Volume 1 | Number 1 | Jan 2013 | Pages 1–100

ChemComm

Chemical Communications
www.rsc.org/chemcomm

ROYAL SOCIETY OF CHEMISTRY

This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the **Information for Authors**.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard **Terms & Conditions** and the **Ethical guidelines** still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

www.rsc.org/chemcomm

COMMUNICATION

Reinforcement of guest selectivity through the self-assembly of host molecules: Selective recognition of lithium ions by dimerizable tricarboxylic acids†

Shoichi Minodani,‡[a] Masaki Owaki,‡[a] Shuhei Sano,[a] Seiji Tsuzuki[b] and Masamichi Yamanaka*[a]

C_3-Symmetric tricarboxylic acids form dimers through intermolecular hydrogen bonds in nonpolar organic solvents. These dimers recognize lithium ions with high selectivities through the formation of 1:1 host-guest complexes between the collapsed dimeric assemblies and guest molecules.

Host-guest chemistry, which originated from Pedersen's discovery of crown ether,[1] is still an attractive subject in supramolecular chemistry because of its wide potential applications in sensors, transporters, machines, switches, etc.[2-5] Numerous molecular recognition technologies have been reported using artificial host molecules with diverse structures such as cryptands,[6,7] calixarenes,[8-10] cucurbiturils,[11] cavitands,[12] pillararenes[13,14] and others.[15-17] Selective recognition of a particular guest is a vitally important issue in host-guest chemistry. The size and shape of the cavity and the degree of preorganization of the host molecule are important factors for improving guest selectivity.[18-20]

Even for a host molecule that has an ideal structure and shows high selectivity for a particular guest, the selectivity between similar guests is essentially finite, owing to the following reason. Guest binding sites (e.g., oxygen of crown ether) of a host molecule are *unmasking* in the absence of a guest. Therefore, host-guest associations with a favorable guest and a similar, but unfavorable guest (e.g., Li⁺ and Na⁺) are both spontaneous exergonic processes ($\Delta G° < 0$). Selectivity can be dramatically reinforced if the association of an unfavorable guest can be rendered as an endergonic process ($\Delta G° > 0$), while retaining the association of the favorable guest as an exergonic process. This demand can be realized by reversibly *masking* the guest binding sites of the host molecule via hydrogen bonding dimerization. Dimers of host molecules are well-known as molecular capsules.

However, their associations with guests are limited to their isolated nano cavities, i.e., encapsulations.[21] In our proposed system, guest recognition proceeds with the dissociation of the host dimer into monomers accompanying 1:1 host-guest complexation. The relative thermodynamic stabilities of each process are shown in Fig. 1. The host dimer is more stable than the monomer. The recognition of the favorable guest [complex (A)] is more stable than the dimer. In marked contrast, the dimer is more stable than the recognition of the unfavorable guest [complex (B)]. As a result, host-guest complexation takes place only with the favorable guest, whose association constant ($K_{host-guest}$) is larger than the dimerization constant (K_{dim}). In nature, some proteins are known to form inert dimers, although they are active in their monomeric states.[22-24] In particular, receptor proteins for phytohormone abscisic acid assemble into inert dimers, in which the individual molecules face the recognition sites of each other.[25] These examples encouraged us to develop a molecular recognition system using an artificial dimerizable host. We report herein, C_3-symmetric tricarboxylic acid host molecules as lithium ion receptors.

A C_3-symmetrical tricarboxylic acid **1** was designed as the host molecule (Fig. 2). Ethyl groups were used to regulate the conformations of the carboxyl groups in one direction. The carboxyl groups were expected to work not only as molecular recognition sites but also as self-complementary hydrogen-bonding sites. The synthesis of **1** was accomplished by the Suzuki-Miyaura cross-coupling reaction of 1,3,5-tris(bromomethyl)-2,4,6-triethylbenzene and 3-methoxycarbonylphenylboronic acid, followed by the hydrolysis of ester groups. The structure of **1** was confirmed by ¹H and ¹³C NMR spectra obtained in DMSO-d_6 as well as electron spray ionization (ESI) mass spectrum (see ESI†).

