COMMUNICATION

ChemComm www.rsc.org/chemcomm

A novel molecular assembly mode of ferulic acid derivatives

Yasuhito Miyake, Asao Hosoda, Masafumi Takagaki, Eisaku Nomura and Hisaji Taniguchi*
Industrial Techmology Center of Wakayama Prefecture, 60 Ogura, Wakayama 649-6261, Japan.
E-mail: taniguti@wakayama-kg.go.jp

Received (in Cambridge, UK) 30th August 2001, Accepted 29th November 2001
First published as an Advance Article on the web 18th December 2001

Ferulic acid derivative assembles with three kinds of non-covalent interactions, *i.e.*, metal coordination, hydrogen bonding and CH–π interaction: X-ray crystallographic study illustrated the molecular assembly mode.

Molecular recognition and self-assembly play a fundamental role in numerous biological processes, for example, the highly specific substrate recognition by enzyme.[1] Supramolecular chemistry generally encompasses the chemistry of molecular recognition and self-assembly.[2] In these systems, processes works through the non-covalent bonds such as hydrogen bonds, metal coordination, π–π stacking, CH–π and van der Waals interactions.[3–5] Here we present a novel 'induced-fit' type molecular assembly relying on three non-covalent interactions. We used a ferulic acid derivative **1** in this study for the following reasons. The derivative **1** has (i) a polyoxyethylene chain and methoxy groups on phenyl rings for metal coordination, (ii) aromatic rings for a π–π or CH–π interaction and (iii) carboxylic acids as hydrogen bonding moieties. Thus we expected that the derivative **1** might form a complex with the aid of different kinds of non-covalent bonds (Fig. 1).

The ferulic acid derivative **1** was synthesized through the Mitsunobu reaction of the ethyl ester of ferulic acid with tetraethylene glycol.† After the reaction, the hydrolysis of the obtained compound gave the compound **1** in a good yield. Nowadays ferulic acid is easily prepared in large quantities from the oily component of rice bran.[6] The titration of a solution of **1** (7.0 mM in acetone-d_6) with potassium picrate was monitored by ^{1}H NMR spectroscopy (Fig. 2). The protons of the polyoxyethylene group were shifted downfield with increasing ratio of potassium picrate : **1**. This indicated that K^+ was bound to the polyoxyethylene group. On the other hand, upfield shifts were observed in the methoxy group and H_a, while H_b shifted downfield. This means that the phenyl groups are coming closer, and the methoxy moiety binding to the benzene ring rides on the other benzene ring. Although similar types of chemical shifts were obtained when either Rb^+ or Cs^+ was used as the metal cation, these shifts were small compared to those of K^+. The association constants for the formation of [**1** · K picrate], [**1** · Rb picrate] and [**1** · Na picrate] calculated from nonlinear curves fitting were estimated to be 8.0×10^2, 5.0×10^2 and 1.5×10^2 M^{-1}, respectively.[7]‡ However, there was no interaction between **1** and Li^+ since no chemical shift occurred in this case.

