester cleavage, k_u, k_c, and k_2 are all dependent on the pH of the medium. This makes direct comparisons between the observed constants for different CD-mediated reactions either difficult or problematical. However, in general, the ratios k_c/k_u and k_2/k_u are independent of pH and so are more useful for comparative purposes.

As remarked already, k_c/k_u measures the maximal acceleration at levels of the CD sufficient to saturate complexation of the substrate. By looking carefully at the variations of this ratio with structure one may obtain insights into the mode of transition state binding (VanEtten *et al.*, 1967a,b; Bender and Komiyama, 1978). More useful is the ratio k_2/k_u ($=k_c/K_S k_u$) because it takes into account the effect of substrate binding and it scales the reactivity of S towards the CD to its intrinsic reactivity in the absence of CD.