11. Sen, E. C.; Jones, R. A. *Tetrahedron* **1972**, *28*, 2871.
12. We used random search method in SYBYL 6.0 (Tripos Associates, 1699 South Hanley Road, Suite 303 St. Louis, Missouri 63144-2913) to find the low energy conformers and then optimized using MM2 (Li, J.-H.; Allinger, N. L. *J. Comput. Chem.* **1991**, *17*, 186).
13. Bothner-By, A. A. *Adv. Magnetic Res.* **1965**, *1*, 195. Tori's equation[14] gave much better result than that of Bothner-By's but still gave high deviations between calculated and observed couplings.
14. Kuriyama, K.; Kondo, E.; Tori, K. *Tetrahedron Lett.* **1963**, 1485.

New Synthetic Receptors Containing Two Binding Sites for the Recognition of Amino Esters

Kyu-Sung Jeong* and Young Lag Cho

Department of Chemistry, Yonsei University, Seoul 120-749, Korea

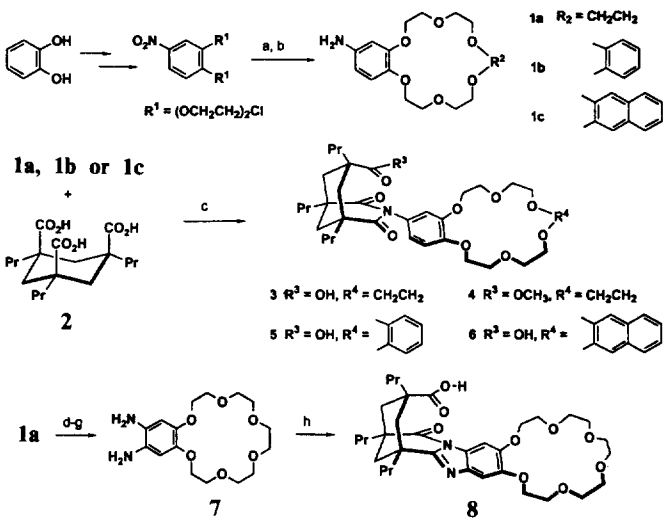
Received June 8, 1994

The design and synthesis of a molecule which can imitate a function of biological systems are of great interest in bioorganic chemistry.[1] Selective recognition of the reaction partner through weak non-covalent interactions is crucial to success of a synthetic molecule as an enzyme model. Several artificial receptors have been reported for the recognition of amino acids or their derivatives.[2]

Herein, we report new receptors for amino esters through multiple hydrogen bonds. New receptors are highly rigid and consist of two recognition sites, crown ether and carboxylic acid. The crown ether part is designed for the binding ammonium group,[3] and the carboxylic acid part for binding ester group of amino ester hydrochlorides. Two binding sites are completely separated from each other and thus their conformations are not affected by each other. This is a great advantage of our receptors because the contribution of each part to the binding phenomena can be evaluated by systematic manipulation.

New receptors, **3-6**, were prepared by heating of a well-ground mixture of triacid[4] **2** and amino-benzocrown ethers **1a-c**, among which **1b** and **1c** were prepared from catechol following literature procedures.[5] More rigid amidine receptor **8** was also prepared from triacid **2** and diamino-benzocrown ether **7**, which was synthesized from **1a** as described in Scheme 1.

All of the receptors and their complexes studied are highly soluble in a variety of organic solvents. Three amino esters, Phe-OMe, Tyr-OMe, and Trp-OMe hydrochloride are chosen for binding studies because they are relatively insoluble in CH_2Cl_2 so that extractions into CH_2Cl_2 layer occur mostly by complexation. The binding affinities have been determined by solid-liquid and liquid-liquid extractions. In the solid-liquid extraction experiments,[4] the amount extracted was measured by GC using triethyleneglycol benzyl methyl ether as an internal standard after amino esters extracted were transformed to the corresponding trifluoroacetyl derivatives. The results of solid-liquid extractions are summarized on Table 1.



