ENANTIOSELECTIVE THIOLYSIS OF α-AMINO ACID p-NITROPHENYL ESTER SALTS BY THIOL-BEARING CHIRAL CROWN ETHERS

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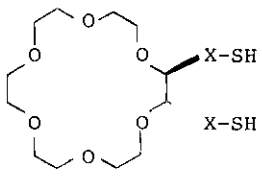
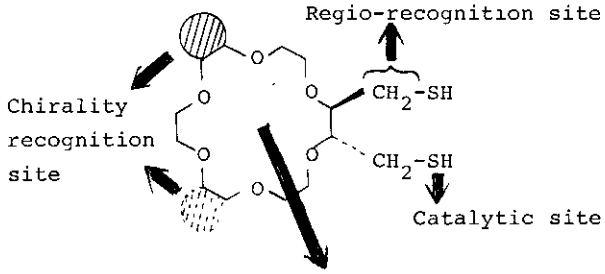
Abstract —— Studies have been made on the design, synthesis, and test of thiol-bearing chiral crown ethers that work enantioselectively in the thiolysis of α-amino acid ester salts. It is shown that crown ethers (3 and 4), prepared from (+)-(1R,2R,3S,4S)-camphane-2,3-diol (12) and (-)-(1R,2S,3R,4S)-camphane-2,3-diol (16) respectively, exhibit enantiomeric discrimination by a factor of 1.7-1.9 in the rates of p-nitrophenol release from alanine p-nitrophenyl ester salts.

Successful demonstrations of enantioselective complexation between chiral primary ammonium salts and chiral crown ethers having binaphthol,[1] tartaric acid,[2] carbohydrates,[3] etc. as chiral sources have been reported and attracted much attention. Recently, chiral crown ethers constructed around thiol-bearing chiral units of 3,3'-bis(mercaptomethyl)-2,2'-dihydroxy-1,1'-binaphthyl[4] or N-tartaroylcysteine methyl ester[5] have been shown to exhibit enantioselective thiolysis of α-amino acid p-nitrophenyl ester salts or di-peptide p-nitrophenyl ester salts, respectively.



1 a : $X=CH_2$
b : $X=CH_2CH_2CH_2$
c : $X=CH_2OCH_2CH_2$



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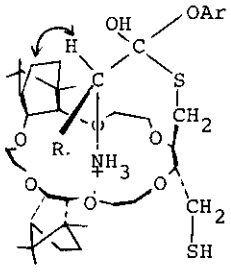
We have previously reported[6] that crown ethers of type 1 showed regio-selectivity depending on X in the thiolysis of α-, β-, γ-, and ε-amino acid p-nitrophenyl ester salts. The present paper describes the approach to the enantio- as well as regio-selective thiolysis of α-amino acid ester salts by the designed crown ethers (3 and 4) of type 2, which have chirality-recognition sites in addition to binding, catalytic, and regio-recognition (CH_2 for α-amino acid ester salts[6]) sites. The present chirality-recognition sites are built from (+)-(1R,2R,3S,4S)-camphane-2,3-diol (12)[7] or (-)-(1R,2S,3R,4S)-camphane-2,3-diol (16)[8] by anticipating the differences in steric repulsions between host and enantiomeric guests in the expected tetrahedral intermediate complexes[4] (5 vs. 6, 7 vs. 8) as shown.



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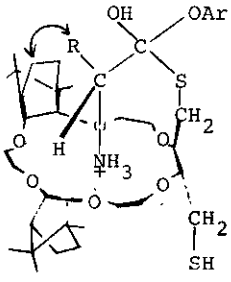
Complex of 3 with (L-) (more stable)



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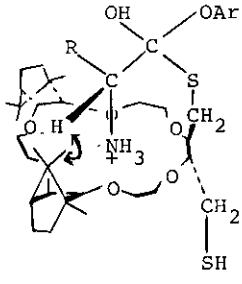
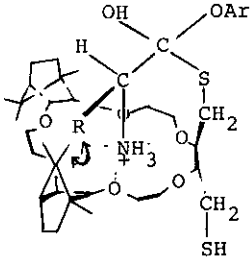
Complex of 3 with (D-) (less stable)



