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APPROACHES TO THE SYNTHESIS OF ENZYME MODEL SYSTEMS. REGIOSELECTIVE TRANSACYLATION REACTIONS BETWEEN THIOL-CONTAINING CROWN ETHERS AND AMINO ACID ESTER SALTS

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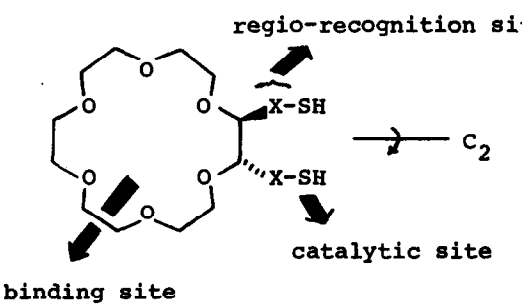
Enzymes, enormously effective catalysts for biological reactions, are known to combine with their substrates to form highly structured enzyme-substrate complexes as an essential step in their catalytic reactions.[1] Evaluating complex formation as one of the possible strategies to effect reactions highly effectively, investigations have hitherto been reported on the utility of macrocyclic compounds such as cyclodextrins,[2] cyclophanes,[3] cyclic peptides,[4] crown ethers,[5] etc,[6] as hosts to catch guests in solution.

Recently, Cram and his co-workers have reported enantioselective transacylation reactions between α-amino acid p-nitrophenyl ester salts and optically active crown ethers having built-in sulfhydryl groups as catalytic sites.[7] The present paper describes the result of examinations on the regioselectivity in the transacylation reactions between crown ethers (1, 2, 3) having functionalized side arms of different length and α-, N-methyl-α-, β-, γ-, and ε-amino acid p-nitrophenyl ester salts (4, 5, 6, 7, 8). These crown ethers were designed to show regioselectivity by the expectation that cyclic polyether part would act as a binding site, side arms constructed with ether oxygen and/or methylene as regio-recognition sites, and sulfhydryl groups at the end of the side arms as catalytic sites.



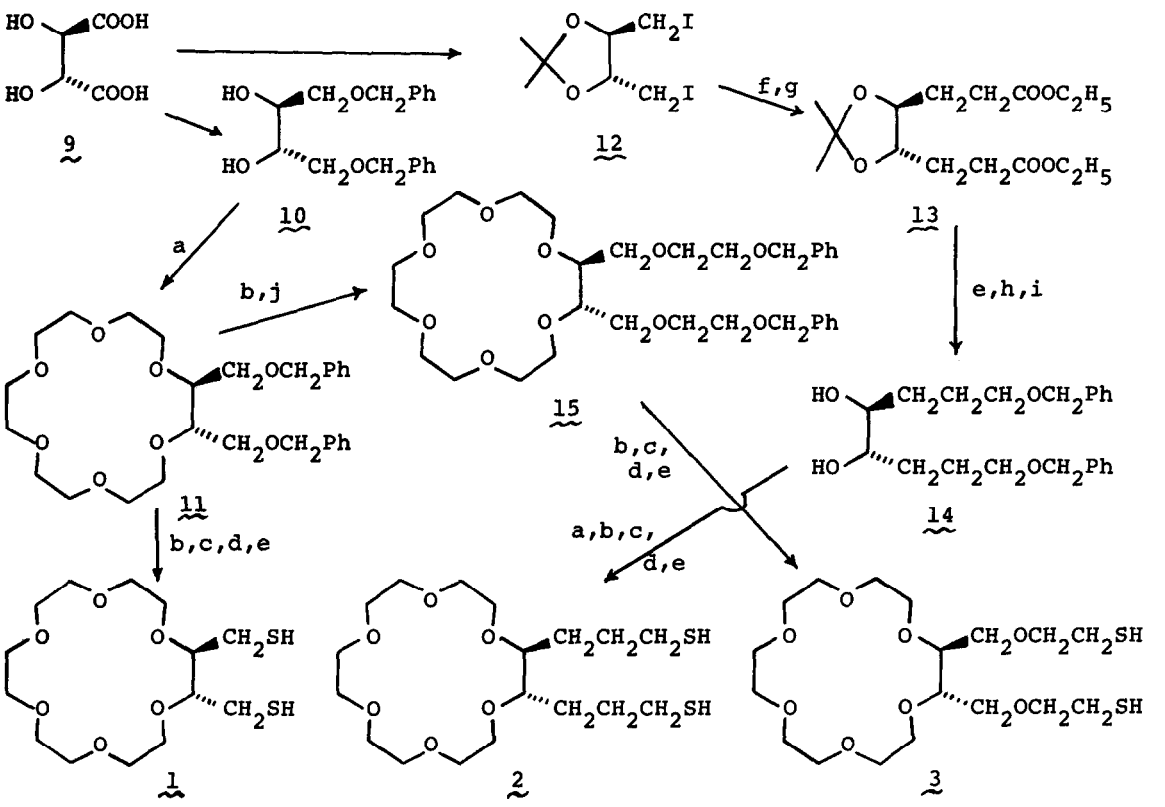


Table 1. Rate Constants for p-Nitrophenol Release from Amino Acid Ester Salts[a)]

