N-Hydroxypyrazinone-bearing homotrioxacalix[3]arene: its cooperative molecular recognition by metal complexation

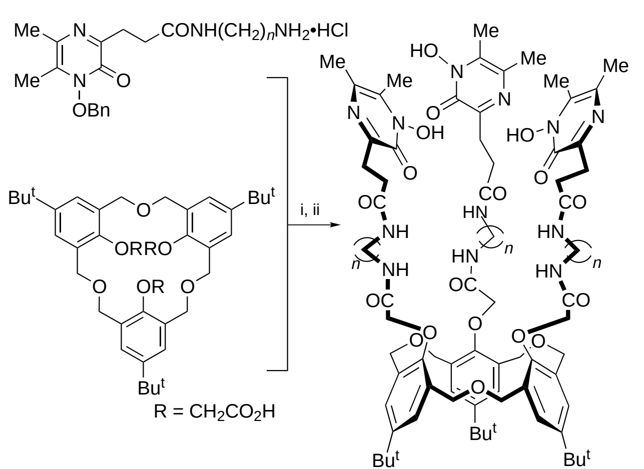
Junko Ohkanda, Hiroyuki Shibui and Akira Katoh*

Department of Industrial Chemistry, Faculty of Engineering, Seikei University, Musashino, Tokyo 180, Japan

Artificial receptors in which three bidentate hydroxypyrazinones are linked to homotrioxacalix[3]arene through an α,ω-diamine as a spacer exhibited cooperative molecular recognition with gallium ion toward ammonium cations.

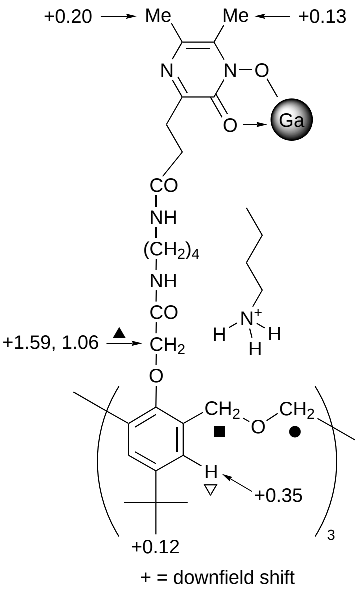
Recently, artificial allosteric receptors have been widely investigated from the viewpoint of the application of regulated functions controlled by cooperativity in natural proteins to biomimetic molecular recognition systems.[1] Previously we have demonstrated that *N*-hydroxyamide-containing diazines such as *N*-hydroxypyrazinones acted as a bidentate ligand to Fe^{III} and Ga^{III}.[2] Homotrioxacalix[3]arene[3] is flexible compared to calix[4]arene due to its ethereal linkages, and has a C_3 symmetrical structure which is expected to be particularly useful in receptors of primary ammonium cations.[4] We focused our interest on this compound as a platform for the construction of a flexible host molecule. In the course of our studies on the application of diazines to multifunctional receptors, new host molecules **1a**,**b**, in which three *N*-hydroxypyrazinones were linked to homotrioxacalix[3]arene by an alkyl spacer group, were synthesized. The hosts would be expected to control their cavity size and rigidity upon transition metal chelation, which enables them to exhibit cooperative molecular recognition toward primary ammonium cations. We describe herein the synthesis of the receptors **1a**,**b** and their ammonium cation extraction abilities.

