Selectivity in Supramolecular Host-Guest Complexes

by Hans-Jörg Schneider and Anatoly K. Yatsimirsky

To Crown ether and cryptand complexes: hole size fitting and other effects

Figure S1 shows the relatively linear correlation between the complexation free energies of complexes with K^+ against those with Na^+ with many ionophores described in the literature, independent of their nature. The slope (m = 0.767) of the correlation reflects the intrinsic affinity differences between these cations with any receptor. As is obvious from the correlation in Fig. S1,1 most of the ionophores, which are used in solution, owe their increased efficiency just to their increased number of oxygen and nitrogen atoms. The only exception is the complexation with the 2.2.1 cryptand, which is too small for the K^+ ion – a classical case of selection by the hole-size effect. Noticeably, the maximal affinity difference between K^+ and Na^+ affinity reported in e.g. methanol solution is only $\Delta\Delta G$ = 3.5 kJ/mol. The ΔG variations in crown ether and cryptand complexes are also due to differences in the electron donor capacity C_D of the heteroatoms, which can be characterized by measurements of related hydrogen bond associations; it has been shown that e.g. the strength of K^+ complexes with all such ionophores correlate with the sum ΣC_D with very little scatter.2

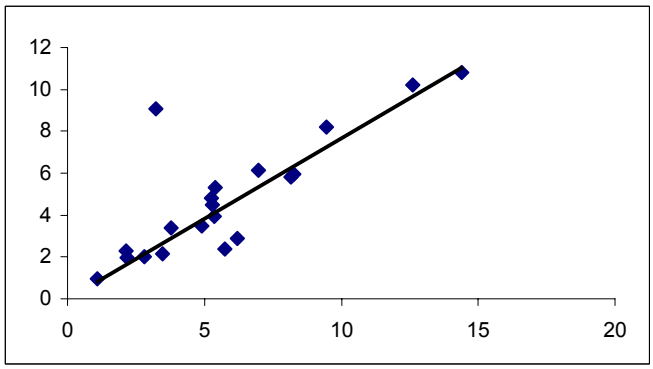


Figure S1. Complexation -ΔG for Na^+ *vs.* K^+ with glymes, crowns, cryptands, and other ionophores. $\Delta G(K^+) = 0.7671\ \Delta G(Na^+)$; $R^2 = 0.9045$ (without 2.1.1 complex); data from compilation in ref. 1

While the correlation in Fig. S1 looks promising, the more explicit correlation of the K^+/Na^+ selectivity against the total affinity (Fig. S2) shows much scatter, which can be ascribed to the error propagation from the slope in Fig. 1, and also to geometric differences leading to different matching (e.g. with benzo- or cyclohexano- crown ethers). It should be emphasized that many data in Fig. S1 and S2 are from extraction experiments which are less accurate.[1]

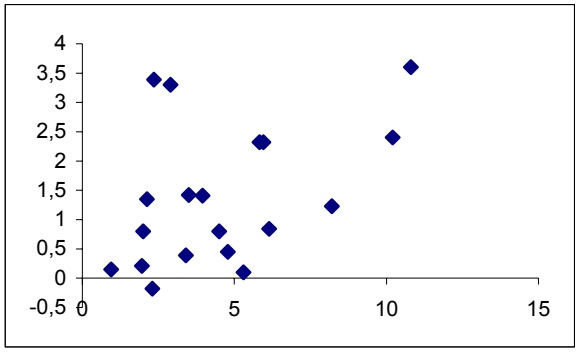


Figure S2. Data from Fig. S1 re-plotted as the selectivity $\Delta\Delta G$ (ΔG_{K^+} - ΔG_{Na^+}) vs. ΔG_{Na^+} (without 2.1.1 complex).

To hydrogen bonded complexes and anion complexation

Besides correlations with anions given in Fig.9, there is also a good correlation for Cl/NO_3, Fig. S3.