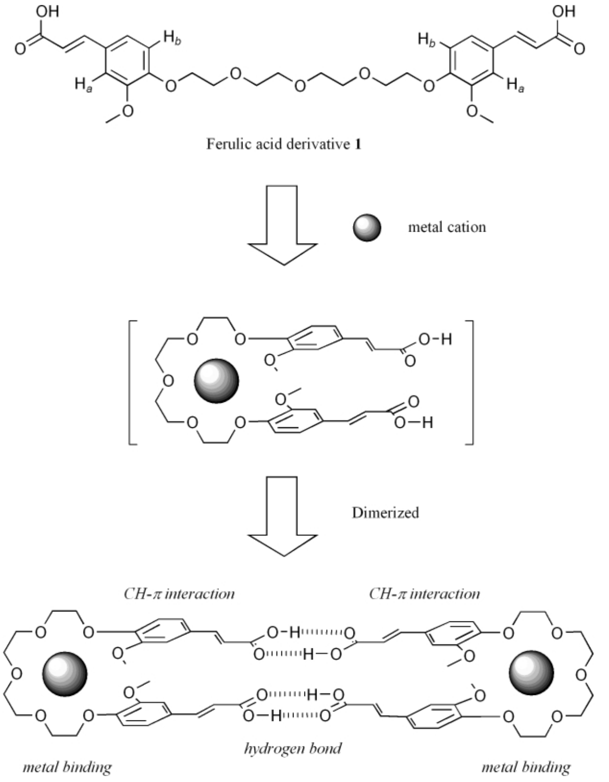

Fig. 1 Schematic representation of **1** and the 'induced-fit' type molecular assembly. The molecular assembly was formed through three non-covalent interactions.

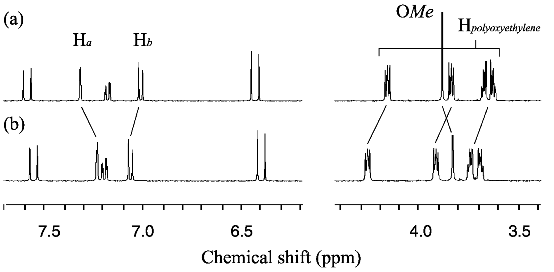

Fig. 2 (a): ^{1}H NMR (400 MHz, acetone-d_6) spectra of **1** and (b): **1** + K picrate (1 : 1).

These results were supported by electrospray ionization mass spectrometry (ESI-MS). Fig. 3 shows the ESI mass spectra of **1** in acetone in the presence of the picrate of alkali metal cations (Li^+, Na^+, K^+, Rb^+ and Cs^+). Although the single-charged signals were observed at m/z = 569, 585, 631 and 679 (corresponding to the $[\mathbf{1} + Na]^+$, $[\mathbf{1} + K]^+$, $[\mathbf{1} + Rb]^+$ and $[\mathbf{1} + Cs]^+$, respectively), no higher binding stoichiometries were observed. Therefore **1** formed stable complexes with alkali metal cations at 1 : 1 stoichiometry. The most intense peak

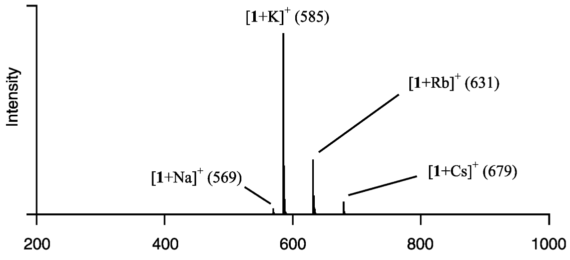

Fig. 3 Mass spectra of solutions of **1** in acetone in the presence of the picrate of Li^+, Na^+, K^+, Rb^+ and Cs^+. *conc.* (**1**) = *conc.* (metal picrate) = 1×10^{-3} mol dm^{-3}.

DOI: 10.1039/b107785f

corresponds to a complex of **1** with K$^+$ and the medium-intensity peak was observed for the Rb$^+$ complex. Peaks for the complexes of **1** with Na$^+$ and Cs$^+$ were very small and no peak was observed for Li$^+$. Thus **1** acts as a pseudo-crown ether, since the ion selectivity is in good accord with that of a crown ether such as 18-crown-6.§