[a.] Department of Chemistry, Faculty of Science, Shizuoka University, 836 Ohya, Suruga-ku, Shizuoka 422-8529, Japan. Fax: +81 54 237 3384; Tel: +81 54 238 4936; E-mail: Yamanaka.masamichi@shizuoka.ac.jp
[b.] Research Institute for Sustainable Chemistry, National Institute of Advanced Industrial Science and Technology (AIST), Tsukuba, Ibaraki 305-8568, Japan
†Electronic Supplementary Information (ESI) available: Experimental details, Fig. S1-S21. See DOI: 10.1039/x0xx00000x

Fig. 1 Schematic representation of dimerization reinforced selectivity of guest recognition.

Fig. 2 (a) Chemical structures of C_3-symmetrical tricarboxylic acids **1–3**. (b) The energy minimized structure of dimer **1**$_2$.

Interestingly, the ^{1}H NMR chemical shifts of **1** in CDCl$_3$ were considerably different from those in DMSO-d_6 (Fig. S1 in ESI†). While dimeric assemblies of **1** would form in CDCl$_3$, quantitative analysis of the assembly was difficult, owing to the low solubility of **1** in CDCl$_3$ (< 0.1 mM). Therefore, C_3-symmetrical tricarboxylic acids **2** and **3** were synthesized as soluble analogs of **1** (Fig. 2 and Fig. SI in ESI†) and these molecules showed satisfactory solubilities in CDCl$_3$ (**2**: > 1.6 mM, **3**: > 20 mM). The ^{1}H NMR spectra of **2** were analogous to those of **1** (Fig. 3). The signal originated from the aromatic protons at the α-position of the carboxyl group (H^a), which was observed at 7.68 ppm in DMSO-d_6, appeared at 7.16 ppm in CDCl$_3$. Dimeric assemblies of **2** formed in CDCl$_3$ through intermolecular hydrogen bonds between carboxyl groups. As a result, the signal originated from the proton H^a appeared in upfield region relative to the typical aromatic proton signal of the α-position of the carboxyl group, which is attributed to the ring-current effect of the core benzene ring. NOESY spectra of **2** supported this consideration. In CDCl$_3$, NOE correlations were observed between H^a and the protons of the benzyl position (H^f), while they were not observed between H^b and H^f (Fig. S2 in ESI†). In contrast, NOE correlations were observed both between H^a and H^f and between H^b and H^f in DMSO-d_6 (Fig. S3 in ESI†). The formation of dimer **2**$_2$ was finally confirmed by the ESI Fourier transform ion cyclotron resonance mass spectrum (FT-ICR-MS).[26,27] The molecular ion peak of the dimer [**2**$_2$+Na]$^+$ appeared at 1403.7614 (theoretical: 1404.7733) (Fig. 4).

Fig. 3 ^{1}H-NMR spectra (600 MHz, 298 K) of (a) **2** in DMSO-d_6, (b) **2** in CDCl$_3$, (c) **3** in DMSO-d_6 and (d) **3** in CDCl$_3$.

Fig. 4 ESI-FT-ICR MS of (a) **2**$_2$ and (b) **3**$_2$.

Analogous ^{1}H NMR spectrum of **3** in CDCl$_3$ and the molecular ion peak of [**3**$_2$+Na]$^+$ (found: 1668.9093, theoretical: 1668.9339) in the ESI FT-ICR-MS indicated the formation of dimer **3**$_2$ (Fig. 3 and 4). ^{1}H NMR spectrum of a mixture of **2** and **3** in CDCl$_3$ exhibited a new set of signals in addition to the original signals corresponding to **2**$_2$ and **3**$_2$ (Fig. S4 in ESI†). These signals could be assigned to a hetero-dimer **2·3**. The molecular ion peak of [**2·3**+Na]$^+$ (found: 1536.8326 theoretical: 1536.8553) in the ESI FT-ICR-MS proved the formation of the hetero-dimer **2·3** (Fig. S5 in ESI†). The ^{1}H NMR spectrum of a mixture of **2** and **3** in DMSO-d_6 was identical to the sum of the individual spectra of the two compounds (Fig. S4 in ESI†). This implies that both **2** and **3** exist as monomer forms in polar DMSO-d_6.