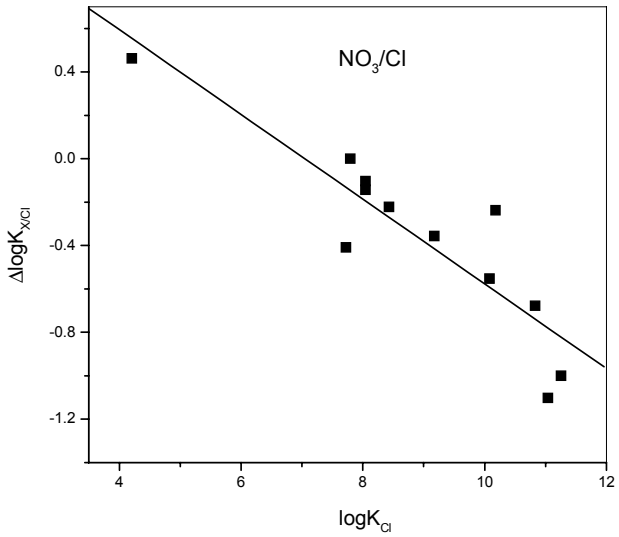


Fig. S3. Selectivity of anion recognition by receptor **18** in chloroform.

However, with non-symmetrical large acetate and ethanesulfonate anions there is no correlation, Fig. S4 most probably because of steric effects.

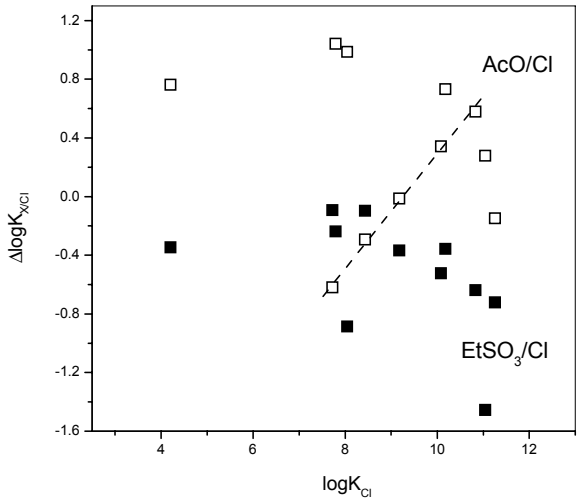


Fig. S4. Selectivity of anion recognition by receptor **18** in chloroform. Open squares - acetate, solid squares – ethanesulfonate. Dashed line is the correlation given by authors 3 through points for a set of selected receptors.

Table S1. Binding constants and selectivities with the open chain bisindole ligand **19** and halide anions (Data : a) K.-J. Chang, K.-S. Jeong; D. Moon, M. S. Lah, *Angew. Chem. Int. Ed*. 2005, **44**, 7926; b) K.S. Jeong, private communication.)

	CD_2Cl_2	$CDCl_3$	CD_3CN	THF-d_8
K_{Cl}	13000	2500	900	9500
K_{Br}	2600	840	160	590
K_I	19	140	12	62
K_{Cl}/K_{Br}	5	3	6	16
K_{Br}/K_I	14	6	13	10

Table S2**.** Binding constants (K in units of 10^4 [M^{-1}]) and selectivities with a open chain tetraindole 20 and halide anions (Data :a) K.-J. Chang, K.-S. Jeong; D. Moon, M. S. Lah, *Angew. Chem. Int. Ed.* 2005, **44**, 7926; b) K.S. Jeong, private communication)

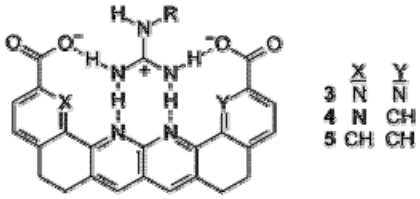
	CD_2Cl_2	CD_3CN	THF	Acetone
K_{Cl}	>500	18	>500	150
K_{Br}	41	0.13	15	13
K_I	0.0018	0.0008	0.024	0.0007
K_{Cl}/K_{Br}	> 10	140	> 30	120
K_{Br}/K_I	2300	160	630	1900

Table S3**.** Complexation[a] and selectivity[b] of diphenylurea with different halides in different solvent (Data: K. Kato and H.-J. Schneider, unpublished results).

