Addition of Bromine to *trans*-Stilbene: Reversal of Stereoselectivity upon Cyclodextrin Complexation

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Abstract

In contrast to the formation of *meso*-stilbene dibromide as the major product in the electrophilic addition of bromine to *trans*-stilbene in nonpolar solvents, stereoselectivity decreases in cyclodextrin cavities and a significant yield of *dl*-stilbene dibromide is also obtained. This reversal of stereoselectivity is attributed to the polar environment provided by the secondary hydroxyl groups of cyclodextrins which stabilises the acylic α-halocarbonium ion intermediate and also hinders the approach of the incoming tribromide ion.

Introduction

Cyclodextrins (CDs), a class of cyclic oligosaccharides are well known hosts to a wide variety of guest molecules through hydrophobic interaction inside their cavity and their complexes can serve as useful enzyme models [1]. CD complexation improves the reaction efficiency, modifies substrate reactivity and thereby increases the product selectivity in many organic reactions [2]. CDs are extensively employed as reaction vessels in electrophilic substitutions such as chlorination [3], carbonylation [4], azo coupling [5] and facilitate regio- [6] as well as enantioselectivities [7] in a number of these reactions.

Generally, electrophilic addition of bromine to olefins proceeds via a bromonium ion intermediate as postulated by Roberts and Kimball [8]. This polar addition of bromine to a variety of olefins [9] has been found to occur by a 1,2- *trans* addition. Analogous addition of chlorine to acenaphthylene [10], phenanthrene [11], *cis*- and *trans*-1-phenylpropenes [12], all of which are capable of forming resonance stabilized benzylic cations, occurs *via* an open ion as evidenced by the formation of substantial amounts of *cis* addition products. However, the addition of bromine to acenaphthylene and phenanthrene leads to *trans* products and this suggests that bromine, unlike chlorine, prefers to form a cyclic bromonium ion intermediate (**I**). When the olefin contains powerful electron-releasing groups or conjugated as in stilbene, the stereoselectivity depends on the solvent polarity [13]. Thus addition of bromine to *cis*- or *trans*- stilbene is found to involve stereoselective *trans*-addition in relatively nonpolar solvents, giving the same *meso*-dibromide in solvents of high polarity (through an α-bromocarbonium ion intermediate **II**). In the accompanying isomerisation, *cis*-stilbene is found to have rearranged to the *trans*-isomer [14]

(Scheme 1). Detailed kinetic studies [15] also show that in non-polar solvents like carbon tetrachloride, the addition of bromine to *cis*- and *trans*-stilbene is first order in stilbene and second order in bromine, thus indicating clearly [15] that the intermediates (**I**)/(**II**) are attacked by tribromide ion, Br_3^- and not by Br^- ion (Schemes 1 and 2).

In this communication we report the results of our studies on the effect of α-, β-, γ- and substituted CDs *viz.*, hydroxypropyl α-, β-, γ- (HP-α-, β- and γ-) and dimethyl β-cyclodextrins (DM-β-CD) on the bromination of *trans*-stilbene, chosen as the substrate of choice. Being a symmetrical alkene containing a hydrophobic phenyl group that can be readily included into the CD cavity, bromination of *trans*-stilbene is expected to provide valuable information about the role of the cyclodextrin cavity in stabilising the halocarbonium ion and hence in controlling the stereoselectivity of the bromine addition. It is relevant to note here that previous studies [2c, 16, 17] on halogenation of alkenes in the presence of cyclodextrins all involve unsymmetrical alkenes (wherein the halocarbonium ion formed is not symmetrical and the direction of the initial halogen addition depends on the nature of the substituents). Among substituted CDs, the hydroxypropyl derivative is more hydrophilic and elongated than normal CD, while the dimethyl derivative is more hydrophobic.
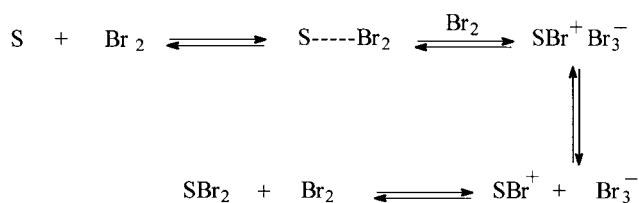
Experimental