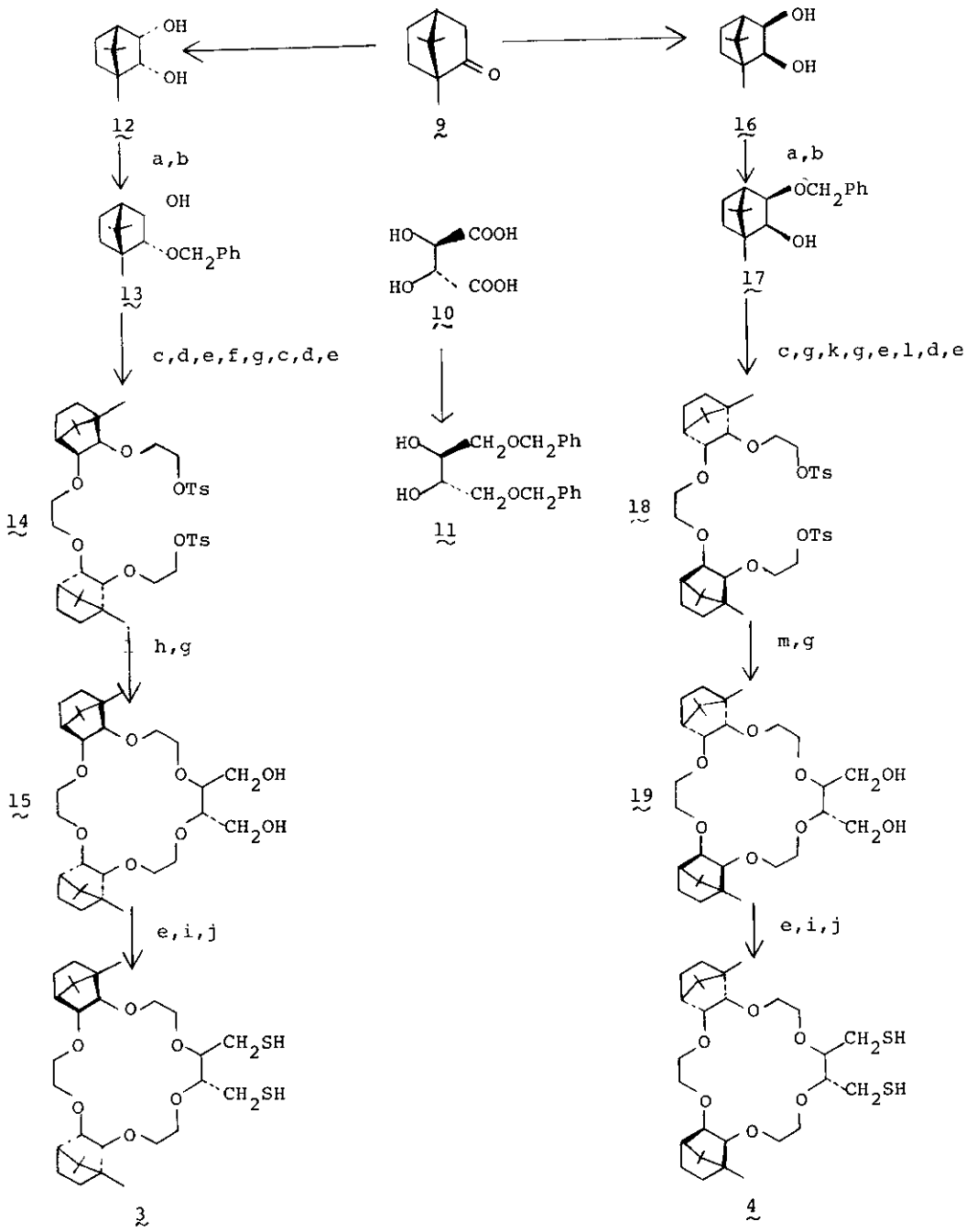
7

Complex of 4 with (D-) (more stable)



8

Complex of 4 with (L-) (less stable)



[a] NaH, $PhCH_2Cl$, DMF. [b] Separation by silica gel column chromatography. [c] NaH, $TsOCH_2CH_2OTHP$, DMF. [d] HCl. [e] TsCl, pyridine. [f] NaH, 13, DMF. [g] Pd-C, H_2. [h] NaH, 11, DMF. [i] $KOBu^t$, PhCOSH. [j] $LiAlH_4$. [k] NaH, $TsOCH_2CH_2OCH_2Ph$, DMF. [l] NaH, 17, DMF. [m] $KOBu^t$, 11, DMSO.