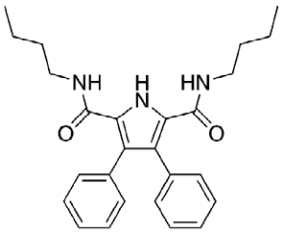
	$(CD_3)_2CO$			CD_3CN			D_6DMSO		
	Cl	Br	I	Cl	Br	I	Cl	Br	I
K_{av} [a)]	14800	3820	260	2140	580	65	40	4	<1
$-\Delta G$ [a)]	23.7	20.3	13.7	18.9	15.7	10.2	9.2	3.4	>0
K_{Cl}/K_{Br}	-	4	15	-	4	9	-	10	<4

[a)]Average values K_{av} and -ΔG (kJ/mol) from single K values for each signal with data weight according the CIS values. [b)] ratios between the K values of chloride and bromide or values of bromide and iodide. Data in DMSO: F. Werner and H. J. Schneider, *Helv. Chim. Acta*, 2000, **83**, 465.

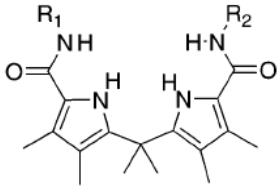
Simultaneous action of salt bridges and discriminating hydrogen bonds (structure **S1**) can amount in methanol to stability constants above 100 000 M^{-1}.[4] Several 2,5-bisamidopyrroles like **S2** show selective oxo-anion complexation whilst bis-amides containing dipyrrolylmethane groups, e.g. **S3**, form strong complexes with dihydrogen phosphate anions in DMSO–water mixtures.[5]



S1

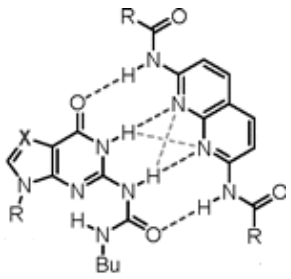


S2



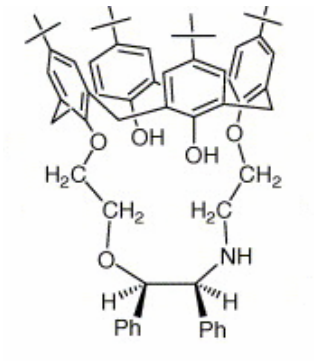
S3

It should be mentioned that hydrogen bonds play a significant role in the selective recognition of nucleic bases by artificial ligands with the help of geometrically matching donor acceptor functions,6 such as shown with structure **S4** (X=N or X=CH); such associations are also useful for selective formation of new materials. [6c]

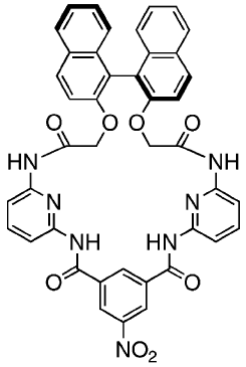


S4

To chiral recognition



S5



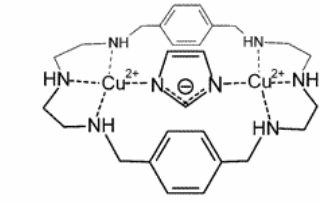
S6

Recently, an association constant ratio as large as 10^2 (corresponding to 98% e.e.) was reported for (S)- and (R)-mandelic acid using a calix[4]crown **S5** which bears an optically active 1,2-diphenyl-1,2-oxyamino residue.7 The hydrogen-bonding macrocycle **S6** functions as a highly effective chiral shift reagent for a wide range of chiral compounds having a carboxylic acid, ester, alcohol, sulfoxide, and other H-acceptor functionalities. [8]

Associations with metal complexes[9]