Materials

Cyclodextrins α- and γ- (American Maize Products, Indiana), β- (Aldrich), hydroxypropyl-β- (DS 6, randomly hydroxypropylated/gift sample from Cerestar, USA) hydroxypropyl-α- and γ- (Nihon Shokuhin Kako Co Ltd.,

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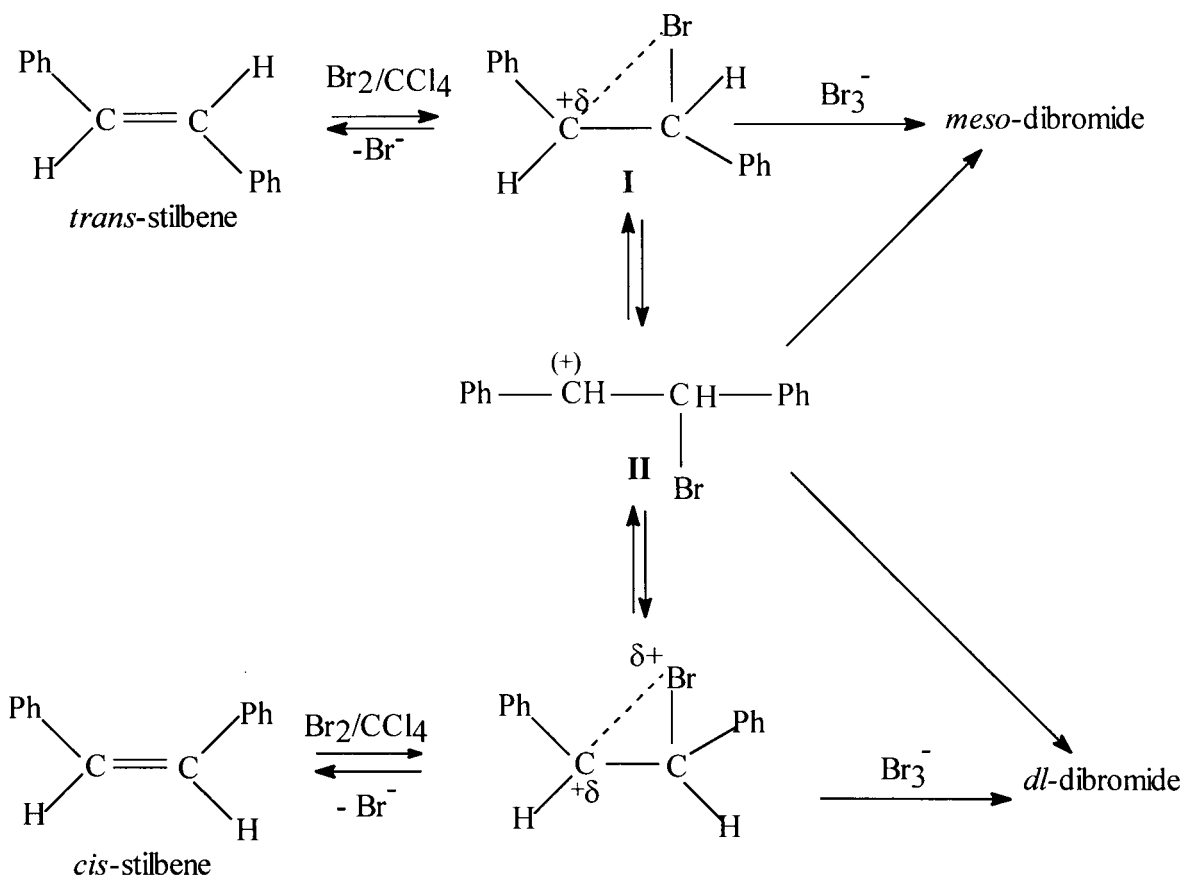
I – cyclic bromonium ion, **II** – acyclic α-bromocarbonium ion

Scheme 1. Mechanism of formation of isomeric dibromides from stilbene.

