# Modification of Face Selectivity by Inclusion in Cyclodextrins

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**Abstract:** The photocycloadditions of 5-X-adamantan-2-ones (5-X-AD, where X = F, Cl, Br, OH, Ph, and *t*-Bu) with fumaronitrile have been studied in acetonitrile and in aqueous solutions. When X is Cl, Br, Ph, or *t*-Bu, irradiation of an aqueous solution containing β-cyclodextrin (β-CD) leads to a dramatic reversal in face selectivity compared to that found in acetonitrile and water; however, there is no significant change in product ratio compared to that found in aqueous solution in the presence of α- and γ-CD. The effect observed with β-CD is interpreted with the assumption that the carbonyl π face syn to the bulky 5-substituent is partially blocked by the torus of the host due to complexation of the AD and CD. $^1$H NMR and concentration dependence studies provide support for this interpretation. Similar reversals of face selectivity upon complexation with β-CD are observed in the thermal reduction of these ketones by sodium borohydride. It is also noted that a much enhanced syn hydride delivery occurs in water as compared to organic solvents and that this enhancement vanishes upon cooling.

Cyclodextrins (CDs) are cyclic oligosaccharides with internal cavities capable of forming complexes with hydrophobic organic and organometallic molecules in aqueous solutions.[1,2] The inner diameters of the cavities are approximately 4.5 Å in α-CD, 7.0 Å in β-CD, and 8.5 Å in γ-CD.[1,2] One of the most fascinating and far-reaching aspects of their chemistry is their ability to serve as enzyme models both in terms of substrate complexation and reactivity. Efforts have recently been made to modify CDs so as to enhance their catalytic powers.[3-5] The physical chemistry of complexation by CDs has been extensively studied.[1-7] Recently the inclusion complexes of CDs were found to modify the intramolecular photoreactions of guest molecules by imposing constraints on the conformations and on the mobility of reactive intermediates.[7,8] However, their use in intermolecular thermal or photoreactions has been limited.[9]

Among the thermal bimolecular reactions studied[10-13] in CDs, Diels-Alder reactions have received the most attention. Breslow and co-workers have found that Diels-Alder reactions are accelerated by β-CD in aqueous solution.[10] Their results suggest a solvophobic congregation of the reactants in the cyclodextrin cavity. It has also been shown[10d,11] that the endo/exo ratios in several Diels-Alder reactions increase dramatically by the use of aqueous solutions and of added CDs. Sangwan's results[11] included the first example of the significant influence of CDs on diastereo selectivities in Diels-Alder reactions. Ramamurthy, Eaton, and co-workers have exploited the use of CDs as host to examine photochemical and photophysical processes that occur in molecules complexed within them and to compare their behavior in aqueous solutions and in the solid state.[7,8] Their studies dealt mostly with intramolecular events, with only a single molecule present in the CD cavity.

We have previously reported that the photocycloadditions of 5-substituted adamantan-2-ones (5-X-ADs, Scheme I) with fumaronitrile in acetonitrile, show anti/syn product ratios varying in the range of 53/47 to 60/40 (Table I).[14] The *anti*-oxetanes, formed through syn-face attack of fumaronitrile, are the major products in all cases (Scheme I). In an earlier paper one of us also reported[15] the general face selectivity in the addition of nucleophiles to 5-X-ADs. Since there is virtually no steric bias in the approach to the carbonyl group, this selectivity must be electronic in nature. It was furthermore noted that this selectivity is for the syn face when X is electron-withdrawing and for the anti face when it is a donor. This phenomenon was explained in terms of the hyperconjugation model of the transition state advocated by Cieplak[16] to explain the well-known preferred axial approach of nucleophiles toward the carbonyl group in cyclohexanones. According to this model, the energy of the activated complex is lowered by hyperconjugation of an antiperiplanar bond with the incipient σ* orbital. We subsequently showed that it is