Receptors **1a**,**b** were synthesized by coupling *N*-3-(1-benzyloxy-5,6-dimethyl-2-oxo-1,2-dihydropyraz-3-yl)propanoyldiaminoalkane hydrochloride (n = 4, 6)[2b] with the cone-type tricarboxylic acid[5] derived from homotrioxacalix[3]arene by using WSC·HCl and HOBt† and subsequent hydrogenation according to Scheme 1. Compounds **1a**,**b** were characterised by IR and ^1H NMR spectroscopy and elemental analysis, respectively.‡



1a n = 4
b n = 6

Scheme 1 *Reagents and conditions*: i, WSC·HCl, HOBt, Et_3N, CH_2Cl_2, room temp., 72 h, 52%; ii, H_2, 10% Pd–C, MeOH, 70%



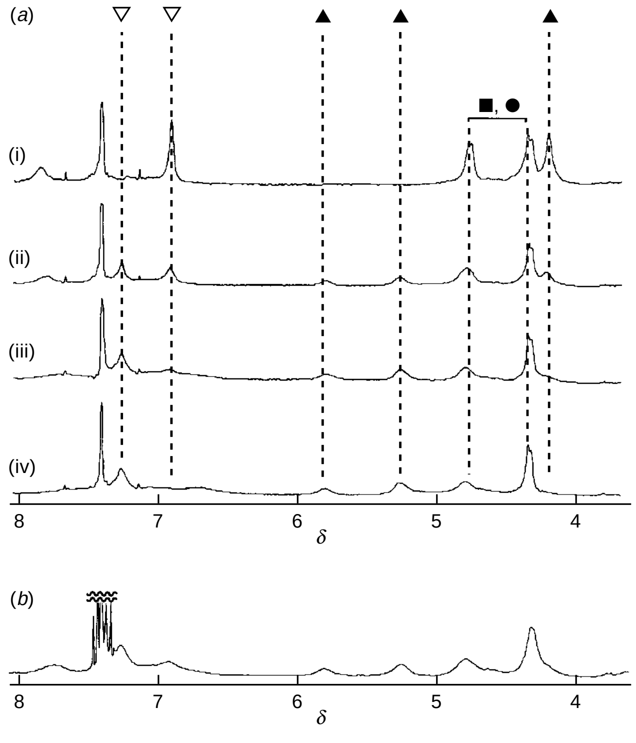


Fig. 1 (*a*) ^1H NMR spectra (400 MHz) of **1a** at [$BuNH_3ClO_4$] = (i) 0, (ii) 0.51, (iii) 1.02 and (iv) 1.53 mM; T = 23 °C, [**1a**] = 0.7 mM, [$Ga(acac)_3$] = 0.84 mM. (*b*) ^1H NMR spectrum of **1a** in the presence of $C_6H_{11}NH_3^+$; [**1a**] = 0.54 mM, [$C_6H_{11}NH_3ClO_4$] = 0.79 mM.

The 1 : 1 gallium complexation was ascertained by a mole ratio plot. In the ^{1}H NMR spectrum of **1a** with 1.2 equiv. of $Ga(acac)_3$ in 25% CD_3CN in $CDCl_3$, only the two singlets of the 5- and 6-methyl groups of the pyrazinone ring showed downfield shifts ($\Delta\delta$ +0.20 for 5-methyl, +0.13 for 6-methyl), whereas titration with $BuNH_3ClO_4$ induced large downfield shifts of the OCH_2CO (▲) and ArH (▽) protons, as shown in Fig. 1(*a*). The formation of 1 : 1 complex of **1a** with $BuNH_3^+$ was confirmed by a Job plot. It has been reported that the triester derivative of homotrioxacalix[3]arene is bound to an ammonium cation *via* the interaction of three phenolic oxygens and three carbonyl oxygens with the cation.[6] As for **1a**, the singlet for the OCH_2CO protons (▲) changed to two broad singlets when the ammonium salt was added, but no apparent downfield shifts were observed for the signals from the ethereal methylene protons (■, ●). Thus, it is likely that **1a** binds to $BuNH_3^+$ through $C{=}O\cdots HN^+$ and $ArO\cdots HN^+$ interactions similar to those previously reported.