Scheme 2. Polar mechanism for bromination of olefins involving a charge-transfer complex.

Japan) and dimethyl-β- (DS 1.8, non-recrystalliziable, randomly methylated/gift sample from Wacker-Chemie, Germany) were used as such. Positive-ion Fast Atom Bombardment Mass spectra of HP-α-CD, HP-β-CD, HP-γ-CD and DM-β-CD showed a relatively symmetric peak distribution around the average molecular weight of the main product (approximately 1217, 1383, 1542 and 1342, respectively). Bromine and *trans*-stilbene (Merck) were used as such and a stock solution of bromine was prepared by dissolving 74 mL of bromine in 100 mL of CCl_4 and making it up to 250 mL in a standard measuring flask.

Preparation and characterisation of complexes

1:1 CD complexes were prepared by mixing an equimolar amount of *trans*-stilbene and the appropriate CD, stirring for 12 h, filtering and washing with a small amount of ether to remove any uncomplexed substrate. This complex was dried in an air oven at 50 °C for 6 h. 2:1 Cyclodextrin complexes were prepared by mixing *trans*-stilbene with twice its mole ratio of the appropriate cyclodextrin and the rest of the procedure was the same as outlined above. The host-guest ratio was calculated by adopting the following procedure [2]. A known amount of the solid complex was dissolved in a minimum amount of distilled water and the guest *trans*-stilbene was extracted with warm chloroform. The amount of the recovered *trans*-stilbene was estimated gravimetrically after the removal of chloroform.

α-, β- and γ-CD complexes were characterised by their ^{1}H-NMR spectra. Comparison of the chemical shifts of the α-, β- and γ-CD protons in the uncomplexed and complexed forms indicate that, while the H-1, H-2, H-4 and H-6 protons are unaffected as a result of complexation, the H-3 and H-5 protons which are oriented towards the interior of the cavity have considerable upfield shifts. This chemical shift behaviour [2c] reflects complexation of *trans*-stilbene with CDs and establishes clearly that the aryl ring is positioned within the cavity. ^{1}H-NMR studies were restricted only to complexes of native CDs and were not extended to that of modified CDs.

Determination of formation constants

Complex formation was inferred by evaluating the formation constants (K_f) using the Benesi–Hildebrand method [18]. A stock solution of *trans*-stilbene (1×10^{-3} M) was prepared by dissolving a known mass in 2% methanol-water mixture. 0.1 mL of this stock solution was transferred into a 10 mL volumetric flask, the respective cyclodextrin (from a 0.01 M freshly prepared stock solution in water) was added, diluted to 10 mL with water and stirred for 6 h to ensure equilibrium in complexation. The absorption spectrum was recorded at the room temperature using a JASCO 7800 UV/Vis spectro-photometer and the absorption maximum for *trans*-stilbene is 295 nm. The formation constants (K_f/mol^{-1} dm^3) for *trans*-stilbene in α-, β-, γ-, HP-α-, HP-β-, HP-γ- and DM-β-CDs are 135, 320, 416,128, 305, 375 and 565 respectively. The values are fairly high indicative of formation of strong complexes between CDs and *trans*-stilbene.

Reaction procedure

Bromination of trans-stilbene in solution

To 5 g of pure *trans*-stilbene dissolved in 15 mL of CCl$_4$ kept at 0 °C, 5.5g (1.72 mol) of bromine dissolved in 6 mL of CCl$_4$ was added. The slow, careful addition was carried out with constant stirring for about 30 minutes in the dark. After completion of the reaction, the bromide was collected in a Buckner funnel, washed with 75% ethanol and dried. Purity was confirmed by their melting [19] point values (*meso*-stilbene dibromide-234 °C and *dl*-stilbene dibromide-111 °C) and also by ^{1}H-NMR spectroscopy.