A dilution ^{1}H NMR experiment provided a lower limit for the association constant of dimerization of **2** in CDCl$_3$.[28] The chemical shift for all the signals completely remained unchanged in the concentration range of 1.6 mM to 10 μM (Fig.

S6 in ESI†). Assuming that there is less than 5% monomer at a concentration of 10 μM, the minimum association constant (K_{dim}) for the dimerization of **2** can be calculated as 1.9 x 10^7 M^{-1}. The same value of minimum association constant (K_{dim} = 1.9 x 10^7 M^{-1}) was also estimated for the dimerization of **3** in CDCl$_3$ through the same dilution experiment (Fig. S7 in ESI†).

Equilibrium between the monomer (**2**) and the dimer (**2**$_2$) was observed in a CDCl$_3$/CD$_3$CN (5:1) solution of **2**. The value of K_{dim} for the dimerization of **2** in this solvent system was estimated to be 2600 M^{-1} at 298 K. Negative values for both ΔH^o (–54.8 kJ/mol) and ΔS^o (–118 J/mol) obtained from the van't Hoff plot of variable-temperature NMR data indicated that the dimerization is an exothermic enthalpy-driven process (Fig. S8 in ESI†).

The stabilization energy (E_{form}) by the formation of the dimer (**1**$_2$) from monomers (**1**) was evaluated by the MP2/6-311G**//HF/6-311G** level *ab initio* molecular orbital calculations (see the Supporting Information for details).[29-32] The energy minimum structure of monomer, which is stabilized by intramolecular hydrogen bonds, is –53.6 kJ/mol more stable than the local energy minimum structure without intramolecular hydrogen bonds (Fig. S9 in ESI†). The E_{form} calculated for the dimer (Fig. 2) was –73.6 kJ/mol. This value is consistent with the experimentally observed large association constants of **2**$_2$ and **3**$_2$ in CDCl$_3$.

The association abilities of alkali metal ions with **2** and **3** were evaluated by ^{1}H NMR experiments. Perchlorate salts (LiClO$_4$, NaClO$_4$ and KClO$_4$) were used to minimize the possible effects of counteranions.[33] The addition of LiClO$_4$ to a CDCl$_3$ solution of **2** caused changes in the chemical shifts compared to those of **2** alone (Fig. 5a and b). Titration experiments with varying amounts of LiClO$_4$ indicated that **2** and Li$^+$ were associated in a 1:1 molar ratio (Fig. S10 in ESI†). In marked contrast, the ^{1}H NMR spectra of mixtures of **2** and NaClO$_4$ and KClO$_4$ were completely identical to that of **2** alone, even in the presence of large excess amounts of these salts (Fig. 5c and d). The CDCl$_3$ solution of **2** recognized only Li$^+$ selectively among the alkali metal ions. Li$^+$ selective recognition was found in homogeneous solutions of **2** and LiClO$_4$ or NaClO$_4$ in CDCl$_3$/CD$_3$CN (110:1) (Fig. S11 in ESI†). The tricarboxylic acid **3** also showed similar Li$^+$ selectivity. Chemical shifts of **3** in CDCl$_3$ were modified by the addition of LiClO$_4$, while they were unchanged by the addition of NaClO$_4$ or KClO$_4$ (Fig. S12 in ESI†).

The diffusion coefficient of a CDCl$_3$ solution of **2** and LiClO$_4$ (D = 5.82 ± 0.37 x 10^{-10} m^2/s), calculated from DOSY experiments,[34] was larger than that of a CDCl$_3$ solution of **2** (D = 4.99 ± 0.23 x 10^{-10} m^2/s). The corresponding hydrodynamic radii of 6.98 ± 0.45 Å and 8.12 ± 0.38 Å for CDCl$_3$ solution of **2** and LiClO$_4$ and for **2** alone, respectively, are in agreement with the sizes of the **2**-Li$^+$ complex and dimer **2**$_2$, respectively. The ^{1}H NMR spectrum of **2**, **3** and LiClO$_4$ in CDCl$_3$ was identical with the sum of the spectra of **2** and LiClO$_4$, and **3** and LiClO$_4$ (Fig. S13 in ESI†). The result also supports the 1:1 association structures of **2**-Li$^+$ and **3**-Li$^+$. Finally, the existence of these 1:1 complexes was confirmed by mass spectra. ESI FT-ICR-MS exhibited molecular ion peaks corresponding to [**2**-Li]$^+$ (found: 697.4105, theoretical: 697.4075) and [**3**-Li]$^+$ (found: 829.4888,