In order to confirm the complexation between **1** and alkali metal cations, the complex of **1** and K picrate was analyzed by X-ray crystallography.¶ Suitable crystals for the analysis were obtained by recrystallization from a solution of **1** and K picrate in methanol. As shown in Fig. 4, K$^+$ was bound to the polyoxyethylene moiety and methoxy groups. The distances of O(polyoxyethylene)···K$^+$ are 2.737(5), 2.827(5), 2.948(5), 3.017(5) and 3.028(4) Å, for O(methoxy)···K$^+$ they are 2.870(5) and 2.998(4) Å, and for O(picrate)···K$^+$ 2.685(5) and 2.765(5) Å, respectively. These bondings induced a U-shaped conformation in **1** so that the two aromatic rings were closer, as the ^{1}H NMR spectroscopy suggested. In the crystal structure, one hydrogen atom of the methoxy group is close to the center of another phenyl ring (2.70 Å), furthermore, one hydrogen atom of the other methoxy group is also close to the corresponding phenyl ring (the distance of H···C is 2.69 Å). These close contacts indicate the existence of CH–π interaction between the methoxy groups and the aromatic rings. That is, the U-shaped conformation would be stabilized by the two CH–π interactions. Then the two U-shape complexes of **1** and K picrate were dimerized *via* four strong hydrogen bonds in a solid state. The hydrogen bonding distances of O···O are 2.613(6) and 2.665(6) Å, respectively. Thus this molecular assembly was formed by three different kinds of non-covalent interaction. In this process, metal binding plays the primary role to induce the conformation to U-shape, *i.e.* an 'induced-fit' type super-molecule. Crystal structures of [**1** · Rb picrate] and [**1** · Cs picrate] were also analyzed by X-ray crystallography. These crystal structures show that **1** forms complexes with Rb$^+$ and Cs$^+$ similar to that of K$^+$, but one of the two methoxy groups could not bind to the metal cations. This means that Rb$^+$ and Cs$^+$ are slightly large for the cavity that is formed by the polyoxyethylene moiety.

In conclusion, we have demonstrated the ferulic acid derivative **1** formed 1 : 1 complexes with alkali metal cations such as K$^+$, Rb$^+$ and Cs$^+$ with non-covalent interactions, *i.e.* hydrogen bonds, metal coordination and CH–π interactions. Although these three interactions work in cooperation with each other, it seems that metal coordination plays the primary role in the formation of such a complex. We have designed a novel artificial induced-fit type of alkali metal cations receptor. Further applications, including photoreactions, are now investigated.

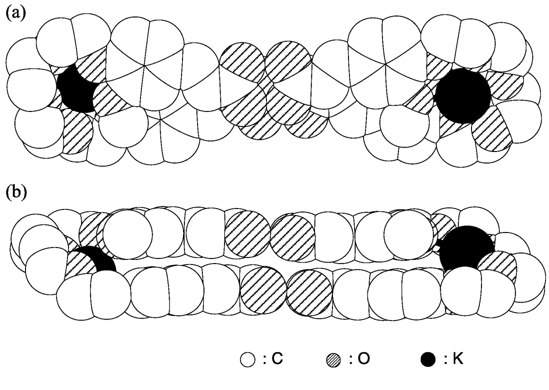

Fig. 4 Crystal structure of **1** · K picrate dimer. Hydrogen atoms and picrates are omitted for clarity. (a) Top view, (b) side view.

This study was performed through support from the Special Coordination Funds for Promoting Science and Technology (Leading Research Utilizing Potential of Regional Science and Technology) of the Ministry of Education, Culture, Sports, Science and Technology of the Japanese Government.

Notes and references

† To a solution of 1.00 g (4.5 mmol) of ethyl ferulate, 1.18 g (4.5 mmol) of triphenylphosphine and 427 mg (2.2 mmol) of tetraethylene glycol in 30 mL anhydrous THF was added 910 mg (4.5 mmol) diisopropyl azodicarboxylate. The mixture was stirred for 5 min at rt and the solvent then removed under reduced pressure to give a white solid. The product was purified through a SiO_2 column (hexane–ethyl acetate = 5 : 1) to afford 1.26 g (95%) of diethyl ester of the titled compound as a white powder.

‡ The association constant of [**1** · Cs picrate] was not calculated because of the low solubility of Cs picrate in a solution of **1** in acetone.

§ We also measured the binding behavior of 18-crown-6 and alkali metal cations under the same conditions. The ESI mass spectrum showed that the peak intensities are in good accord with their association constants.