Ester \ Crown ether	$10^5 k (sec^{-1})$ None	18-Crown-6	18-Crown-6 + BuSH[b)]	1[c)]	2[c)]	3[c)]
Br^- H_3N^+-CH_2-$COOC_6H_4$-NO_2-p (4)	3	0.9	1	1,170	50	2,500
Br^- $CH_3NH_2^+$-CH_2-$COOC_6H_4$-NO_2-p (5)	5	5	4	6	4	37
Br^- H_3N^+-$(CH_2)_2$-$COOC_6H_4$-NO_2-p (6)	<0.1	<0.05	<0.05	0.4	7	2
Br^- H_3N^+-$(CH_2)_3$-$COOC_6H_4$-NO_2-p (7)	310	1	0.9	6	42	41
Br^- H_3N^+-$(CH_2)_5$-$COOC_6H_4$-NO_2-p (8)	<0.05	<0.05	<0.05	<0.05	<0.05	<0.05

[a)] Pseudo-first-order rate constants determined spectrometrically at 320 nm in 20% EtOH-CH_2Cl_2, buffered with 0.01 M AcOH and 0.005 M pyridine (pH 4.60 in water) at 25°C, 10^{-4}M in substrates, 5×10^{-3}M in crown ethers. [b)] 10^{-2}M. [c)] Corrected for buffer solvolysis in the presence of 18-crown-6.

Table 2. Relative Rates for p-Nitrophenol Release

Ester	k_2/k_1	k_3/k_1
4	0.043	2.1
6	17.5	5.0
7	7.0	6.8

Crown ethers (1, 2, 3)[8,9] were synthesized from (+)-tartaric acid (9) as shown in the Chart. Amino acid ester salts (4, 5, 6, 7, 8)[8] were prepared by the established method.[10]

Table 1 records the rate constants and conditions for the release of p-nitrophenol from amino acid p-nitrophenyl ester salts in the absence and presence of 18-crown-6, 18-crown-6 and butanethiol, 1, 2, and 3. Table 2 records values of k_2/k_1 and k_3/k_1, relative rates for p-nitrophenol release by 2 and 3 using 1 as a standard.

Conclusions from the present data are as follows:

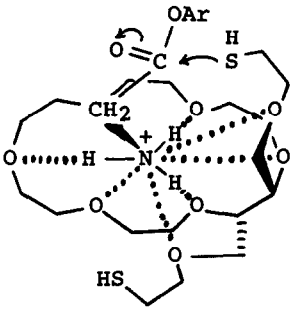
(1) In the presence of 1, the rate of the release of p-nitrophenol from α-amino acid ester salt (4) is substantially larger than that from its N-methyl derivative (5). This fact is considered to be due to the effective complex formation in the case of 4, resulting in the increase in the concentration of 4 near the sulfhydryl group of 1. The same phenomena are observed in the presence of 2 and 3.

(2) In the presence of 1, α-amino acid ester salt (4) showed extraordinary large rate increase among the ester salts examined. This result agrees well with our prediction by CPK molecular model that ester carbonyl group of 4 has the possibility to orient itself in close proximity to the sulfhydryl group of 1 by complex formation.

(3) Increase in the length of side arms from 1 to 2 changes the rates dramatically as summarized in Table 2. Thus, the rate of α-amino acid ester salt (4) decreased (0.043 fold), while that of β-amino acid ester salt (6) increased (17.5 fold) and that of γ-amino acid ester salt (7) increased (7 fold). This tendency also agrees with our prediction that the regioselectivity of the reaction will move away from the ammonium group as the position of the catalytic sites in crown ethers move away from the polyether ring.

(4) Increase in the length of side arms from 1 to 3 also changes the rates. Contrary to our prediction, however, the rate of α-amino acid ester salt (4) increased (2.1 fold). It is also striking to note that the rate of 4 by 3, having side arms longer than those of 2, is fairly higher than the rate of 4 by 2. This result is considered to be rationalized by supposing additional pole-dipole interaction[11] between the ammonium cation and the ether oxygen of the side arm as shown, or hydrogen bond formation between one of the hydrogens

attached on the ammonium nitrogen and the ether oxygen of the side arm, resulting in the fixation of side arm conformation preferable for the reaction with 4. In crown ethers, therefore, introduction of ether oxygen in the side arm is found to be a method to keep the side arm sticking up from the polyether ring in the complex.



The present data clearly demonstrates the feasibility of getting regioselectivity in the reactions catalyzed by functionalized crown ethers.

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8) a) Elemental analyses were within 0.3 % of theory. b) IR and PMR spectra were reasonable for the assigned structure.
9) Optical rotations were measured in $CHCl_3$: 1, $[\alpha]_D^{19.5}$ -10.8° (c, 3.40); 2, $[\alpha]_D^{19.5}$ -26.9° (c, 2.85); 3, $[\alpha]_D^{19.5}$ +2.5° (c, 2.60).
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