COMMUNICATION

theoretical: 829.4863) (Fig. 6). Conformational information on the **2**-Li$^+$ complex was obtained from the NOESY spectrum of a mixture of **2** and LiClO$_4$ in CDCl$_3$. NOE correlation was observed between H^a and H^f, while not between H^b and H^f (Fig. S14 in ESI†). This is similar to the NOESY spectrum of **2** in CDCl$_3$ (Fig. S2 in ESI†). Therefore, the conformation of **2** in the **2**-Li$^+$ complex is likely to be rigid, similar to the dimeric assembly of **2**.

Fig. 5 ^{1}H-NMR spectra (600 MHz, CDCl$_3$, 298 K) of **2** (0.5 mM): (a) alone, (b) with 1 equiv of LiClO$_4$, (c) with 527 equiv of NaClO$_4$ and (d) with 352 equiv of KClO$_4$.

Fig. 6 ESI-FT-ICR MS of (a) **2**-Li$^+$ and (b) **3**-Li$^+$.
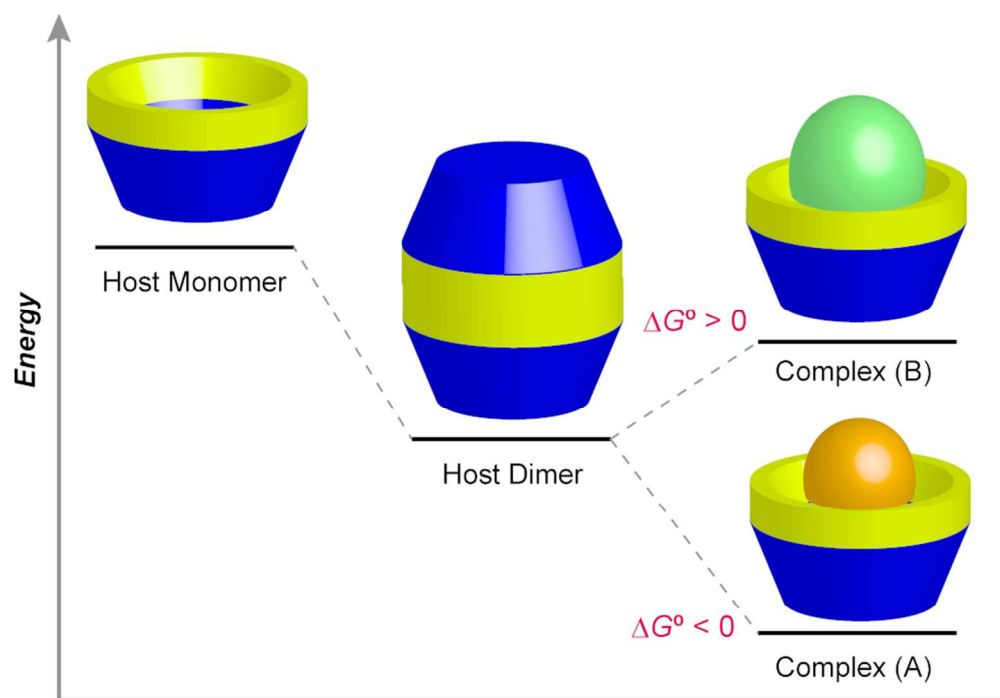
A dilution ^{1}H NMR experiment provided a lower limit for the association constant of the **2**-Li$^+$ complex from **2**$_2$ in CDCl$_3$.[28] The chemical shifts of all the signals were completely retained from 1.0 to 0.1 mM (Fig. S15 in ESI†). Assuming that there is less than 5% monomer at a concentration of 0.1 mM, the minimum association constant ($K_{2\text{-Li+}}$) for the **2**-Li$^+$ complexation can be calculated as 7.2 x 10^7 M^{-1}. The same value of minimum association constant ($K_{3\text{-Li+}}$ = 7.2 x 10^7 M^{-1}) was also estimated for the **3**-Li$^+$ complex in CDCl$_3$ through the same dilution experiment (Fig. S16 in ESI†). A mixture of **3** (1.0 mM) and an insufficient amount of LiClO$_4$ (0.5 equiv) in CDCl$_3$ showed both the presence of a **3**-Li$^+$ complex and dimer **3**$_2$ in a 2:1 ratio in the ^{1}H NMR spectrum. The chemical shift and integration ratio of all the signals were completely retained from 1.0 to 0.1 mM (Fig. S17 in ESI†).