Bromination in solid CD complexes of trans-stilbene

0.1 g of the complex was dissolved in 5 mL of CCl$_4$ in the dark at 0 °C. An equimolar amount of bromine in CCl$_4$ was added dropwise for a duration of 10 minutes. After completion of the reaction, the excess bromine was removed and the complex was dissolved in water. The product was then extracted with diethyl ether, the organic layer was dried over anhydrous sodium sulphate and removal of the solvent yielded a white solid. The products were analysed by capillary GC (Shimadzu 17A-SE30-10%), FID detector with high purity nitrogen as the carrier gas.

Results and discussion

The results presented in Table 1 show that, in accordance with previous data [13], bromination of *trans*-stilbene in CCl$_4$, a nonpolar solvent, has yielded *meso*-stilbene dibromide in larger amount, with the addition taking place in a stereoselective *trans*-mode. A drastic change in the product composition, with a consequent loss of stereoselectivity, is observed when bromine addition is carried out on CD complexes of stilbene (Table 1).

The *meso/dl* ratio is less than one in the 1:1 complexes of all three CDs and their hydroxypropyl derivatives. With an increase in cavity diameter (from α- to γ-CD), the ratio decreases (less *meso* isomer is formed) and the largest yield

of *dl*-isomer (the lowest *meso/dl* ratio) is observed in the case of dimethyl-β-CD. An increase in the amount of CD (as in the 2:1 complexes) causes a decrease in the yield of brominated products and a marked increase in the amount of *dl*-isomer.

This significant reduction in stereoselectivity upon CD complexation is attributed to two aspects: (a) the presence of a polar environment at the top of the wider rim of CD due to the presence of secondary hydroxyl/methoxyl groups and (b) steric hindrance to the attack of the tribromide ion on intermediates **I/II** in the second stage of bromination. As a consequence of (a), the cyclic bromonium ion, **I** (which is the major species in CCl$_4$) converts itself completely to the acyclic bromocarbonium ion intermediate (**II**) and is stabilized by the more polar environment around the top of the wider rim of the cyclodextrin cavity (Scheme 3). As the attack of the tribromide (predominant brominating species in CCl$_4$, as established by kinetic studies [15]) is sterically hindered by the secondary hydroxyl groups (b), there is significant reduction in the formation of the *meso*-dibromide. Consequently, free rotation around the carbon–carbon single bond takes place (Scheme 3) and the bromocarbonium ion (**II**), can now be attacked also from the less hindered other side, (which leads to the *dl*-isomer), thus causing a marked reduction in stereoselectivity.

The above conclusions are supported by three observations: (i) an increase in cavity diameter (from α-, β- to γ-CD) facilitates easier rotation around the C–C bond, thus causing an increase in the yield of the *dl*-isomer. This is also the case with HP-α-, -β- and -γ-CDs; (ii) with the 2:1 β-CD-stilbene complexes, the rotation is expected to be less likely (Scheme 3), and indeed, an increase in the yield of *meso*-isomer (compared to 1:1 complexes) is observed and (iii) in DM-β-CD, the methoxyl groups are expected to offer the largest hindrance to attack of the tribromide ion. Under this circumstance the C–C rotation is the more viable option. Indeed the formation of *dl*-dibromide is the highest in this case.

Conclusions

The observed results amply demonstrate the efficiency of CDs in stabilizing some selected intermediates over others and hence modify the reactivity of the included guest. This is also an example in which a bimolecular reactivity is significantly altered upon inclusion into the CD cavity, with a subsequent shift in the mechanistic pathway. The results also provide chemical evidence for the presence of adjacent hydrophobic and hydrophilic pockets (present inside and on the periphery of the CD cavity) which can be construed as an elegant illustration of multiple recognition in an enzyme mimic, such as CD. This is more significant as this aspect of multiple recognition is demonstrated for the first time in a bimolecular reaction in a CD cavity. This is also evident from the bromination of styrene, methyl cinnamate, phenylacetylene and allylbenzene [20] in the presence of cyclodextrins. Except in allylbenzene (where the product

Table 1. Amounts of recovered starting material and brominated products (given in percentage) in the bromination of *trans*-stilbene[a]

