NOVEL BICYCLIC CHIRAL CROWN ETHERS HAVING A *p*-XYLENEDIOXY UNIT WITH IMPROVED COMPLEX STABILITY AND RATE-ENHANCEMENT IN THE INTRA-COMPLEX THIOLYSIS OF α-AMINO ACID ESTER SALTS

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Novel bicyclic chiral crown ethers having an α, α'-*p*-xylenedioxy unit were synthesized. Crown dithiol **1** with a *p*-xylenedioxy bridge-structure performed intra-complex thiolysis with α-amino acid *p*-nitrophenyl ester HBr salts much faster than the corresponding dithiol **3** without the bridge-structure. A ^{1}H-NMR study suggested that the increased rate of intra-complex thiolysis is due to increased stability of the intermediary complex during the reaction.

KEYWORDS chiral crown ether; intra-complex thiolysis; host-guest complex; pseudo first-order rate constant; stability constant

One of the most important steps in enzyme-catalyzed reactions is the formation of a non-covalent enzyme-substrate complex prior to the reactions.[2] Since the first report by Pedersen, crown ethers have been widely used as artificial hosts for various cations,[3] and applied to the study of enzyme-mimetic reactions.[4] Introduction of bridge-structure to macrocyclic hosts has been undertaken to fix the host cyclic conformation and has realized more stable complex formation.[5] We have already reported enantio-selective thiolysis of D- or L-α-amino acid ester salts (**Fig. 1**) by dithiol-bearing chiral crown ethers[6] and an approach to the enzyme model for the synthesis of peptides.[7] Here, we report novel crown ethers with a *p*-xylenedioxy *bridge-structure*, which form more stable host-guest complexes and perform intra-complex thiolysis faster.

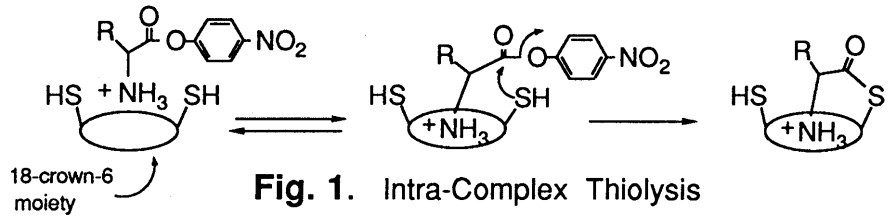
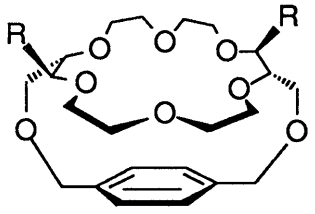
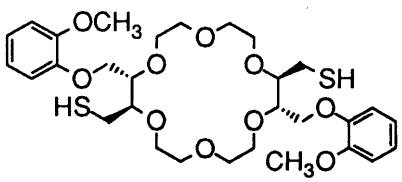


Fig. 1. Intra-Complex Thiolysis

Novel crown ethers **1** and **2** were designed by conceiving that the *p*-xylenedioxy bridge-structure would restrain conformational changes of crown rings and fix the cavity to be more favorable to forming complexes with primary ammonium cations.



1 : R = -CH_2SH
2 : R = -CH_3



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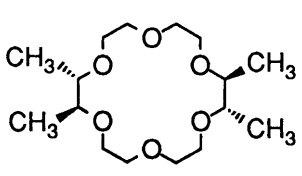

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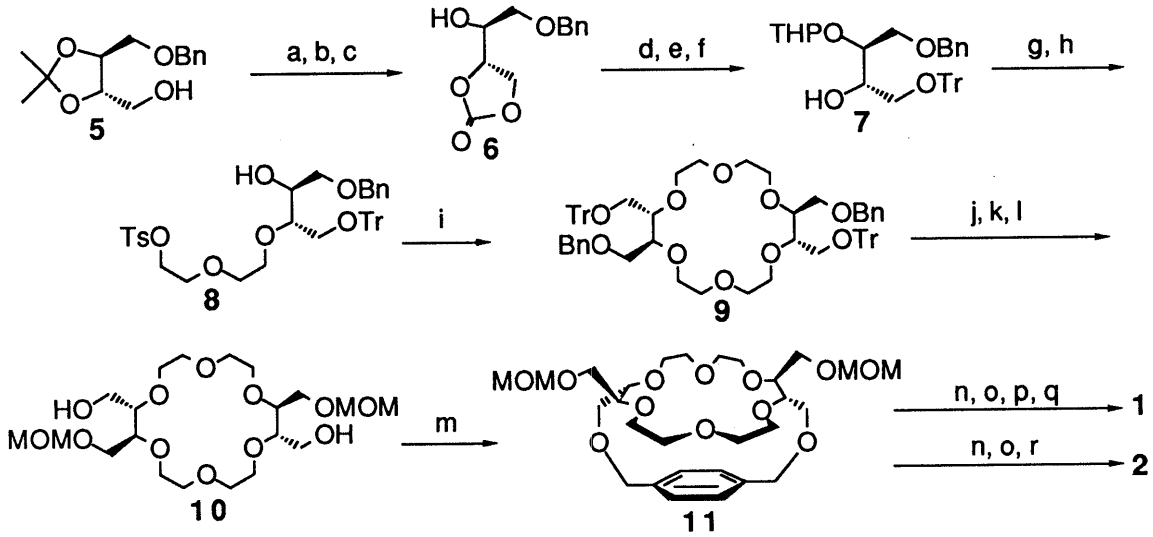
Bridged crown ethers **1** and **2** were synthesized as summarized in **Fig. 2**.[8] The crown ether **10**, having the protected hydroxymethyl groups on one face of the crown ring and free hydroxymethyl groups on the other, was chosen as a key intermediate from the preliminary experiments for the introduction of the bridge-structure. A selectively protected chiral threitol derivative **7**, which was readily accessible from alcohol **5**[6] through a cyclic carbonate **6**, was transformed to the crown intermediate **9**. The reaction of introducing the bridge-structure (**10**→**11**) proceeded successfully using **10** and α, α'-dibromo-*p*-xylene in the presence of ^{t}BuOK as a base in THF. Conversions of **11** to **1** and **2** were attained by the conventional method.[6]