Alkali metal ion recognitions of monomeric **2** and **3** were investigated (Fig. S18-S21 in ESI†). The association constant for the dimerization of **2** was estimated to be 25 M^{-1} at 298 K in CDCl$_3$/CD$_3$CN (2:1). Therefore, 0.5 mM solution of **2** in CDCl$_3$/CD$_3$CN (1:1) was used as the monomer solution of **2** and the association constant of Li$^+$ to **2** in this solution was calculated to be 54.8 M^{-1} at 298 K. In this solvent system, **2** was also able to recognize Na$^+$, and the association constant for this pair was 2.9 M^{-1} at 298 K. CDCl$_3$/CD$_3$CN (1:1) solutions of **3** were also able to recognize both Li$^+$ and Na$^+$, and their association constants were 100 M^{-1} and 39 M^{-1} at 298 K, respectively. Similarly, monomeric **2** and **3** recognized both Li$^+$ and Na$^+$ with moderate selectivities (**2**: Li$^+$/Na$^+$ = 19; **3**: Li$^+$/Na$^+$ = 2.6), although dimeric **2**$_2$ and **3**$_2$ showed high selectivities for Li$^+$. These results indicate that the self-assembled dimerizations of host molecules reinforce guest selectivities through the mechanism shown in Fig. 1.

In conclusion, we synthesized C_3-symmetrical tricarboxylic acids that formed dimers in nonpolar organic solvents through intermolecular hydrogen bonds. These solutions recognized Li$^+$ with extremely high selectivities. The dimers, which are more thermodynamically stable than the monomeric form, can make the recognition of an undesired guest a thermodynamically disadvantageous process. Highly selective molecular recognition systems can be developed by using this host self-assembly strategy.