Scheme 1. (a) catechol, or 2,3-dihydroxylnaphthalene/Cs_2CO_3/DMF, 100℃, 24 h. (b) H_2/Pd-C, 3 h. (c) 180℃/1.5 h, 35-45% isolated yield for three steps (a-c). (d) Ac_2O/CH_2Cl_2-1 M Na_2CO_3 aq. (e) NH_4NO_3-$(CF_3CO)_2O/CHCl_3$. (f) K_2CO_3/MeOH. (g) H_2/Pd-C, 2 days. (h) **2**, 180℃, 1.5 h, 11% isolated yield from **1a**.

Table 1. Solid-Liquid Extractions of Amino Ester Hydrochlorides into CH_2Cl_2 at 23± 1℃.[a]

Receptor	Molar equivalents[b]		
	Phe-OMe	Tyr-OMe	Trp-OMe
blank	0.31	nd[c]	nd[c]
dibenzo-18-C-6	0.41	<0.05	<0.05
3	2.2	0.49	0.73
4	2.2	0.18	0.21
5	2.1	0.37	0.53
6	2.2	0.30	0.43
8	2.0	0.39	0.34

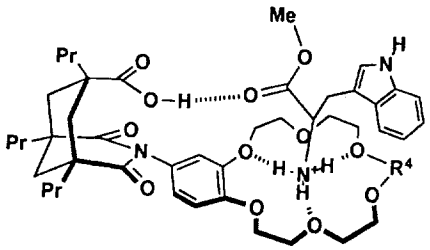
[a] In all cases, 0.5 mL of 15 mM receptor and 10 mg of L-amino ester hydrochloride were used for extraction experiments. [b] All are the average values of two or three extractions and errors are within 10%. [c] not detected.

Solubility depends on the relative strength of solute-solute, solute-solvent, and solute-receptor interactions. As shown in Table 1, Phe-OMe hyrochloride is appreciably soluble in CH_2Cl_2 without any receptor, and thus weak solute-receptor interaction is enough to extract it. Two equivalents of Phe-OMe hydrochloride are roughly extracted by all of our synthetic receptors.

Extraction experiments for Tyr-OMe and Trp-OMe hydrochlorides demonstrate an importance of the basicity of an oxygen in the strength of hydrogen bonds. As an example, monobenzo receptor **3**, having four dialkyl and two alkyl aryl oxygens, is more effective on extractions of Tyr-OMe and Trp-OMe hydrochlorides than both dibenzo receptor **5** and

benzo-naphtho receptor **6**, having two dialkyl and four alkyl aryl oxygens. The dibenzo receptor **5** shows slightly higher extractabilities than benzo-naphtho receptor **6** does. This might indicate that a phenolic oxygen is more efficient acceptor in the hydrogen bond than a naphtholic oxygen. Additionally, a contribution of π-stacking interactions in these receptors is too small compared with the hydrogen-bonding interactions to notice it.

The receptor **3** extracts both Tyr-OMe and Trp-OMe hydrochlorides much more efficiently than its methyl ester derivative **4** does. As shown in complex **9**, this could be rationalized by an additional hydrogen bond between the carboxylic acid of the receptor **3** and the carbonyl oxygen of amino esters. This hydrogen bond greatly enhances extractabilities of our receptors, though an ester group has been hardly utilized as a hydrogen-bonding acceptor in artificial receptors.[6]



9

The imide receptor **3** and amidine receptor **8** are same two binding sites, crown ether and carboxylic acid. Small difference in geometrical position of two binding sites caused to decrease considerably extractability of the receptor **8**, in which it might not be possible to achieve an optimum hydrogen bond between the carboxylic acid of the receptor **8** and the carbonyl oxygen of amino esters. Another possible explanation for different extractabilities of **3** and **8** is that the N-C bond (imide-phenyl) in the receptor **3** is freely rotatable to form simultaneous hydrogen bonds in two binding sites. Quantitative analysis of this hydrogen bond has been determined by liquid-liquid extraction method described by Cram.[7] The extraction experiments have been performed employing 0.15 M of the receptor, **3** or **4**, in CH_2Cl_2 and 0.015 M of amino ester hydrochloride in 1.0 N aqueous HCl. Under these conditions receptors **3** and **4** extract, respectively, 60± 2% and 10± 2% of Trp-OMe hydrochloride from aqueous into organic layer, while the extraction of more hydrophilic Tyr-OMe hydrochloride[8] by both of the receptors are negligible. The amount extracted has been determined by measuring changes in absorbances of Trp-OMe hydrochloride in aqueous 1 N HCl layer at 279 nm ($\varepsilon = 5250\ M^{-1}\ cm^{-1}$). The difference of 50% extraction is corresponding to 30 times differences of binding constant (K_a),[7] and thus an additional hydrogen bond between the carboxylic acid and the carbonyl oxygen is estimated to be $\Delta G^\circ = 2.0$ kcal/mol.