By using a CH_2Cl_2 solution of **1** or a mixture of **1** and an equimolar amount of $Ga(acac)_3$, extraction of primary ammonium picrate from an aqueous phase was carried out. The amounts of ammonium picrates extracted into the organic phase are shown in Fig. 2.§ $Bu^tNH_3^+$ was not extracted efficiently when compared to $BuNH_3^+$ and $HexNH_3^+$, suggesting that the bulky substituent disturbs inclusion of the guest into the cavity. This result also indicates that the extracted amounts of $BuNH_3^+$ and $Bu^tNH_3^+$ increased in the presence of Ga^{3+}, indicating a cooperative molecular recognition of **1** and Ga^{3+} toward the primary ammonium cation. Furthermore, it was noted that the amount of $HexNH_3^+$ extracted by **1a** decreased in the presence of Ga^{3+}. This result was consistent with the difference in the association constants of **1a**–$HexNH_3^+$ in the absence [K_a 4375, Fig. 1(*b*)] and in the presence of Ga^{3+} (K_a 2833).¶ On the basis of molecular modelling, this observation might be attributed to the regulation of the cavity size by metal complexation; the Ga–**1** complex thus provides a rigid cavity that is suitable for selective recognition of ammonium cations.

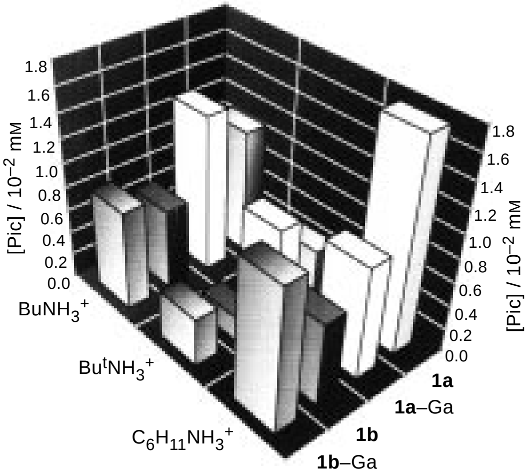


Fig. 2 Two phase solvent extraction of primary ammonium cations

This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan.

Notes and References

* E-mail: katoh@chgw.ch.seikei.ac.jp

† *Abbreviations*: WSC·HCl = 1-[3-(dimethylamino)propyl]- 3-ethylcarbodiimide hydrochloride (water soluble carbodiimide); HOBt = 1-hydroxybenzotriazole.

‡ *Selected data* for **1a**: ν_{max}(KBr)/cm^{-1} 3310, 1651; δ_H [$(CD_3)_2SO$, 23 °C] 1.03 (s, 27 H), 1.45 (m, 12 H), 2.09, 2.20, 2.45 (each s, 18 H), 2.43 (m, 6 H), 2.84 (m, 6 H), 3.06 (m, 6 H), 3.19 (m, 6 H), 4.12 (s, 6 H), 4.42 (d, *J* 12, 6 H), 4.64 (d, *J* 12, 6 H), 6.89 (s, 6 H), 7.95 (br s, 3 H), 8.01 (br s, 3 H); Calc. for $C_{81}H_{102}N_{12}O_{18}\cdot 4H_2O$: C, 60.65; H, 6.9; N, 10.4. Found: C, 60.6; H, 7.2; N, 10.1%.

§ A CH_2Cl_2 solution (2 ml) containing **1** (0.045 mM) was shaken with an aqueous solution (2 ml) containing ammonium picrate (0.12 mM) and the corresponding hydrochloride salt (0.1 M) at 23 °C for 9 h. The amount of each ammonium cation extracted into the CH_2Cl_2 phase was estimated from $[Pic]_c - [Pic]_f$, $[Pic]_f$ and $[Pic]_c$ being the picrate concentrations in the aqueous phase after the extraction and in the corresponding control sample, respectively.

¶ The association constant (K_a) of the 1 : 1 complex of **1a** with $HexNH_3ClO_4$ was directly estimated from the ^{1}H NMR spectra. Error estimated to be $< 15\%$.

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Received in Cambridge, UK, 23rd September 1997; 7/06869G