Notes and references

‡ These authors contributed equally to this work.
1 C. J. Pedersen, *J. Am. Chem. Soc.*, 1967, **89**, 7017–7036.
2 E. V. Anslyn, *J. Org. Chem.*, 2007, **72**, 687–699.
3 R. Pinalli and E. Dalcanale, *Acc. Chem. Res.*, 2013, **46**, 399–411.
4 Y.-W. Yang, Y.-L. Sun and N. Song, *Acc. Chem. Res.*, 2014, **47**, 1950–1960.
5 X. Ma and Y. Zhao, *Chem. Rev.*, DOI: 10.1021/cr500392w.
6 J.-M. Lehn, *Acc. Chem. Res.*, 1978, **11**, 49–57.
7 S. O. Kang, J. M. Llinares, V. W. Day and K. Bowman-James, *Chem. Soc. Rev.*, 2010, **39**, 3980–4003.
8 A. Ikeda and S. Shinkai, *Chem. Rev.*, 1997, **97**, 1713–1734.
9 R. Joseph and C. P. Rao, *Chem. Rev.*, 2011, **111**, 4658–4702.
10 S. K. Kim and J. L. Sessler, *Acc. Chem. Res.*, 2014, **47**, 2525–2536.
11 J. W. Lee, S. S. N. Selvapalam, H.-J. Kim and K. Kim, *Acc. Chem. Res.*, 2003, **36**, 621–630.
12 B. W. Purse and J. Rebek, Jr., *Proc. Nat. Acad. Sci. U.S.A.*, 2005, **102**, 10777–10782.
13 M. Xue, Y. Yang, X. Chi, Z. Zhang and F. Huang, *Acc. Chem. Res.*, 2012, **45**, 1294–1308.
14 T. Ogoshi and T. Yamagishi, *Chem. Commun.*, 2014, **50**, 4776–4787.
15 G. Hennrich and E. V. Anslyn, *Chem. Eur. J.*, 2002, **8**, 2218–2224.
16 P. A. Gale, N. Busschaert, C. J. E. Haynes, L. E. Karagiannidis and I. L. Kirby, *Chem. Soc. Rev.*, 2014, **43**, 205–241.
17 K. Hermann, Y. Ruan, A. M. Hardin, C. M. Hadad and J. D. Badjić, *Chem. Soc. Rev.*, 2015, **44**, 500–514.
18 D. J. Cram, *Angew. Chem. Int. Ed. Engl.*, 1986, **25**, 1039–1057.
19 J. M. Lehn and J. P. Sauvage, *J. Am. Chem. Soc.*, 1975, **97**, 6700–6707.