(I) Discrimination by host-metal acid and guest Lewis base

Coordinatively unsaturated metal complexes can provide strong binding sites to Lewis base units of organic ligands. Introduction of additional organic residues in the metal complex allow the design of selective host systems. The metal ion center alone will of course already discriminate e.g. basic aminoacids or peptides from others. For example, the Cu complexes of cyclic bis-diene with the fluorescence dye eosin ($K = 10^7$ [M^{-1}]) shows as result of the Cu ion total quenching of fluorescence, which is regenerated only by His in contrast to other aminoacids.[10]



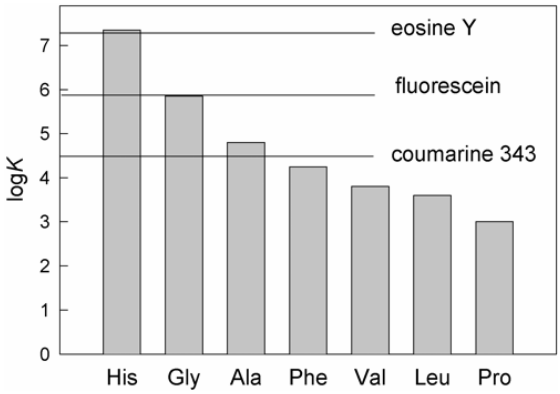
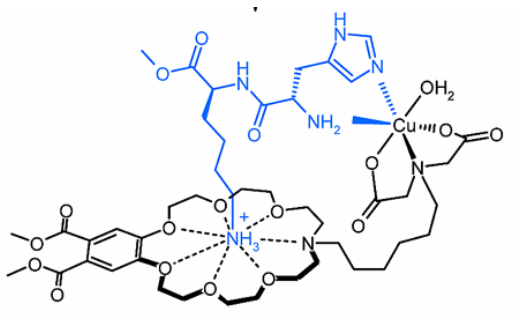


Fig. S5. Equilibrium constants for the interaction of the Cu(II)-diene host with amino acids (bars) and for comparison with fluorescent indicators alone (horizontal solid lines). The position of the horizontal line with respect to the bars determines the selectivity of the chemosensing ensemble diene/Cu(II)/ indicator toward the chosen amino acid.[10] (M.A. Hortala, L. Fabbrizzi, N. Marcotte,F. Stomeo, A. Taglietti, *J. Am. Chem. Soc.* **2003**, *125*, 20.)

The relatively weak binding of crown ethers to NH_3-groups of peptides in water can be significantly enlarged by a pendant copper imidodiacetic acid complex, which coordinates with high affinity to histidine. This allows selective detection of only His containing peptides.11

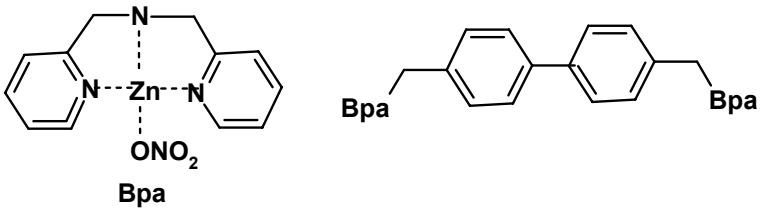


(M. Kruppa, C. Mandl, S. Miltschitzky, B. König, *J. Am. Chem. Soc.*, **2005**, *127*, 3362)