**Scheme I**

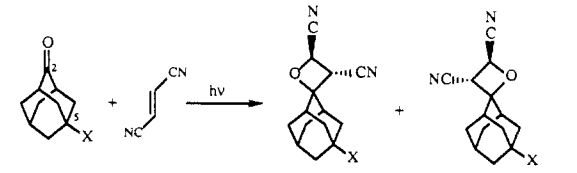


**Table I.** Stereochemical Course of Photocycloaddition of 5-Substituted Adamantan-2-ones (5-X-ADs) with Fumaronitrile in Aqueous Solution Containing Cyclodextrins as a Function of CD and in Acetonitrile Solution at Room Temperature

| | *trans*-oxetane, anti/syn[a] | | | | |
|---|---|---|---|---|---|
| X | $CH_3CN$ | $H_2O$ | α-CD | β-CD | γ-CD |
| F | 57/43[b] | 53/47[c] | 57/43[d] | 48/52[d]<br>45/55[e] | 57/43[d] |
| Cl | 58/42[b] | 57/43[c] | 59/41[d] | 37/63[d]<br>26/74[e] | 62/38[d] |
| Br | 59/41[b] | 56/44[c] | 58/42[d] | 33/67[d]<br>20/80[e] | 61/39[d] |
| OH | 53/47[b] | 57/43[c] | 59/41[d] | 47/53[d]<br>38/62[f] | 60/40[d] |
| Ph | 65/35 | 62/38[c] | 58/42[d] | 38/62[d]<br>23/77[e] | 58/42[d] |
| *t*-Bu | 64/36 | 62/38[c] | 60/40[d] | 14/86[f] | 55/45[d] |

[a] Analysis by VPC, error limit ±2%. In the case of Br the product ratio was also determined by $^1$H NMR. [b] Comparable results apply to *cis*-oxetanes: anti/syn = 60/40 for X = F, Cl, Br. Data from ref 14a. [c] 1 mM 5-substituted-adamantanone, 20 mM fumaronitrile in water. [d] 5 mM 5-substituted-adamantanone, 5 mM CDs and 100 mM fumaronitrile in water; 5-X-AD to CD = 1:1. [e] 5-X-AD to β-CD = 1:5, where 1.5 mM of 5-X-AD was used. [f] 5-X-AD to β-CD = 1:3.

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[‡] At Stony Brook.

(1) Bender, M. L.; Komiyama, M. *Cyclodextrin Chemistry*; Springer-Verlag: New York, 1978.
(2) Saenger, W. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 344.
(3) Breslow, R. *Science (Washington, DC)* **1982**, *218*, 532.
(4) Tabushi, I. *Acc. Chem. Res.* **1982**, *15*, 66.
(5) D'Souza, V. T.; Bender, M. L. *Acc. Chem. Res.* **1987**, *20*, 146.
(6) Saenger, W. In *Inclusion Compounds*; Atwood, J. L., Davies, J. E., MacNicol, D. D., Eds.; Academic Press: New York, 1984; Vol. 2, 231.
(7) Ramamurthy, V.; Eaton, D. F. *Acc. Chem. Res.* **1988**, *21*, 300.
(8) (a) Ramamurthy, V. *Tetrahedron* **1986**, *42*, 5753 and references cited therein. (b) Syamala, M. S.; Ramamurthy, V. *Tetrahedron* **1988**, *44*, 7223. (c) Syamala, M. S.; Rao, B. N.; Ramamurthy, V. *Tetrahedron* **1988**, *44*, 7234.

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applicable to the capture of nucleophiles by carbocations and of electrophiles by olefins as well.[17]

Two general problems are encountered in achieving bimolecular reactions in CD solutions: (1) both substrates must have the proper solubilities, and (2) the molecules must have the proper size and shape to form inclusion complexes. Adamantane derivatives have long been known to form strong complexes with CDs.[18] An X-ray diffraction study, for example, clearly showed that 2-adamantanol can be encapsulated into the cavity of β-CD in one of two conformations.[18a,d] It is therefore expected that adamantanones (AD) could also form complexes with β-CD. We report here that bimolecular reactions of β-CD complexed ADs show a dramatic reversal in their syn/anti face selectivities during photocycloaddition and sodium borohydride reduction reactions.

## Experimental Section

NMR spectra were recorded on either a Varian VXR-400 or a QE-300 spectrometer with TMS in $CDCl_3$ as an external standard. Gas chromatography was done on a Hewlett-Packard 5890 instrument equipped with an FID detector and either a 25 m HP-1 cross-linked methyl silicone column or an OV-225 column at 200 °C. Absorption measurements were obtained with a Perkin-Elmer 559A UV/vis spectrophotometer. Fumaronitrile (Aldrich) was decolorized with activated carbon (Fisher Scientific) and recrystallized from 50% (v/v) methylene chloride in *n*-hexane until no residual absorption above 240 nm was observed. α-, β-, and γ-CDs (Aldrich) were used as received, except in UV studies for which β-CD was recrystallized from $H_2O$.