20 D. J. Cram, T. Kaneda, R. C. Helgeson and G. M. Lein, *J. Am. Chem. Soc.*, 1979, **101**, 6752–6754.
21 F. Hof, S. L. Craig, C. Nuckolls and J. Rebek, Jr., *Angew. Chem. Int. Ed.*, 2002, **41**, 1488–1508.
22 C. H. Lillig, C. Berndt, O. Vergnolle, M. E. Lönn, C. Hudemann, E. Bill and A. Holmgren, *Proc. Natl. Acad. Sci. U.S.A.*, 2005, **102**, 8168–8173.
23 E. Or and T. Rapoport, *FEBS Lett.*, 2007, **581**, 2616–2620.
24 Q. Hao, P. Yin, W. Li, L. Wang, C. Yan, Z. Lin, J. Z. Wu, J. Wang, S. F. Yan and N. Yan, *Mol. Cell*, 2011, **42**, 662–672.
25 K. Melcher, L.-M. Ng, X. E. Zhou, F.-F. Soon, Y. Xu, K. M. Suino-Powell, S.-Y. Park, J. J. Weiner, H. Fujii, V. Chinnusamy, A. Kovach, J. Li, Y. Wang, J. Li, F. C. Peterson, D. R. Jensen, E.-L. Yong, B. F. Volkam, S. R. Cutler, J.-K. Zhu and H. E. Xu, *Nature*, 2009, **462**, 602–608.
26 A. G. Marshall, C. L. Hendrickson and G. S. Jackson, *Mass Spectrom. Rev.*, 1998, **17**, 1–35.
27 A. G. Marshall, *Int. J. Mass Spectrom.*, 2000, **200**, 331–356.
28 C. L. D. Gibb and B. C. Gibb, *J. Am. Chem. Soc.*, 2004, **126**, 11408–11409.
29 C. Møller and M. S. Plesset, *Phys. Rev.*, 1934, **46**, 618–622.
30 M. Head-Gordon, J. A. Pople and M. J. Frisch, *Chem. Phys. Lett.*, 1988, **153**, 503–506.
31 S. Tsuzuki and A. Fujii, *Phys. Chem. Chem. Phys.*, 2008, **10**, 2584–2594.
32 S. Tsuzuki, T. Uchimaru, M. Mikami, H. Kitagawa and K. Kobayashi, *J. Phys. Chem. B*, 2010, **114**, 5335–5341.
33 R. Gotor, A. M. Costero, S. Gil, P. Gaviña and K. Rurack, *Eur. J. Org. Chem.*, 2014, 4005–4013.
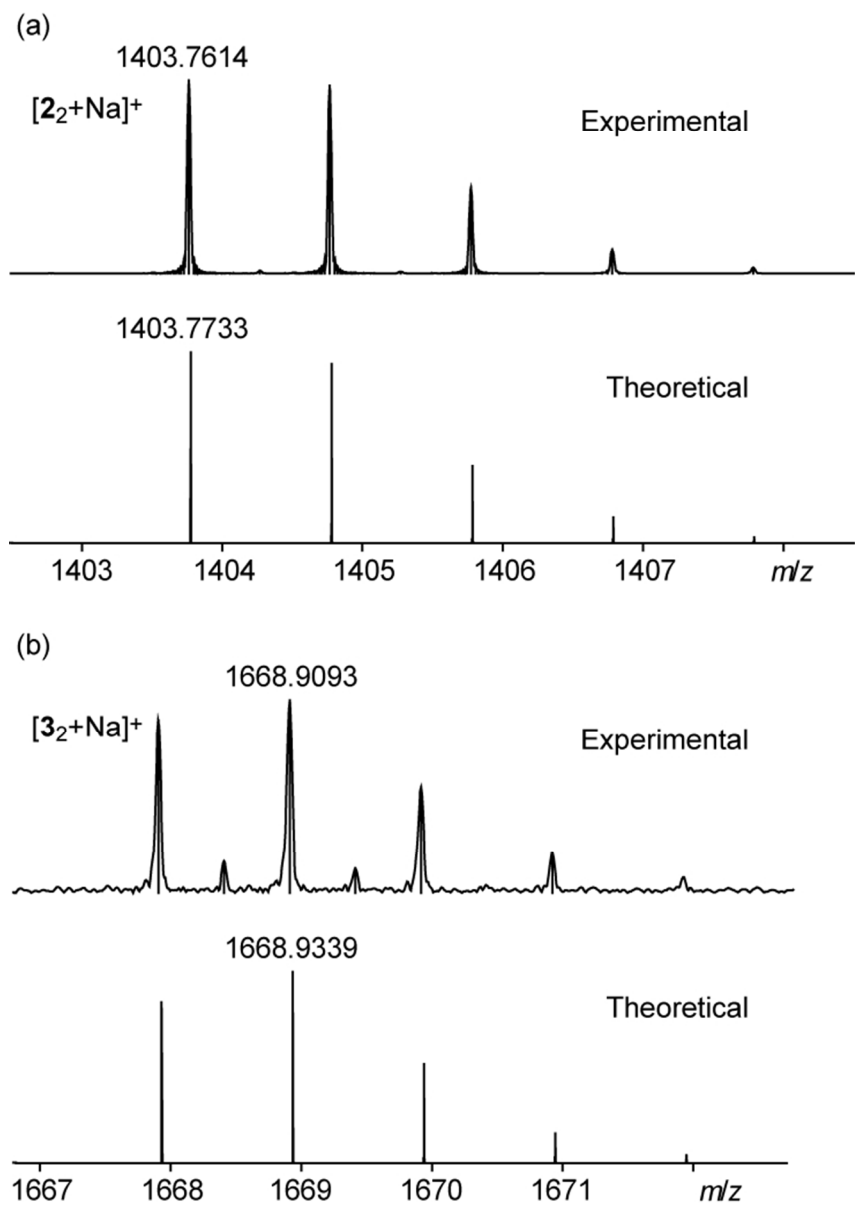34 Y. Cohen, L. Avram and L. Frish, *Angew. Chem. Int. Ed.*, 2005, **44**, 520–554.