Medium	*trans*-stilbene	*dl*-dibromide	*meso*-dibromide	*meso/dl* ratio
CCl$_4$	9.0	13	78	6.00
α-CD(1:1)[b]	10	53	37	0.70
β-CD(1:1)[b]	13	55	32	0.58
γ-CD(1:1)[b]	21	53	26	0.49
HP-α-CD(1:1)[b]	14	53	33	0.62
HP-β-CD(1:1)[b]	17	52	31	0.60
HP-γ-CD(1:1)[b]	15	55	30	0.55
DM-β-CD(1:1)[b]	11	64	25	0.39
α-CD(2:1)[b]	17	34	49	1.44
β-CD(2:1)[b]	51	20	29	1.45

[a] Analysed by GC, error limit $\pm$ 2%.
[b] Numbers in parentheses are the ratio of CD to guest.

1:1 complex
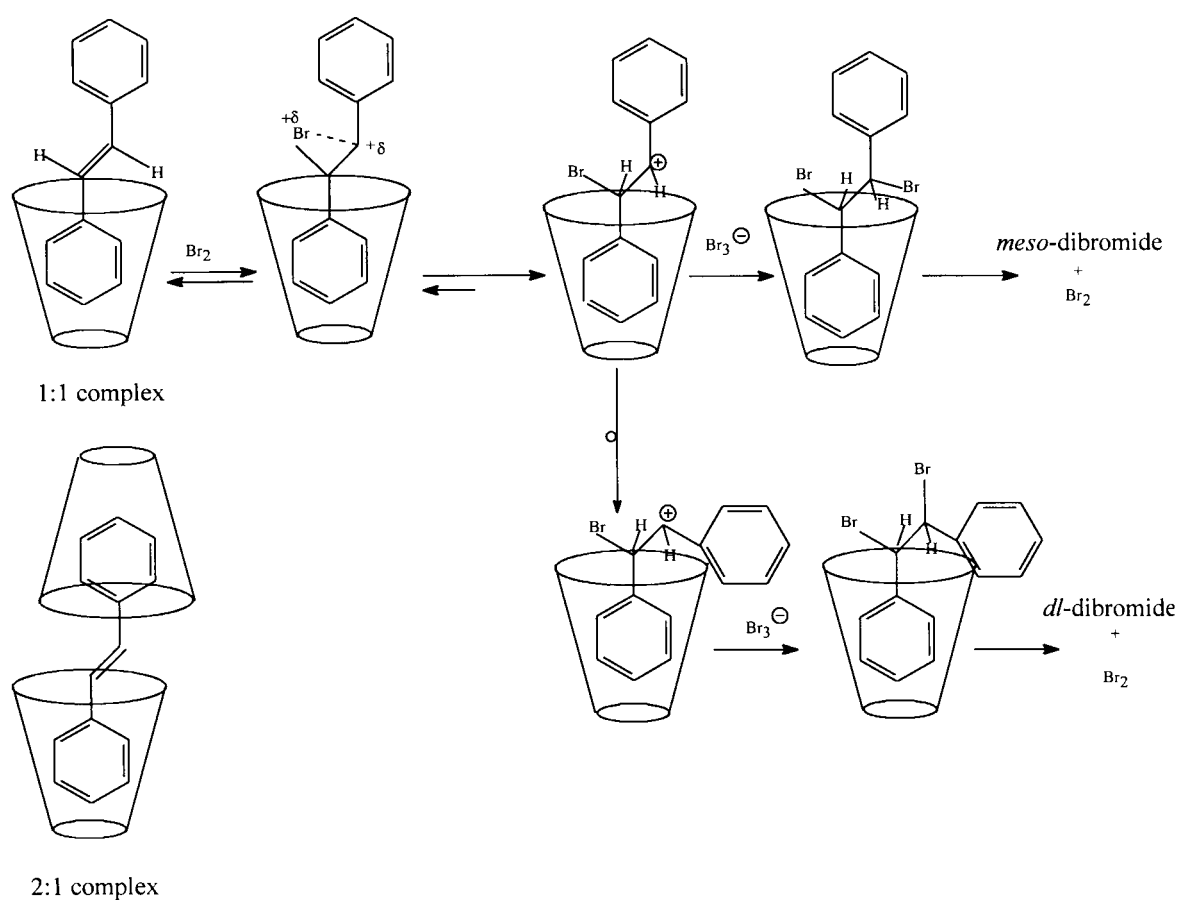
2:1 complex

Scheme 3. Mechanism of bromination of *trans*-stilbene included in the cyclodextrin cavity.