**Materials.** The synthesis of 5-*tert*-butyladamantan-2-one (5-tBu-AD),[19] 5-phenyladamantan-2-one (5-Ph-AD),[20] 5-hydroxy-,[20,21] 5-chloro-,[20] 5-bromo-,[22] and 5-fluoroadamantan-2-ones[15,23] have all been described. The 5-fluoro ketone was obtained by the adaption of a procedure given by Schleyer for 1-fluoroadamantane[24] (refluxing a mixture of 20 mL of the bromo ketone in 150 mL of cyclohexane with 50 mM anhydrous silver fluoride).[15] This method, giving a 96% yield, is superior to that given by Tabushi.[23] All compounds mentioned in this paper have been completely characterized by NMR analysis and method of synthesis[14a] (see also supplementary material for details). The assignment of configuration of the anti and syn isomers on the basis of $^{13}C$ NMR spectroscopy is described elsewhere.[17c]

**Photocycloaddition.** 5-X-ADs (1.5 or 5 mM) were added to water or to aqueous solutions of CDs (varying amounts) and ultrasonically agitated for 50 min to promote the dissolution of ketones. An excess of fumaronitrile (100 mM) was then added to 20 mL of the solution and dissolved by magnetic stirring for 1 h. Each sample (20 mL) was allowed to equilibrate for 2 h at 25 °C, after which it was irradiated at ambient temperature in stoppered Pyrex tubes for 12 h by the output from a high-pressure Xe/Hg lamp (1 kW) with a $K_2CrO_4$ filter solution. The solutions were clear except for those of 5-Ph- and 5-tBu-ADs, in which cloudy solutions were irradiated. The solutions were then extracted with ether (3 × 20 mL); after drying with $Na_2SO_4$, the ether was removed by rotary evaporation to give a white solid. Under these conditions, the conversions are 10–80% and the yields of oxetanes (Scheme I) are larger than 90%. The product ratios were determined by GC. At low conversion only *trans*-oxetanes are formed; *cis*-oxetanes obtained only after the cis/trans isomerization of fumaronitrile has set in.[14] As in acetonitrile, the aqueous reactions exhibit a clear preference for syn approach to form the *anti*-oxetane (Table I).

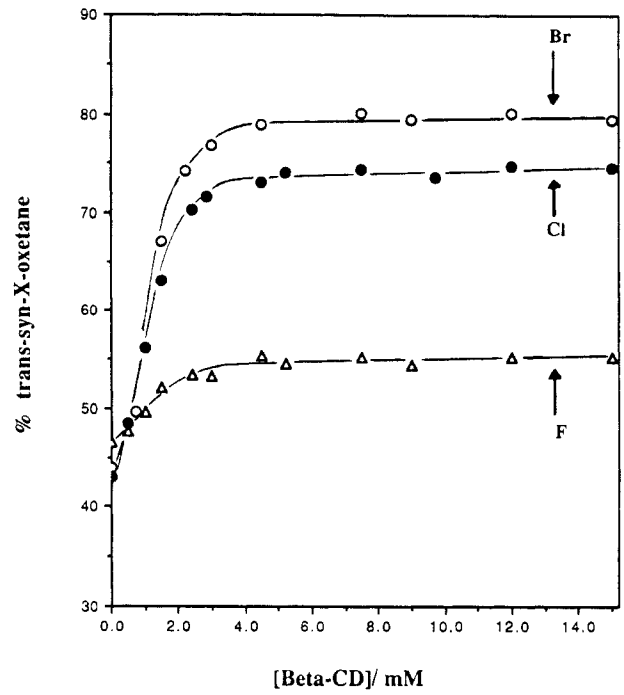


**Figure 1.** The % *syn*-oxetane from anti approach of fumaronitrile to 5-F-, 5-Cl-, and 5-Br-ADs as a function of β-CD concentration.

**Sodium Borohydride Reduction.** 5-X-AD (0.22 or 0.65 mmol) was dissolved in methanol to make a 1.00-mL solution. A sample of 0.10 mL of this solution was added with stirring to each 50-mL aqueous solution of 0.01 N NaOH containing various concentrations of β-CD. Each mixture was allowed to equilibrate for 3 h at 25 °C after which 20 mg (0.53 mmol) of $NaBH_4$ was added with stirring. The reaction was quenched after 20 min by the addition of 1 N HCl followed by extraction (3 × 10 mL) with methylene chloride. The methylene chloride was removed by rotary evaporation to give a white solid. The product ratios were determined by GC on an OV-225 column at 170 °C for 5-Br-AD and determined by $^1H$ NMR for 5-Ph-AD.