¶ *Crystal data* for (*a*) **1** · (K picrate), (*b*) **1** · (Rb picrate) and (*c*) **1** · (Cs picrate): (*a*) $C_{34}H_{36}O_{18}N_3K_1$, (296 K) M = 813.77, triclinic, space group P-1, a = 11.910(3), b = 21.460(4), c = 7.556(1) Å, α = 97.547(10), β = 103.75(1), γ = 89.281(6)°, V = 1859.2(7) Å^3, Z = 2, D_c = 1.453 g cm^{-1}. CCDC 171528. (*b*) $C_{34}H_{36}O_{18}N_3Rb_1$ (243 K) M = 860.14, triclinic, space group P-1, a = 12.993(2), b = 14.212(1), c = 11.799(2) Å, α = 101.057(5), β = 103.398(3), γ = 69.709(6)°, V = 1973.0(4) Å^3, Z = 2, D_c = 1.448 g cm^{-1}. CCDC 171527. (*c*) $C_{34}H_{36}O_{18}N_3Cs_1$ (243 K) M = 907.57, triclinic, space group P-1, a = 13.007(2), b = 13.927(2), c = 12.012(2) Å, α = 98.457(5), β = 103.291(4), γ = 69.952(4)°, V = 1983.9(5) Å^3, Z = 2, D_c = 1.519 g cm^{-1}. CCDC 171526. See http://www.rsc.org/suppdata/cc/b1/b107785f/ for crystallographic files in .cif format. Intensity data were measured on a RIGAKU RAXIS-RAPID imaging plate diffractometer with graphite monochromated Cu-Kα radiation. 6113, 6586 and 6622 reflections for the crystals (*a*), (*b*) and (*c*) were unique. 3663 observed reflections with $I > 1.5\,\sigma(I)$ for the crystals (*a*) and 4051 and 6622 observed reflections with $I > 2.0\,\sigma(I)$ for the crystals (*b*) and (*c*) were used for further calculations after Lorenz and polarization corrections. A total of (*a*) 505, (*b*) 505 and (*c*) 505 parameters were refined to final residuals (*a*) R_1 = 0.065 and Rw = 0.188, (*b*) R_1 = 0.087 and Rw = 0.231 and (*c*) R_1 = 0.073 and Rw = 0.216 (refinement on F^2).

1 R. J. P. Williams, *Chem. Soc. Rev.*, 1980, 281; A. Fersht, *Enzyme Structure and Mechanism*, 2nd edn. W. H. Freeman, New York, 1985, pp. 263–291M. F. Peruts, *Mechanisms of Cooperativity and Allosteric Regulation in Protein*, Cambridge University Press, Cambridge, England, 1989.
2 *Comprehensive Supramolecular Chemistry*, ed. J. L. Atwood, J. E. D. Davies, D. D. MacNicol and F. Vögtle), Pergamon, New York, 1996.
3 D. J. Duchamp and R. E. Marsh, *Acta Crystallogr.*, 1969, **B25**, 5; R. F. Bryan and D. P. Freyberg, *J. Chem. Soc., Perkin Trans. 2*, 1975, 1835; J. Yang, J.-L. Marendaz, S. J. Geib and A. D. Hamilton, *Tetrahedron Lett.*, 1994, **35**, 3665.
4 G. W. Gokel, *Crown Ethers and Cryptands*, Royal Society of Chemistry, Cambridge, 1994; *Comprehensive Supramolecular Chemistry, Molecular Recognition: Receptors for Cationic Guests, Vol. 1*, eds. G. W. Gokel, Pergamon, New York, 1996.
5 M. Nishio, M. Hirota and Y. Umezawa, *The CH/π Interaction*, Wiley-VCH, 1998.
6 H. Taniguchi, E. Nomura, T. Tsuno, S. Minami, K. Kato and C. Hayashi, *Jpn. Pat. No.* 2095088 (Oct. 2. 1996) and *US Pat. No.* 5,288,902 (Feb. 22. 1994)H. Taniguchi, A. Hosoda, T. Tsuno, Y. Maruta and E. Nomura, *Anticancer Res.*, 1999, **19**, 3757.
7 H. Tsukube and H. Sohmiya, *J. Org. Chem.*, 1991, **56**, 875; M. Sawada, Y. Okumura, M. Shizuma, Y. Takai, Y. Hidaka, H. Yamada, T. Tanaka, T. Kaneda, K. Hirose, S. Misumi and S. Takahashi, *J. Am. Chem. Soc.*, 1993, **115**, 7381.