In conclusion, we synthesized geometrically well-defined receptors which recognize amino esters through multiple hydrogen bonds. Our system can be further utilized as a model of the protease enzyme;[9] the crown ether part in our receptors may function as a binding site and the carboxylic acid as a catalytic site. The efforts to elucidate this possibility are underway in our laboratory.

Acknowledgment. This work was financially supported by the Yonsei University and the Organic Chemistry Research Center.

References

1. (a) Atwood, J. L.; Orr, G. W.; Juneja, R. K.; Bott, S. G.; Hamada, F. *Pure Appl. Chem.* **1993** *65*, 1471. (b) Branda, N; Wyler, R.; Rebek, J., Jr. *Science* **1994**, *263*, 1267.
2. (a) Behr, J.-P.; Lehn, J.-M.; Vierling, P. *Helv. Chim. Acta.* **1982**, *65*, 1853. (b) Rebek, J., Jr.; Askew, B.; Nemeth, D.; Parris, K. *J. Am. Chem. Soc.* **1987**, *109*, 2432. (c) Galan, A.; Andreu, D.; Echavarren, A. M.; Prados, P.; de Mendoza, J. *J. Am. Chem. Soc.* **1992**, *114*, 1511.
3. Izatt, R. M.; Pawlak, K.; Bradshaw, J. S.; Bruening, R. M. *Chem. Rev.* **1991**, *91*, 1721, and references are therein.
4. We used the tripropyl triacid **2** instead of commecially available Kemp triacid to increase solubilities of receptors in organic solvents. For a preparation of **2**, see: Jeong K. S.; Tjivikua, T.; Muehldorf, A.; Deslongchamps, G.; Famulok, M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 201.
5. (a) van Keulen, B. J.; Kellogg, R. M.; Piepers, O. *J. Chem. Soc., Chem. Comm.* **1979**, 285. (b) Weber, E.; Josel, H.-P.; Puff, H.; Franken, S. *J. Org. Chem.* **1985**, *50*, 3125.
6. For the hydrogen bond between amino esters and aromatic hydroxyl groups, see: (a) Aoyama, Y.; Yamagishi, A.; Asagawa, M.; Toi, H.; Ogoshi, H. *J. Am. Chem. Soc.* **1988**, *110*, 4076. (b) Mizutani, T.; Ema, T.; Tomita, T.; Kuroda, Y.; Ogoshi, H. *J. Am. Chem. Soc.* **1994**, *116*, 4240.
7. (a) Moore, S. S.; Tarnowski, T. T.; Newcomb, M.; Cram, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 6398. (b) Koenig, K. E.; Lein, G. M.; Stuckler, P.; Kaneda, T.; Cram, D. J. *J. Am. Chem. Soc.* **1979**, *101*, 3553.
8. Wolfenden, R.; Andersson, L.; Cullis, R. M.; Southgate, C. C. B. *Biochemistry* **1981**, *20*, 849.
9. Sasaki, S.; Koga, K. In *Crown Ethers and Analogous Compound*; Studies in Organic Chemistry 45; Hiraoka, M., Ed.; Elsevier: Amsterdam, 1992; p 265-310.

Hexadecols. New Bisfunctional Molecular Vessels from Condensation Reaction among Resorcinol, Monoaldehyde, and Dialdehyde

Kyungsoo Paek

Department of Chemistry, Soong-Sil University, Seoul 156-743
Center for Biofunctional Molecules, P.O. Box 125, Pohang 790-600, Korea

Received June 22, 1994

Octols **1** are cyclotetramers from the fourfold homogeneous condensations of various aldehydes with resorcinol or 2-substituted resorcinols as shown in Scheme 1.[1] With aliphatic aldehydes and resorcinol or 2-methylresorcinol, only C_{4v}-octols are yielded, whose crystal structures exhibit bowl-shaped