## Results

The effect of CD complexation on the syn/anti selectivity is very dependent on the CD used (Table I). For each 5-X-AD, the product ratio was dependent on the amount of CD employed; the more extreme values in Table I in the presence of β-CD are from the plateau regions of the curves such as those shown in Figure 1. With 5-Cl- and 5-Br-AD and β-CD, syn/anti face selectivities were reversed from those in aqueous solution, ca. 60/40 to 26/74 and 20/80, respectively. The phenyl and *tert*-butyl substituents also give rise to a pronounced change in syn/anti face selectivity ratio if β-CD is added, from ca. 60/40 to 23/77 and 14/86, respectively. However, with all of these substituents, the syn/anti ratios are unchanged when α-CD is used. This result was expected because the α-CD cavity is known to be too small to accommodate AD derivatives.[18b] The results in γ-CD show a slight increase in syn/anti face selectivity for halo derivatives and a slight decrease in syn/anti face selectivity for the 5-Ph and 5-tBu derivatives relative to the selectivity found in aqueous solution.

A similar effect of CD complexation on the face selectivity was observed in the thermal reactions of sodium borohydride with the

(9) Some of the few examples are photodimerization of anthracenes and photosubstitution of 2- and 4-fluoroanisoles: (a) Tamaki, T.; Kokubu, T.; Ichimura, K. *Tetrahedron* **1987**, *43*, 1485. (b) Tamaki, T. *Chem. Lett.* **1984**, *53*. (c) Liu, J. H.; Weiss, R. G. *Isr. J. Chem.* **1985**, *25*, 228. (d) Liu, J. H.; Weiss, R. G. *J. Photochem.* **1985**, *30*, 303.

(10) (a) Rideout, D. C.; Breslow, R. *J. Am. Chem. Soc.* **1980**, *102*, 7816. (b) Breslow, R.; Maitra, U.; Rideout, D. *Tetrahedron Lett.* **1983**, *24*, 1901. (c) Breslow, R.; Maitra, U. *Tetrahedron Lett.* **1984**, *25*, 1239. (d) Breslow, R.; Guo, T. *J. Am. Chem. Soc.* **1988**, *110*, 5613.

(11) Schneider, H.-J.; Sangwan, N. K. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 896.

(12) Breslow, R.; Campbell, P. *J. Am. Chem. Soc.* **1969**, *91*, 3085.

(13) (a) Komiyama, M.; Hirai, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2053. (b) Komiyama, M.; Hirai, H. *Makromol. Chem., Rapid Commun.* **1981**, *2*, 707. (c) Komiyama, M.; Hirai, H. *J. Am. Chem. Soc.* **1984**, *106*, 174.

(14) (a) Chung, W.-S.; Turro, N. J.; Srivastava, S.; Li, H.; le Noble, W. J. *J. Am. Chem. Soc.* **1988**, *110*, 7882. (b) Turro, N. J.; Chung, W.-S.; Okamoto, M. *J. Photochem. Photobiol. A* **1988**, *45*, 17.

(15) Cheung, C. K.; Tseng, L. T.; Lin, M. H.; Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 1598; **1987**, *109*, 7239.

(16) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540.

(17) (a) Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 5874. (b) Johnson, C. R.; Tait, B. D.; Cieplak, A. S. *J. Am. Chem. Soc.* **1987**, *109*, 5875. (c) Srivastava, S.; Cheung, C. K.; le Noble, W. J. *Magn. Reson. Chem.* **1985**, *23*, 232. (Note: in Table I in this paper, in 2-chloroadamantane, $C_5$ should read 68.54 rather than 63.54.)

(18) (a) Hamilton, J. A.; Steinrauf, L. K.; vanEtten, R. L. *Acta Crystallogr.* **1968**, *B24*, 1560. (b) Komiyama, M.; Bender, M. L. *J. Am. Chem. Soc.* **1978**, *100*, 2259. (c) Komiyama, M.; Inoue, S. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2330 and 3266. (d) Czugler, M.; Eckle, E.; Stezowski, J. J. *J. Chem. Soc., Chem. Commun.* **1981**, 1291. (e) Harrison, J. C.; Eftink, M. R. *Biopolymers* **1982**, *21*, 1153.