distribution is the same as in solution bromination), bromohydrins are also obtained as products with other substrates upon cyclodextrin complexation. In fact, in the bromination of styrene in α-CD, styrene bromohydrin is the predominant product and its amount decreases as the cavity size increases, thus demonstrating clearly the participation by the CD hydroxyl groups. A detailed study enlisting all these aspects is being carried out and will be communicated later.

References

1. W. Saenger: *Angew. Chem. Int. Ed. Engl.* **19**, 344 (1980).
2. (a) K. Pitchumani, M. C. Durai Manickam, and C. Srinivasan: *Tetrahedron Lett.* **35**, 2975 (1991); (b) V. Ramamurthy: *Tetrahedron*

42, 5753 (1986); (c) K. Pitchumani, P. Velusamy, S. Sabithamala and C. Srinivasan: *Tetrahedron* **50**, 7903 (1994); (d) H. S. Banu, K. Pitchumani, and C. Srinivasan: *Tetrahedron* **55**, 9601 (1999).

3. R. Breslow and P. Campbell: *J. Am. Chem. Soc.* **91**, 3085 (1969).
4. M. Komiyama and H. Hirai: *J. Am. Chem. Soc.* **106**, 174 (1984).
5. H. Ye. D. Rong, and V. T. D'Souza: *Tetrahedron Lett.* **32**, 5231 (1991).
6. M. S. Syamala, B. Nageswer Rao, and V. Ramamurthy: *Tetrahedron* **44**, 7234 (1988).
7. S. Colonna, A. Manfredi, R. Annunziata, N. Gaggero, and L. Casella: *J. Org. Chem.* **55**, 5862 (1990).
8. I. Roberts and G. E. Kimball: *J. Am. Chem. Soc.* **59**, 947 (1937).
9. W. G. Young, R. T. Dillon, and H. J. Lucas: *J. Am. Chem. Soc.* **51**, 2528 (1929); R. T. Dillon, W. G. Young, and H. J. Lucas: *J. Am. Chem. Soc.* **52**, 1953 (1930).
10. S. J. Cristol, F. R. Stermitz, and P. S. Ramey: *J. Am. Chem. Soc.* **78**, 4956 (1956).
11. P. B. D. de la Mare and R. Koenigsberger: *J. Chem. Soc.* 5327 (1964).
12. R. C. Fahey and C. Schubert: *J. Am. Chem. Soc.* **87**, 5172 (1965).
13. R. E. Buckles, J. M. Bader, and R. J. Thurmaier: *J. Org. Chem.* **27**, 4523 (1962).
14. P. B. D. de la Mare and R. Bolton: *Electrophilic Addition to Unsaturated Systems*, Elsevier, Amsterdam, 136 (1966).
15. R. E. Buckles, J. L. Miller, and R. J. Thurmaier: *J. Org. Chem.* **32**, 88 (1967).
16. W. Y. Liu, T. Xie, Y. M. Liang, W. M. Liu, and Y. X. Ma: *J. Organomet. Chem.* **627**, 93 (2001)
17. Y. Tanaka, H. Sakuraba, and H. Nakanishi: *J. Chem. Soc., Chem. Commun.*, 947 (1983)
18. A. Benesi and J. H. Hildebrand: *J. Am. Chem. Soc.* **71**, 2703 (1949).
19. *Dictionary of Organic Compounds*, Eyre & Spottiswoode Publishers Ltd., London, vol. **2**, 923 (1965).
20. M. C. Durai Manickam, K. Pitchumani, and C. Srinivasan (Unpublished results).