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THE PSEUDO-ENZYMATIC ACTION OF TRI-o-THYMOTIDE CLATHRATES APPLIED TO THE DETERMINATION OF THE ABSOLUTE CONFIGURATION OF FOUR HALOHYDRINS

Raymond Gerdil* and Giacomo Barchietto
Department of Organic Chemistry, University of Geneva
CH-1211 Geneva 4, Switzerland

The heterogeneous reactions of gaseous HCl and HBr, as external agents, with *trans*-2,3-dimethyloxirane and 2,2,3-trimethyloxirane as guest molecules in tri-o-thymotide clathrates are shown to allow the ready determination of the absolute configuration of the end-products owing to highly specific host-reactant interactions.

Tri-o-thymotide (TOT) clathrates are enantiomorphous (the host lattice of any single crystal consists entirely of the same TOT antipodes) and enantioselective (dissymmetric receptors). It has been shown that an external gaseous agent can permeate the crystal lattice and react with the included guest molecules [1]. The included molecule 2 (scheme) undergoes firstly an acid-catalyzed stereoselective allylic rearrangement (3; 100%) in contrast to the strongly basic conditions required to promote the same type of transformation in solution. Then, the allylic fragment adds the HX molecule still present in the receptor, resulting in an overall 100% regioselective ring-opening of 2 yielding the halohydrin 4. No intervening allylic alcohol has been detected in the reaction of 1, which is readily converted into the *erythro* isomer [2] (100%) of the halohydrin 5 [3]. Hydrohalogenation of 2 in the liquid-phase furnishes mainly a mixture of both halohydrins (about 90%) together with 3-methyl-butane-2-one. The absolute configurations of the substrates 1 and 2 were previously known [4] and their e.e. in the clathrate was assessed by complexation gas chromatography [5]. Complete retention of configuration at C(3) obtains in the transformations A and B (scheme). Furthermore, complete inversion takes place at C(2) of 1, whereas the corresponding assymetric center C(2) of 2 vanishes, following allylic rearrangement. Consequently, it is reasonable to consider the e.e. of the substrate as expressing the true value of the e.e. of the end-product. After cautious desolvation of the clathrate, the optical activity of the recovered halohydrin was measured, thus assigning the absolute configuration by reference to the stereochemistry of the major enclathrated oxirane enantiomer [6].

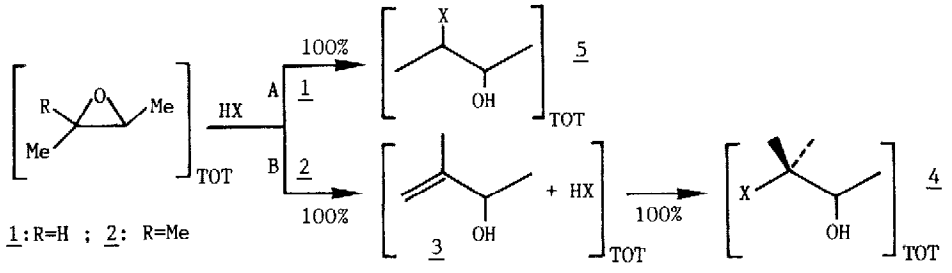

Table: absolute configurations of the halohydrins formed in (M)-(-)-TOT clathrates.

A.	Substrate[a]:	(2R,3R)-*trans*-dimethyloxirane (1) (ee=51; 55%)[b]	
	Product:	(2R,3S)-(+)-3-chlorobutane-2-ol	$[\alpha]_D = +9.12^0$ [c] (c=9.4, $CHCl_3$)
		(2R,3S)-(+)-3-bromobutane-2-ol	$[\alpha]_D = +18.0\pm0.4^0$ (c=30, $CHCl_3$)
B.	Substrate[a]:	(3R)-(+)-2,2,3-trimethyloxirane (2) (ee=12.8; 13.8%)[b]	
	Product:	(2R)-(-)-3-chloro-3-methylbutane-2-ol	$[\alpha]_D = -3.14^0$ (c=9, CH_2Cl_2)[d]
		(2R)-(-)-3-bromo-3-methylbutane-2-ol	$[\alpha]_D = -5.57^0$ (c=23, $CHCl_3$)[e]

a) Guest preferentially accomodated in (-)-TOT; b) Enantiomeric excess of the guest in two different clathrate batches; c) The value $[\alpha]_D = +8.73^0$ (neat, d=1.061) is in good agreement with the value $+8.92^0$ reported by *H.J.Lucas* and *H.K.Garner*, J.Am.Chem.Soc 70, 990 (1948); d) Complementary value from (+)-TOT: $[\alpha]_D = +3.09^0$ (c=16, CH_2Cl_2); e) $\alpha_D = -6.1^0$ (neat), complementary value: $\alpha_D = +5.8^0$ (neat).

REFERENCES AND NOTES

[1] *R. Gerdil* and *G. Barchietto*, Tetrahedron Lett. 28, 4685 (1987).

[2] A thorough inspection of the ^{1}H-NMR spectra of the end-products of several experiments has never revealed the presence of the *threo* isomer, thus supporting the general view of a total inversion of configuration at the center of attack.

[3] A detailed account of the kinetic aspects of the present type of heterogeneous reactions will be reported elsewhere.

[4] *V. Schurig* and *W. Bürkle*, J.Am.Chem.Soc.104, 7573 (1982); *A. Gedanken* and *V. Schurig*, J.Phys.Chem. 91, 1324 (1987).

[5] *V. Schurig* and *W. Bürkle*, Angew.Chem.Int.Ed.Engl.17, 132 (1978).

[6] The following general procedure is representative: crystalline powder of the clathrate containing a large e.e. of crystals of one handedness (90-100%) is obtained by seeding a TOT solution in the guest. Optically active microcrystals of TOT/2 (ca.30 mg) were desolvated at 170^0 in a sealed evacuated glass tube and the vaporized phase analyzed for the e.e. by complexation chromatography on Ni(HFB-1R-Cam)$_2$ in SE54 (column: 25m x 0.25mm fused glass). In this approach, no correction for the actual optical purity of the reacted microcrystalline batch is necessary. Batches of 4-6 g of TOT/2 of known chirality were reacted ($22-23^0$) in a stream of dry hydrogen halide until completion of the two-step reaction (HCl:20h; HBr:6h) as checked by NMR measurements. "Normal" high-temperature desolvation being inappropriate owing to the thermal lability of the halohydrins, a "soft" method was devised: the reacted powder was dissolved in a minimum amount of high-grade CH_2Cl_2 (15-20ml), the solution flash-distilled (12 Torr) at 60^0 (30 min), then at 90^0 (1h), and the volatile mixture collected at -70^0. The solid residue consisted of the clathrate TOT/CH_2Cl_2. The solvent was separated from the halohydrin by using a rotarory evaporator (-15^0C, bath/12 Torr) until complete elimination (NMR). The optical activity of the recovered colorless oil (0.28-0.39g; 0.25-0.3ml) was measured on a Perkin-Elmer Model 241 polarimeter (accuracy: $\pm0.002^0$ for rotations $<1^0$) and the NMR spectra were recorded on a Brucker WM 360 spectrometer.

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