(19) le Noble, W. J.; Srivastava, S.; Cheung, C. K. *J. Org. Chem.* **1983**, *48*, 1099.

(20) Geluk, H. W. *Synthesis* **1972**, 374.

(21) Srivastava, S.; le Noble, W. J. *Synth. Commun.* **1984**, *14*, 65.

(22) Klein, H.; Wiartalla, R. *Synth. Commun.* **1979**, *9*, 825.

(23) Tabushi, I.; Aoyama, Y. *J. Org. Chem.* **1973**, *28*, 3447.

(24) Fort, R. C.; Schleyer, P. v. R. *J. Org. Chem.* **1965**, *30*, 789.

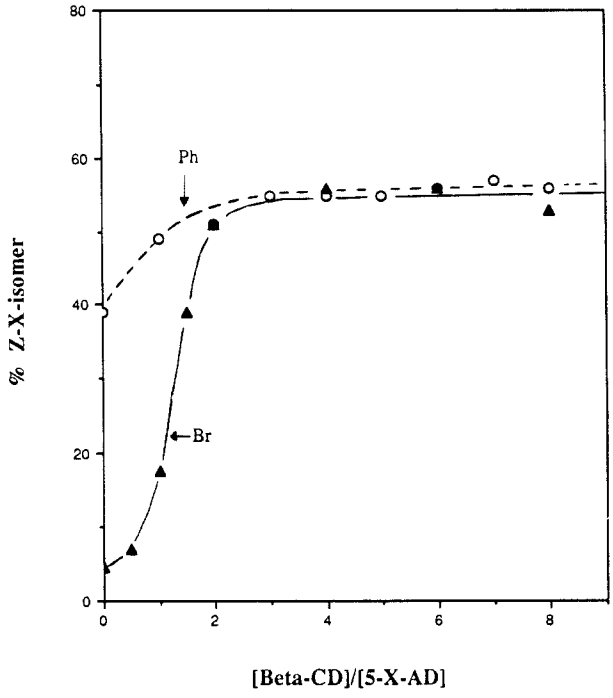


**Figure 2.** Product ratio of the $NaBH_4$ reduction of 5-Br-AD and 5-Ph-AD as a function of the relative amount of $\beta$-CD.

5-X-ADs to yield the corresponding (*E*)- and (*Z*)-adamantanols. Reversal from predominant syn to excess anti approach occurs with both the 5-Br- and 5-Ph-ADs if $\beta$-CD is present in the aqueous solution (Figure 2).

As in the photochemical reactions, the product ratio varies with the concentration of $\beta$-CD in the way expected from the fact that saturation must be approached if the concentration of $\beta$-CD is made sufficiently high (e.g., in the manner shown in Figure 1).[25] Complexes formed between 5-X-ADs and $\beta$-CD most likely have 1:1 stoichiometries, as found in several instances by X-ray crystallography.[18a,d] The binding constants for complexes of $\beta$-CD were determined by a nonlinear curve fitting program.[25] In these experiments, the guest concentration is fixed and the product ratio is measured as a function of $\beta$-CD concentration (see Figures 1 and 2). If the relative ratio of product is employed as a binding parameter in both photocycloaddition and sodium borohydride reduction, binding constants of $(8.7 \pm 3.5) \times 10^2$ $M^{-1}$ (for 5-F-AD), $(8.7 \pm 2.6) \times 10^2$ $M^{-1}$ (for 5-Cl-AD), $(8.4 \pm 3.5) \times 10^2$ $M^{-1}$ (for 5-Br-AD), and $(1.33 \pm 0.39) \times 10^3$ $M^{-1}$ (for 5-Ph-AD) are obtained, which are about the expected magnitude if one employs the reported binding constants for similar complexes as a guide.[27] For example, the binding constant of $\beta$-CD with 1-adamantane-carboxylate, a compound of similar molecular structure, has been found to be $1.9 \times 10^3$ $M^{-1}$,[18b] within a factor of 2 of values measured for 5-Cl-, 5-Br-, and 5-Ph-ADs and $\beta$-CD.

