Asymmetric Halogenation and Hydrohalogenation of Olefins in Crystalline Cyclodextrin Complexes

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The asymmetric halogenation and hydrohalogenation of olefins have been achieved in the microcrystals of cyclodextrin complexes which act as chiral matrices.

Asymmetric bromination of olefins *via* a gas–solid reaction has been achieved by Penzien and Schmidt,[1] using a single chiral crystal of 4,4′-dimethylchalcone. We have investigated[2,3] the asymmetric halogenation of olefins such as crotonic, methacrylic, *trans*-cinnamic, and maleic acids in crystalline cyclodextrin complexes. The advantage of this method is that a variety of olefins can be used without the problem of large single crystal formation or concern about their chirality.

A typical experimental procedure is as follows: *trans*-cinnamic acid (0.8—1.0 mol. equiv.) was added to an aqueous solution of β-cyclodextrin and dissolved with mixing. The resultant precipitate was filtered and dried *in vacuo*. The ^{1}H n.m.r. spectrum in $(CD_3)_2SO$ showed that the white powder obtained contained 100 mol% of the acid. By similar treatment, various complexes (see Table 1) were obtained. The *X*-ray powder diffraction patterns of these complexes showed

Table 1. Asymmetric hydrobromination and halogenation of unsaturated acids in crystalline cyclodextrin complexes.

Acid	Cyclo-dextrin[a]	Reaction state[b]	Reagent	Temp. /°C	Time /h	Yield, %	$[\alpha]_D^{25}$ [c] °	c	Solvent	Optical yield[d] %	Ref.
Crotonic[e]	α-CD	I	HBr	25	20	28.6	+5.0	1.22	Et_2O	29[f]	4
	"	"	Br_2	"	"	0.0	—	—	—	—	
Methacrylic	"	"	Cl_2	"	"	17.4	−15.0	0.29	MeOH	100	5
	β-CD	"	"	"	"	53.0	+13.2	1.20	"	88	5
	α-CD	"	Br_2	"	"	0.0	—	—	—	—	
	β-CD	"	"	"	5	3.5	+5.8	0.61	MeOH		
Maleic	"	"	"	50	8	1.5	−22.0	0.62	AcOEt	15	6
trans-	"	"	"	0	5	2.5	−27.2	0.55	EtOH	40	7
Cinnamic	"	II	"	25	2	4.4	−3.8	0.60	"	6	7
	"	III	—	—	—	—	+2.5	1.23	"	4	7

[a] α-CD = α-cyclodextrin; β-CD = β-cyclodextrin. [b] I, gas–solid; II, in Me_2SO; III, optical resolution by the method of Cramer and Dietsch (ref. 9). [c] Measured by a Perkin-Elmer 241 photopolarimeter using 1 dm cell. [d] Calculated from the reported $[\alpha]_D^{25}$ values given in the references. [e] *trans*-But-2-enoic acid. [f] As *S*-(+)-3-bromobutanoic acid.

that they are highly crystalline. Complexes of α-cyclodextrin with maleic acid and β-cyclodextrin with crotonic acid could not be obtained.

The β-cyclodextrin complex of *trans*-cinnamic acid was exposed to bromine vapour in a dessicator in the dark at 25 °C. After exposure for 5 h the excess of bromine was removed by evacuation, and the product was extracted with diethyl ether. The extract was recovered in 90—98% yield and was chromatographed with 1,2-dichloroethane over silica gel to give the dibromide which was identified as *erythro*-2,3-dibromo-3-phenylpropanoic acid by n.m.r. and mass spectra. Bromination, chlorination, and hydrobromination of other complexes were also carried out in a similar manner. As seen from Table 1, all the products showed significant specific rotation, whereas the halogenated products from pure single crystals of these olefins showed none. The enantiomeric excess (e.e.) was calculated from the optical rotation of the pure compounds given in the literature.[4–7]

It is well-known that cyclodextrins[8] bring about the optical resolution of some racemic compounds by means of complex formation. Therefore, it was possible that the present results were simply due to optical resolution of racemic products formed in the reaction. This was checked using β-cyclodextrin and the racemic dibromide of *trans*-cinnamic acid. The optical resolution of the racemic dibromide was carried out according to the procedure described by Cramer and Dietsch.[9] As shown in Table 1, the optical yield of the dibromide from the resolution treatment is much smaller than that from the gas–solid reaction; in fact the absolute configuration is opposite in sign. Thus, it is clear that the observed asymmetric induction in the gas–solid reaction is not due to optical resolution but to the reaction itself which is influenced by the chiral frame of cyclodextrin.