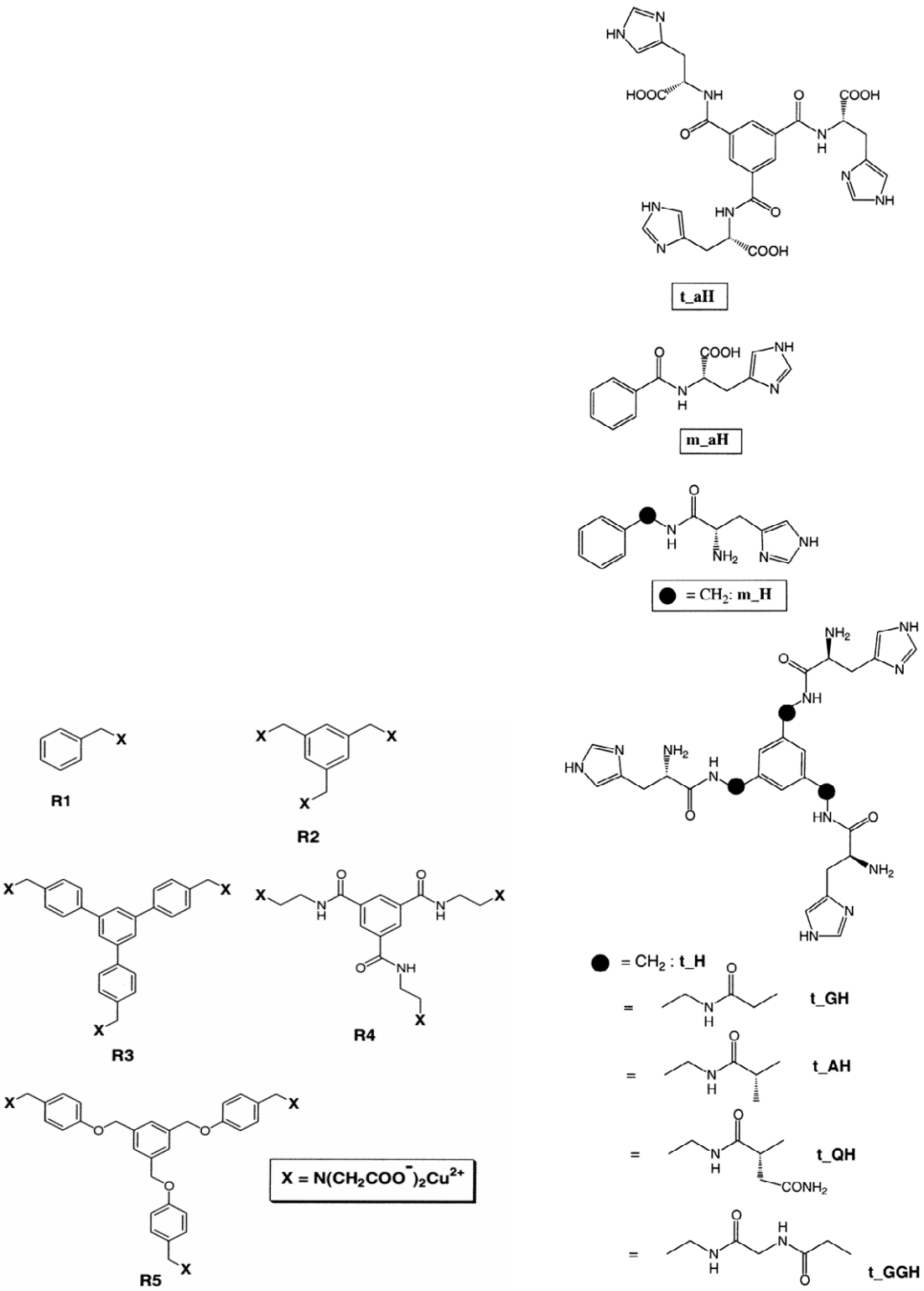
(II) Discrimination by geometric matching between host-metal and guest Lewis base centers

Placement of several metal centers in distances designed e.g. with the help of computer aided molecular modelling allows by geometric matching distinction of e.g. peptides and even proteins containing e.g. lysine or histidine. Obviously, a optimal match will lead to optimal strength **and** selectivity, in particular if the interactions are not "soft" as in the case of ion pairing or Coulombic forces, but fall off significantly with non-ideal distances between interacting sites. Since such a situation is more typical for metal complexes one may expect affinity – selectivity correlations to hold more often than with other non-covalent interactions.