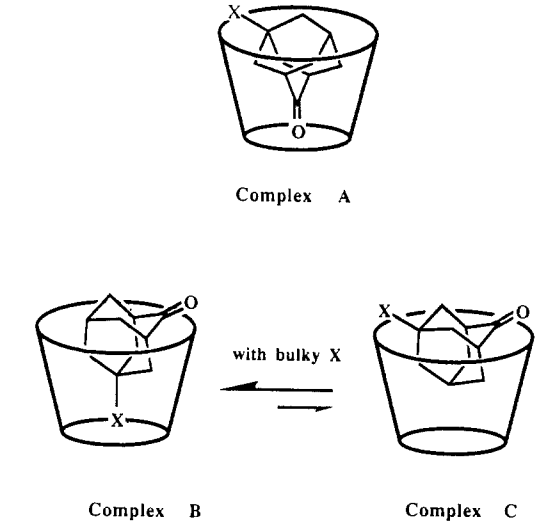


**Figure 3.** Possible complexations of 5-X-ADs with $\beta$-CD.

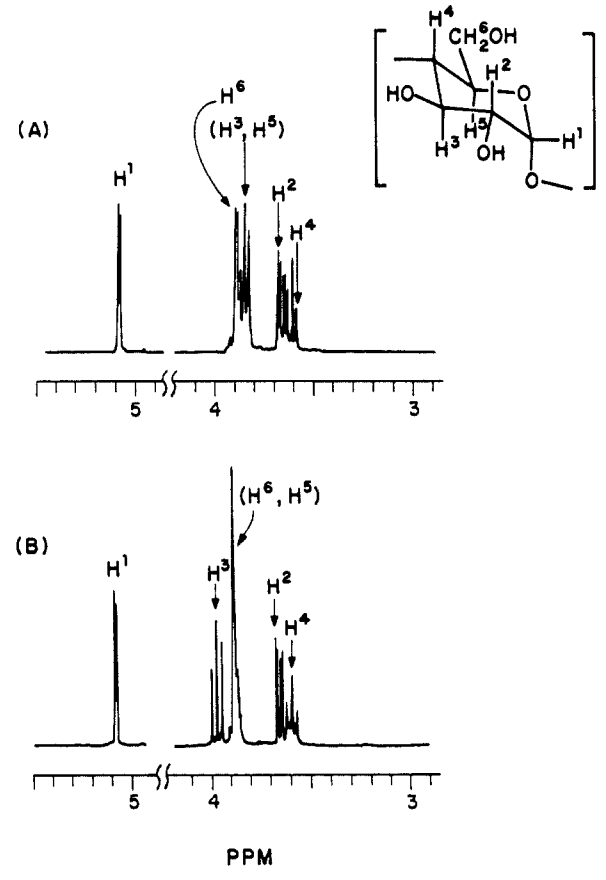


**Figure 4.** Effect of 5-Br-AD on the $^1H$ NMR spectra of $\beta$-CD (5 mM) in $D_2O$: (A) $\beta$-CD and 5-Br-AD (1:1), (B) $\beta$-CD.

Further evidence for complexation was obtained from $^1H$ NMR spectra, which show that $H^3$ and $H^5$ of $\beta$-CD (which are oriented toward the interior of the CD cavity) are shifted upfield considerably in the presence of 5-Br-AD. By contrast, $H^1$, $H^2$, and $H^4$, all located on the exterior wall, either have small downfield shifts or are unaffected (Figure 4).[26] These observations are consistent with the notion that a complex is formed between $\beta$-CD and 5-X-AD.

There are growing number of reports of successful use of CDs to achieve kinetic resolutions of racemic substrates[29c] or optical

(25) For reviews of the determination of host–guest complexation: (a) Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 362 and references cited therein. (b) Connors, K. A. *Binding Constants, the measurement of molecular complex stability*; Wiley: New York, 1987.

(26) Similar results in $^1H$ NMR spectroscopy in the studies of $\beta$-CD complexes were observed. For example: (a) Greatbanks, D.; Pickford, R. *Magn. Reson. Chem.* **1987**, *25*, 208. (b) Reddy, G. D.; Usha, G.; Ramanathan, K. V.; Ramamurthy, V. *J. Org. Chem.* **1986**, *51*, 3085. (c) Casy, A. F.; Mercer, A. D. *Magn. Reson. Chem.* **1988**, *26*, 765. (d) Eaton, D. F. *Tetrahedron* **1987**, *43*, 1551.

