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HETEROGENEOUS ASYMMETRIC RING-OPENING REACTIONS OF PROCHIRAL EPOXIDES INCLUDED AS GUEST MOLECULES IN TRI-o-THYMOTIDE CLATHRATES.

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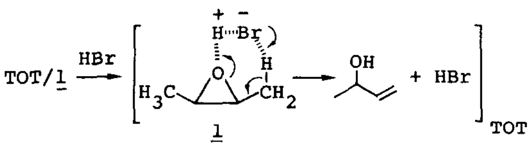
Abstract : Enantiomorphous tri-o-thymotide clathrates of prochiral oxiranes were submitted to the action of gaseous hydrogen halides. Ring-opening reactions ensued that differ from those reported in homogeneous phase, showing a considerable modification of the chemical reactivity of the external reagent in the host lattice. Chirality transfer from the host receptors to the guest products was also observed, but with a poor efficiency.

It has been shown that a bimolecular reaction between an included prochiral substrate and an external reagent can be stereocontrolled by the chirality of the crystalline host receptors in tri-o-thymotide (TOT) clathrates[1]. Encouraged by these results we have investigated the ring-opening reactions of simple enclathrated epoxides under acidic conditions. Clathrates of TOT with *cis*-2,3-dimethyloxirane (1) and 1,2-epoxycyclohexane (2) as prochiral guest molecules were prepared. The crystals are enantiomorphous (space group $P3_121$) and therefore spontaneous resolution occurs on crystallisation. The guest molecules are included in dissymmetric cages with a host-guest ratio (2:1)[2]. Large crystals can be grown and the pure antipodes sorted out from the conglomerates. The crystalline phase was submitted to a flow of gaseous dry hydrobromic (or hydrochloric) acid at various temperatures. X-ray powder diagrams showed that the clathrate lattice is preserved during the reaction, with no conversion to crystalline unsolvated TOT. In addition, the reacted crystals have to be heated *in vacuo* near to their m.p. (160-180°) to extract the guest molecules. On the whole, this is good evidence that the reaction is taking place within the cages.

In solution, oxiranes are very sensitive to the action of hydrogen halides which promote the opening of the ring followed by the addition of a molecule of reagent to form halohydrins[3]. Accordingly, the formation of (optically active) 3-bromobutan-2-ol (3) was expected to take place within the crystalline receptor of the TOT / *cis*-2,3-dimethyloxirane clathrate on the action of HBr. Instead, optically active 3-buten-2-ol was formed in 98 % yield[4] together with less than 2 % of 3. It has been shown that *strongly basic reagents*, such as lithium alkylamines[5], promote the rearrangement of epoxides to allylic alcohols. On the basis of the sterochemical model proposed for the base-catalyzed ring-opening[6] we are confronted with a highly enhanced basicity of the halide "anions" in the clathrate. The cage can be considered as a rigid solvation shell, the nature of which prohibits the significant development of solvation forces. The cationoid end of the $H^+ \ldots X^-$ ion pair formed in the cage is presumably linked to the oxirane oxygen[7], whereas the *counterion X^- can behave as a highly reactive entity similar to a "naked anion"*. Additional favourable stereochemical factors originating in the rigidity of the host-guest aggregate are likely to contribute to the facile proton abstraction from a methyl group.



The same reaction scheme is also valid for the dominant reaction of the TOT / 2-methyloxirane clathrate in presence of gaseous HCl[8]. Allyl alcohol was obtained in 87 % yield, together with a mixture of 1-chloropropan-2-ol (8 %) and 2-chloropropan-1-ol (5 %). The presence of significant amounts of halohydrins shows the occurence of a restricted nucleophilic attack of Cl^- on an oxirane C atom. The regioselectivity is similar to that observed in various liquid phases[9].

Different mechanisms become obviously competitive in the reaction with the TOT/2 clathrate. Mixtures of 3-bromocyclohexene (4) and *trans*-2-bromocyclohexanol (5) were readily formed in various proportions depending on the reaction temperature (the 4:5 ratio varied from 88:12 to 5:95 when the temperature was decreased from 30° to -12°C, respectively).

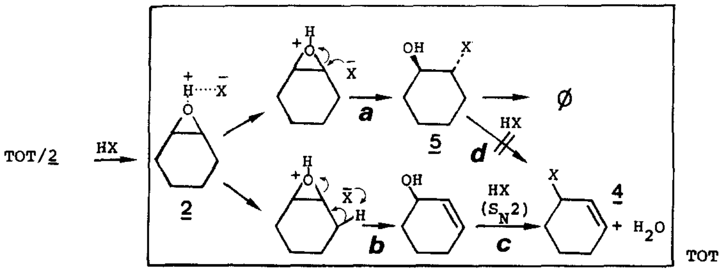


Table : Optical activity and configuration of the main products obtained from clathrates with (M)-(-)-TOT as host molecule.

Guest	Product	Yield %	e.e. %
1 [a]	(R)-(-)-3-buten-1-ol [b]	98	≈ 5
2	(1R, 2R)-(-)-*trans*-2-bromocyclohexanol [c,d]	95	10
2	(+)-3-chlorocyclohexene	95	-

a) reagent : HBr; b) *H. C. Brown & G. G. Pai*, J. Org. Chem. 50, 1387 (1985); c) *G. Dauphin, A. Kergomard* & A. *Scarset*, Bull, Soc. chim. France 1976, 862; d) Reaction temperature: -12°C.