Table Kinetic Data for the Release of p-Nitrophenol from α-Amino Acid Ester Salts at 25.0°C

Run[a]	Substrate[b] RONp·HBr	($10^5 k_\psi \cdot s^{-1}$)[c]	Crown ether[d]	Rate constant[e] $10^5 \cdot k_\psi \cdot s^{-1}$	Rate ratio
1A	Gly	(2)	3	450	2A/1A=0.24
2A	Gly	(2)	3+18-crown-6	110	
3B	Gly	(3)	1a	7700	
4B	L-Ala	(3)	1a	3800	
5B	L-Phe	(1)	1a	200	
6B	L-Val	(<1)	1a	5	
7B	Gly	(3)	3	750	
8B	L-Ala	(3)	3	200	8B/9B=1.7
9B	D-Ala	(3)	3	120	
10C	L-Ala	(3)	3	130	10C/11C=1.9
11C	D-Ala	(3)	3	70	
12B	L-Phe	(1)	3	10	
13B	D-Phe	(1)	3	11	
14B	L-Val	(<1)	3	< 1	
15B	D-Val	(<1)	3	< 1	
16B	L-Ala	(3)	4	14	17B/16B=1.9
17B	D-Ala	(3)	4	27	

[a]Capital letters indicate the medium. A: CH_2Cl_2-hexane (1:1) buffered with 0.01M AcOH, 0.02M pyridine (pH 5.4 in H_2O); B: CH_2Cl_2-EtOH (95:5) buffered with 0.01M AcOH, 0.02M pyridine (pH 5.4 in H_2O); C: CH_2Cl_2-EtOH (95:5) buffered with 0.02M AcOH, 0.01M pyridine (pH 4.0 in H_2O).

[b]All substrates are α-amino acid p-nitrophenyl ester hydrobromides (10^{-4}M).

[c]Pseudo-first order rate constant in the absence of crown ether (buffer solvoysis) in the medium indicated.

[d]5×10^{-3}M in 1a, 3 or 4, 2×10^{-2}M in 18-crown-6.

[e]Pseudo-first order rate constant, corrected for buffer solvolysis, followed by appearance of p-nitrophenol (320 nm).

Crown ethers (3[9] and 4[10]) were synthesized using (+)-camphor (9) and (+)-tartaric acid (10) as shown in the Chart.[11] The table records the rate constants for the release of p-nitrophenol from α-amino acid ester salts in the absence (buffer solvolysis) and presence of the crown ether. Conclusions from the present data are as follows:

(1) The rate of p-nitrophenol release from glycine ester salt is substantially increased by the addition of 3 (run 1A). However, this enhanced rate is decreased to about one-fourth by further addition of excess 18-crown-6 (run 2A). These facts strongly suggest the initial complexation of crown ether with α-amino acid ester salt followed by nucleophilic attack of neighboring surfhydryl group in the present thiolysis reaction by thiol-bearing crown ether.

(2) The degree of enhancement in rates of p-nitrophenol release in the presence of crown ether (1a, 3, or 4) is in the order of glycine ester salt > alanine ester salt > phenylalanine ester salt > valine ester salt (runs 3B~15B). This order clearly shows that complexation of crown ether with α-amino acid ester salt is highly sensitive to the steric bulkiness of α-substituent of the latter.[12]

(3) The effectiveness of crown ethers in the enhancement of rate of p-nitrophenol release from alanine ester salt is in the order of 1a > 3 > 4 (runs 4B, 8B~11C, 16B, 17B). This order shows that complexation of crown ether with α-amino acid ester salt is also highly sensitive to the steric bulkiness around the polyether ring of the former.[13]

(4) Crown ethers (3 and 4) having designed chirality-recognition sites are found to exhibit enantiomeric discrimination by a factor of 1.7-1.9 in the rates of p-nitrophenol release from enantiomeric alanine ester salts (runs 8B~11C, 16B, 17B). The direction of enantioselectivity agrees with that predicted by evaluating the relative stabilities of tetrahedral intermediate complexes (5, 6, 7, 8).

The present result clearly shows the possibility of designing enantioselective and regioselective reactions by functionalized crown ethers.

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9. $[\alpha]_D^{20}$ +47.7° (c=0.99, $CHCl_3$).
10. $[\alpha]_D^{20}$ -14.1° (c=0.39, $CHCl_3$).
11. Satisfactory elemental analyses or high mass spectral data were obtained for all new compounds shown in the Chart.
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