(27) In general, one might use the differences of optical density or the differences of fluorescence intensity to determine the binding constants.[25] The UV absorption experiment was performed; however, the small difference of optical density at the highest CD concentration studied (ca. 15 mM in $H_2O$) made the estimation of binding constant very difficult. The fluorescence experiment was hampered by the impurity existing in the commercially available $\beta$-CD.

(28) (a) vanEtten, R. L.; Sebastian, J. F.; Clowes, G. A.; Bender, M. L. *J. Am. Chem. Soc.* **1967**, *89*, 3242. (b) vanEtten, R. L.; Clowes, G. A.; Sebastian, J. F.; Bender, M. L. *J. Am. Chem. Soc.* **1967**, *89*, 3253.

(29) (a) Emert, J.; Breslow, R. *J. Am. Chem. Soc.* **1975**, *97*, 670. (b) Breslow, R.; Czarniecki, M. F.; Emert, J.; Hamaguchi, H. *J. Am. Chem. Soc.* **1980**, *102*, 762. (c) Trainor, G. L.; Breslow, R. *J. Am. Chem. Soc.* **1981**, *103*, 154.

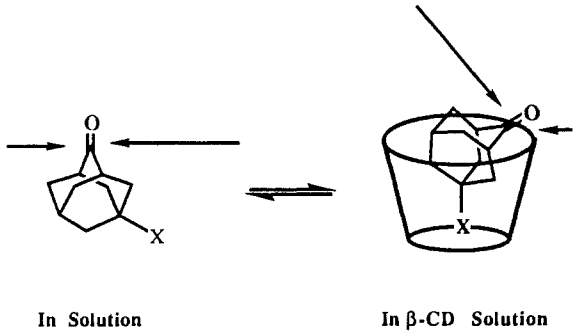


Figure 5.

induction in reactions involving prochiral centers.[31] It is possible, though not necessary, that a reaction in the chiral CD cavity may lead to induced optical activity in the product.[11,26a,29c,31] This possibility was investigated for the addition of fumaronitrile to 5-Br-AD in $D_2O$. The $^1H$ NMR spectrum of the irradiation product mixture (before extraction) showed four resolved doublets in the region of the methine proton in the oxetane rings ($H^{12}$); without β-CD, only two doublets show in this region. Any enantiomeric excess can thus be determined from the area ratios of the respective oxetanes; however, the enantiomers are present in 1:1 ratio within the experimental error.

## Discussion

Our interpretation of both the thermal and photochemical results is that β-CD complexes the 5-X-ADs (with the bulkier 5-substituents) so that the normally preferred carbonyl face is protected by the torus of the host (complex B, Figure 3). The possibility of a second complex (complex A, Figure 3) also exists, but it is expected to be both photochemically and thermally inactive because the carbonyl is encapsulated within the hydrophobic pocket of the CD. With relatively "large" substituents of 5-X-AD, complex B is, in fact, expected to be favored in the equilibrium between complexes B and C;[29b] complex C should increase in importance when the 5-substituents are "small". CPK models convincingly confirm these orientations. In their study of hydrolysis rates within β-CD complexes, Breslow et al. have invoked similar orientations in order to explain the observed acceleration rates of (*tert*-butyl adamantyl)propiolic ester.[29b] Furthermore, when the more extreme values in the presence of β-CD of the halogen substituents (see Table I) were plotted vs their van der Waals radii, a clear linear correlation was observed: the larger the substituent, the higher the anti-face selectivity. Our results thus show that the size and hydrophobic character of the 5-substituents are important factors in the formation of inclusion complexes with CDs and in controlling the syn-/anti-face selectivity.

It may be noted that the stereochemical results described here somewhat resemble the special effects observed by Bender and Breslow on the hydrolysis rates of phenyl esters when meta substituents are introduced.[6,28,29] They found that the acceleration caused by CD is larger than that for the corresponding para-substituted phenyl esters. An important observation in their studies is that the magnitudes of the rate accelerations do not parallel the stabilities of the CD–esters complexes but can be explained on the basis of the *stereochemistry* of the CD–guest complexes.[18a,29] Improvement of the acylation rates within CD complexes was achieved by "capping" of the CD and by adjusting the shape of the substrate.[29] In our systems with α-CD, the 5-X-AD is too bulky to be completely included in the cavity ad probably located on top of it;[18b,30] hence, no change in the product distribution was observed. With γ-CD, the cavity may be large enough to accommodate *both* the AD and the fumaronitrile, or to allow a variety of conformations of the 5-X-AD within the cavity.