The mode of formation of 5 (step *a*) is that dictated by the accepted mechanism in solution, whereas the occurence of 4 is thought to proceed *via* a rearrangement to 2-cyclohexen-1-ol (6) (step *b*) which is then submitted to S_N2 conditions (step *c*), i.e. attack by the reactive Br^- anion in the cage. Although 6 was not identified in the reaction products the possibility of its transient existence is attractive since the TOT/6 clathrate, prepared separately, furnishes 4 in quasi quantitative yield on the action of gaseous HBr. Similar reactions are brought about by the action of gaseous HCl: on heating TOT/2 at 70°C 3-chlorocyclohexene (7, 95 %) and 2-chlorocyclohexanol (3 %) are produced with traces of unidentified products[10]. Disregarding the unknown contribution of the by-products the following optical rotations (e.e. unknown) were calculated for 7 from two complementary experiments[11] :

$$(M)\text{-}(-)\text{-TOT} : [\alpha]^{20} = +5.7° \; ; \; (P)\text{-}(+)\text{-TOT} : [\alpha]^{20} = -4.8° .$$

The asymmetric induction in the acid-catalyzed rearrangement of 1 is low, however the configuration of the *major* enantiomer of 3-buten-2-ol is sterically closely related to that of (R)-(-)-2-butanol which is *preferentially included* in the (-)-TOT lattice[12] with low chiral discrimination (e.e. ≤ 5 %). This observation adds support to the idea that heterogeneous chirality transfer might be correlated with the actual enantioselectivity demonstrated by TOT for the product molecule, or any isosteric molecule, included as guest in the clathrate prepared separately.

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1. *R. Gerdil, G. Barchietto* and *C.W. Jefford*, J. Am. Chem. Soc. 106, 8004 (1984).
2. Recent review of TOT inclusion compounds and host-guest interaction : *R. Gerdil*, "Tri-o-thymotide Clathrates", Topics in Current Chemistry, Vol. 140, Springer-Verlag, Berlin Heidelberg 1987, pp. 71-105.
3. *M. Bartok* and *K. L. Lang*, "Oxiranes", Heterocyclic Compounds, Vol. 42, Part 3 (A. Hassner, ed.) Wiley, New York 1985, pp. 1-196.
4. The following experimental procedure is representative: single crystals (average weight 20-25 mg) of clathrate TOT/1 were sorted and had their chirality assigned from polarimetric measurements made on small chips. A coarsely crushed sample of (-)-TOT/1 crystals (147 mg) was reacted (2 h; 20°C) in a thin stream of dry HBr (generated by the action of Br_2 on tetrahydronaphthalene). The sample was then flushed out with argon and kept overnight over KOH pellets (m.p. of the sample 166-7°C). Desolvation was carried out on heating at 170°C under reduced pressure (0.05 mmHg) and the volatile products trapped at liq. N_2 temperature. The recovered liquid (ca. 10 mg) was examined by VPC, NMR and MS, and identified as 3-buten-2-ol (98 %). 3 was identified by comparison with an authentic sample (VPC). Polarimetry showed a rotation $[\alpha]_D^{20}$ of ca. -2° ($CDCl_3$, 0.81 g / 100 ml).
5. a) *A. C. Cope* and *J. K. Heeren*, J. Am. Chem. Soc. 87, 3125 (1965); b) *C. L. Kissel* and *B. Rickborn*, J. Org. Chem. 37, 2060 (1972).
6. a) *R. P. Thummel* and *B. Rickborn*, J. Am. Chem. Soc. 92, 2064 (1970); b) *A. C. Cope, G. A. Berchtold, P. E. Peterson* and *S. H. Sharman*, J. Am. Chem. Soc. 82, 6370 (1970).
7. The coordination of H^+ to one of the O atoms of TOT and its subsequent transfer to the oxirane oxygen seems sterically unrealistic in view of the guest orientation within the cavity, as revealed by X-ray structure analysis (R. Gerdil and G. Bernardinelli, to be published). See also Ref. 2, p. 87.
8. HCl reacts less readily than HBr and the reaction must be carried out at higher temperatures (ca. 60-70°C) and for longer periods of time (6-7 h). Spontaneous desolvation is however kept to a very low level (< 0.1 %) under these conditions.
9. a) *C. A. Stewart* and *C. A. VanderWerf*, J. Am. Chem. Soc. 76, 1259 (1954); b) *R. E. Parker* and *N. S. Isaacs*, Chem. Rev. 59, 737 (1959).
10. Despite of the particular environmental effects exerted by the cavity upon the reactants, the possibility of a β-elimination of H_2O from the halohydrin to yield the corresponding 3-halocyclohexene (step *d*) was rejected on the ground that, in a separate experiment, *trans*-2-chlorocyclohexanol remained unchanged in the clathrate on the action of HCl for 24 h at 90°C.
11. Optical rotations were determined on a Perkin-Elmer Model 241 polarimeter (accuracy: ± 0.002° for rotations < 1°). The concentrations of the samples were of the order of 0.03 g/ml, in $CHCl_3$. The error for one measurement is estimated at ± 0.4°.
12. See Ref. 2, pp. 87-88.

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