Next, the asymmetric halogenation of the cyclodextrin complexes in the solid state was compared with the homogeneous reaction in Me_2SO solution. The result for the β-cyclodextrin complex of *trans*-cinnamic acid is given in Table 1. The optical yield from the homogeneous reaction is much smaller than that from the gas–solid reaction, although the absolute configurations are the same. This result shows that the gas-solid reaction is topochemically controlled by the crystalline lattice of the cyclodextrin complex.

The gas–solid reaction shows a molecular size effect, *e.g.*, crotonic and methacrylic acids in α-cyclodextrin do not react with bromine but do with gases of smaller molecular size, such as chlorine and hydrogen bromide. In addition, methacrylic acid in β-cyclodextrin has a sufficiently wide cavity to react with bromine.

Strong chiral induction has been found for the chlorination of methacrylic acid. When the acid in the α-cyclodextrin complex was chlorinated, (−)-2,3-dichloro-2-methylpropanoic acid was isolated in 100% optical yield. Interestingly, chlorination of the same substrate in the β-cyclodextrin complex gave the dichloride with the opposite configuration at 88% e.e. These results clearly show that methacrylic acid forms complexes with α- and β-cyclodextrins such that the *anti*-addition of chlorine occurs with high but different enantioselectivities in the two cases to yield dichloro derivatives of opposite chiralities.

It has been found[2] for the crystalline complex of crotonic acid with α-cyclodextrin that the acid molecule is entirely within the cavity, the carboxy group being located at the narrower opening of the cyclodextrin. The mean plane of the carbon–carbon double bond is inclined slightly with respect to the pseudo-six-fold axis of the cyclodextrin, suggesting that the attack of a halonium cation on this plane is more likely from the side facing the wider opening than from that facing the narrower opening. This may be also assumed to be the case for the complexes of methacrylic acid in α- and β-cyclodextrin, and the side of the plane facing the wider opening becomes enantiomorphic in the two complexes. To confirm this model, an *X*-ray structure analysis is in progress.

We conclude that the gas–solid reaction with cyclodextrin complexes has great potential in preparative chemistry. For instance, halogenocarboxylic acids are useful intermediates in the synthesis of amino acids.[10]

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References

1 K. Penzien and G. M. Schmidt, *Angew. Chem., Int. Ed. Engl.*, 1969, **8**, 608.
2 H. Nakanishi, Y. Tanaka, and H. Sakuraba, The 28th IUPAC Congress, OR162, August 16—21, 1981, Vancouver, Canada.
3 H. Sakuraba, Y. Tanaka, and H. Nakanishi, The 2nd Int. Kyoto Conf. New Aspect Org. Chem., C-30, August 17—20, 1982, Kyoto, Japan.
4 L. J. Andrews and J. E. Hardwiche, *J. Am. Chem. Soc.*, 1952, **74**, 3582.
5 C. D. Glassick and W. E. Adcock, *Ind. Eng. Chem., Prod. Res. Dev.*, 1969, **3**, 14.
6 A. McKenzie, *J. Chem. Soc.*, 1912, **101**, 1196.
7 E. Erlenmeyer, Jr., *Ber. Dtsch. Chem. Ges.*, 1906, **39**, 790.
8 M. L. Bender and M. Komiyama, 'Cyclodextrin Chemistry,' Springer-Verlag, Berlin, 1978.
9 F. Cramer and W. Dietsch, *Chem. Ber.*, 1959, **92**, 378.
10 K. Ohkawa and H. Tani, *Nippon Kagaku Zasshi* (*J. Chem. Soc. Jpn.*), 1954, **75**, 1202.