There are various ways in which CDs could influence a chemical reaction. One would be by sterically blocking certain potential sites of the substrate from intermolecular attack by the very mode of complexation.[12,13] In their studies of unimolecular rearrangements, Ramamurthy and co-workers succeeded in exploiting this unique feature of CD complexations to "direct the traffic" of reacting radical pairs, e.g., in photo-Fries[8c] and photo-Claisen[8b] rearrangements. Our results show that the attack of fumaronitrile can be directed toward the exposed anti face of the carbonyl group through complexation with β-CD, and as such, they are a novel application of "molecular traffic control"[7] in bimolecular reactions in CDs. This molecular traffic control could probably be used to explain the observed optical induction in the asymmetric reduction of prochiral ketone–β-CD complexes.[31]

One of the results we found in water invites special mention. The syn/anti ratios in water are, in all cases but one, similar to those observed in other solvents; the exception is the borohydride reduction of 5-Br-AD. We had previously observed that the syn/anti ratio in methanol at 0 °C is about 60/40;[15] in water, at temperatures between 5 and 15 °C, it equals 74/26 and then rises with temperature to more than 95/5 at 25 °C. This effect is probably related to the water structure around the reacting solutes (no such effects were seen in the photocycloadditions), but no more than that can be said at the moment.

## Conclusion

Electronically dictated face selectivities can be altered, and in favorable cases, reversed, by means of host–guest complexation employing the readily available cyclodextrins. These changes of the face selectivity are proposed to result from protection of the normally favored syn face to attack, by complexation with β-CD (Figure 5). The complex is proposed to favor structure B in Figure 3 for the larger substituents and to be a mixture of structures B and C for the smaller substituents. In complex B, the syn face "rests" on the CD surface and only the anti face is accessible for attack by reagents from the aqueous phase. For α-CD, there is no significant effect on face selectivity because of poor binding as expected from the small size of the cavity. In the case of γ-CD, some selectivity occurs but the large size of the cavity allows a range of complexes to exist, and substituents do not control the conformation of these complexes as in the case for β-CD. Since the cyclodextrins have reasonable solubilities in such "organic" solvents as ethylene glycol and DMSO, this phenomenon clearly has synthetic potential.

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**Note Added in Proof**. After this paper was submitted for publication, there appeared a paper by M. R. Eftink et al. (*J. Am. Chem. Soc.* **1989**, *111*, 6765) in which the values to which we refer in ref 18b are actually smaller by a factor of 10. This does not change our interpretation of the results.

**Registry No.** 5-F-AD, 41171-83-9; 5-Cl-AD, 20098-17-3; 5-Br-AD, 20098-20-8; 5-OH-AD, 20098-14-0; 5-Ph-AD, 38584-33-7; 5-*t*-Bu-AD, 84454-67-1; α-CD, 10016-20-3; β-CD, 7585-39-9; γ-CD, 17465-86-0; (±)-5-F-Anti, 124440-60-4; (±)-5-F-Syn, 124440-61-5; (±)-5-Cl-Anti, 124440-62-6; (±)-5-Cl-Syn, 124440-63-7; (±)-5-Br-Anti, 124440-64-8; (±)-5-Br-Syn, 124440-65-9; (±)-5-OH-Anti, 124440-66-0; (±)-5-OH-Syn, 124440-67-1; (±)-5-Ph-Anti, 124382-52-1; (±)-5-Ph-Syn, 124440-68-2; (±)-5-*t*-Bu-Anti, 124382-53-2; (±)-5-*t*-Bu-Syn, 124440-69-3; β-CD/5-F-AD inclusion complex, 124399-65-1; β-CD/5-Cl-AD inclusion complex, 124399-66-2; β-CD/5-Br-AD inclusion complex, 124399-67-3; β-CD/5-Ph-AD inclusion complex, 124417-96-5; fumaronitrile, 764-42-1.

**Supplementary Material Available:** Tables of $^{13}C$ and $^1H$ NMR data of all compounds mentioned in this paper (4 pages). Ordering information is given on any currest masthead page.

(30) See ref 1, Chapter III for similar descriptions.
(31) (a) Fornasier, R.; Reniero, F.; Scrimin, P.; Tonellato, U. *J. Org. Chem.* **1985**, *50*, 3209 and references cited therein. (b) Sakuraba, H.; Inomata, N.; Tanaka, Y. *J. Org. Chem.* **1989**, *54*, 3482.