a) PhOCOCl, CH_2Cl_2, pyridine, (quant.); b) 4N-HCl aq., THF; c) K_2CO_3, THF, (69%, 2 steps); d) DHP, PPTS, CH_2Cl_2; e) 1N-NaOH aq., MeOH; f) TrCl, pyridine, (96%, 3 steps); g) $(TsOCH_2CH_2)_2O$, NaH, DMF, (77%); h) PPTS, EtOH, (87%); i) NaH, DMF, (76%); j) c.HCl, MeOH; k) MOMCl, $^{i}Pr_2NEt$, CH_2Cl_2, (92%, 2 steps); l) H_2, 5%-Pd/C, EtOH; m) α, α'-Dibromo-*p*-xylene, ^{t}BuOK, THF, (55%, 2 steps); n) c.HCl, MeOH; o) TsCl, pyridine, (80%, 2 steps); p) PhCOSK, CH_3CN, (78%); q) 4N-NaOH aq., MeOH, THF, (77%); r) $LiAlH_4$, THF, (80%).

Fig. 2. Syntheses of Bridged Crown Ethers **1** and **2**

The intra-complex thiolysis[6,7] of α-amino acid *p*-nitrophenyl ester HBr salts was performed in the presence of **1** or **3** in AcOH-pyridine buffer, and pseudo first-order rate constants of intra-complex thiolysis were obtained by observing the release of *p*-nitrophenol at UV-320 nm. The results are summarized in **Table I**, and the rate using bridged host **1** was compared with that using the corresponding un-bridged **3**. As shown in **Table I** (**1**/**3** ratio in $k\phi$), bridged host **1** performs the intra-complex thiolysis much faster for all the guests examined than un-bridged **3** does. So the introduction of the bridge-structure greatly enhanced the rate of intra-complex thiolysis. We could not determine the stability of the complex formed during the thiolysis from kinetic experiment by the method previously reported.[6] So we compared the stability of the complexes between the bridged host **2** or un-bridged **4** and primary ammonium salt $^{t}BuNH_3^{+}SCN^{-}$. The stability constants *Ks* were measured by ^{1}H-NMR in CD_3CN, and the results are shown in **Table II**. Bridged host **2** exhibits increased complex stability by a factor of 14 as a result of the introduction of the bridge-structure.

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Table I. Pseudo First-Order Rate Constants of Intra-Complex Thiolysis (Fig. 1)

$k\phi$ x10^{-3} [mol/sec]

Crown \ Substrate	Gly	D-Ala	L-Ala	D-Phe	L-Phe	D-Val	L-Val
1	240	530	420	120	27	9.8	3.1
3	26	74	34	12	2.5	2.1	0.24
1/3 Ratio	9.2	7.2	16	10	11	4.8	13

Pseudo first-order rate constants were determined photometrically at 320 nm in 5% EtOH-CH_2Cl_2 buffered with 0.01 M AcOH and 0.02 M pyridine at 25.0°C, using 10^{-4} M α-amino acid ester salts and 5×10^{-3} M dithiol-bearing crown ethers.

Table II. Stability Constants

(Crown • $^tBuNH_3^+SCN^-$)

Host	*Ks* x 10^3 [M^{-1}]
2	84
4	6.2
2/4 Ratio	14

Stability constants were determined by ^{1}H-NMR (400 MHz) in CD_3CN at 30°C, using 0.01-0.06 M $^tBuNH_3^+SCN^-$ in the presence of 0.02 M crown hosts.

Apparently the rate enhancement of intra-complex thiolysis resulting from the introduction of the bridge-structure is due to the increased stability of the intermediary complex, since the reaction proceeds through the complex formed between the crown host and the amino acid substrate[6] (**Fig. 1**). The present study demonstrated an improvement in the efficiency of the enzyme-mimetic reaction, and this methodology can be used to design more efficient enzyme models.

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8) Satisfactory spectral and/or analytical data were obtained for all new compounds listed in **Fig. 2**.

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