For example, two Zn(II) bispicolylamine units (Bpa) can e.g. be attached to spacers such as biphenyl as host for helical oligopeptides containing His in different positions; the binding constants in water are between K = 10^4 to 10^5 [M^{-1}] , and depend on the geometrical matching between the Zn and His location.12



From the library of e.g. 8 His-containg synthetic and quite flexible peptides (Scheme S2) Cu(II)complexes with iminodiacetate derivatives (IDA, (HOOC-CH_2-)$_2$NH) shows affinities , which for the most exact geometric match (peptide 5) reach binding constants above K = 10^6 M^{-1}] . Figure S7 illustrates that indeed the highest selectivity is obtained with the Cu complex showing the highest affinity.13 Based on the same principle it is possible to recognize unique patterns of surface-exposed Histidines in proteins such as carbonic anhydrase.14



Scheme S1 (left side). Five Zn(II) bispicolylamine (Bpa) host used for recognition of peptides.[13] (Scheme S2 (right side) . A library of peptides recognized with derivatives of iminodiacetate (IDA)-Cu(II) complexes. [13] (S. Sun, M.A. Fazal, B. C. Roy, B. Chandra, S. Mallik, *Inorg. Chem.* **2002**, *41*, 1584)

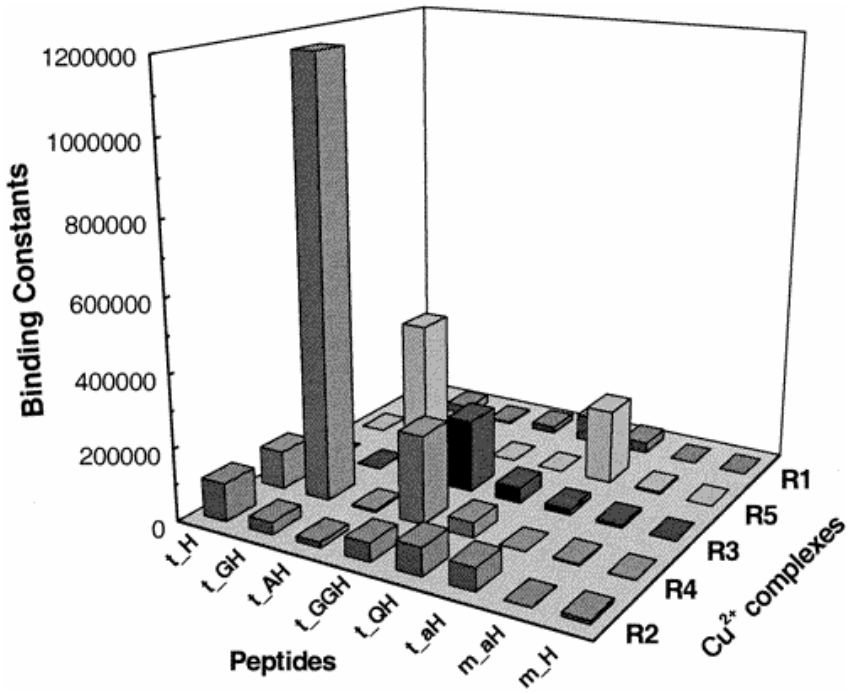


Fig S7**.** Binding constants of 8 peptides (Scheme S2) with Cu complexes of iminodiacetate (IDA) derivatives (Scheme S1) . [13] (S. Sun, M.A. Fazal, B. C. Roy, B. Chandra, S. Mallik, *Inorg. Chem.* **2002**, *41*, 1584.)

Foldamers derived e.g. from peptides as recognition systems

Peptides provide a large variety of binding elements which if brought to conformational order can be designed to be very promising host systems. Such conformations can reached not only in the form of well known α-helices, ß-sheets and other coils, but also by association between the chains in the form of socalled foldamers.[15] Until now such foldamers have been largely used as templates, for enyzme mimics , and for new nanoscale materials.[16] There are not yet enough data to overview any correlations between affinitity and selectivities with such hosts, but it is clear that both ´binding strength and selectivity should increase primarily with the number of interactions, controlled, , however , by the exposure goups which are interact with guest molecules and not which each other. One interesting feature of such oligopeptides is, that the host conformation can be controlled e.g. by the solvent.[17]

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(12) See e.g. A. Ojida, Y. Mito-oka, K. Sada; I. Hamachi *J. Am. Chem. Soc.***2004**, 126, 2454.

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