175x120mm (150 x 150 DPI)

(a)

1: R = CH3, R' = H

2: R = CH2CH(CH3)2, R' = H

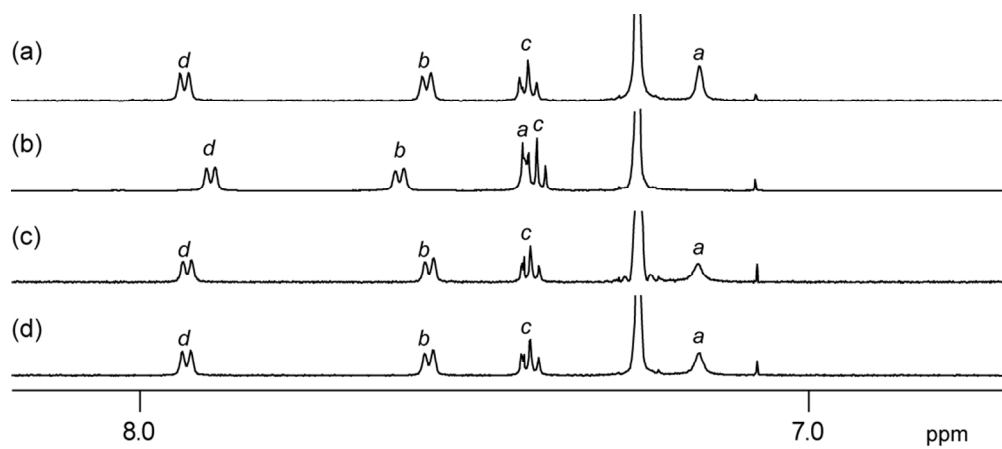3: R = CH3, R' = O(CH2)2CH(CH3)2
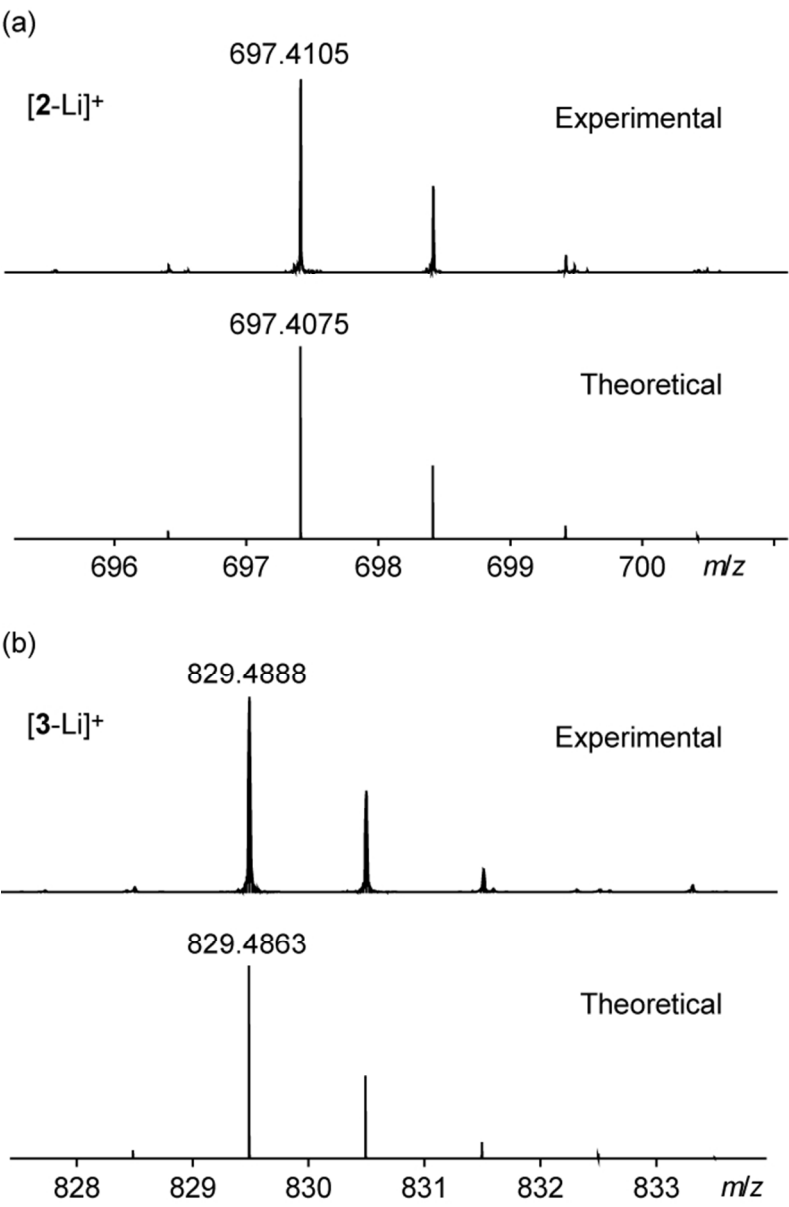
(b)
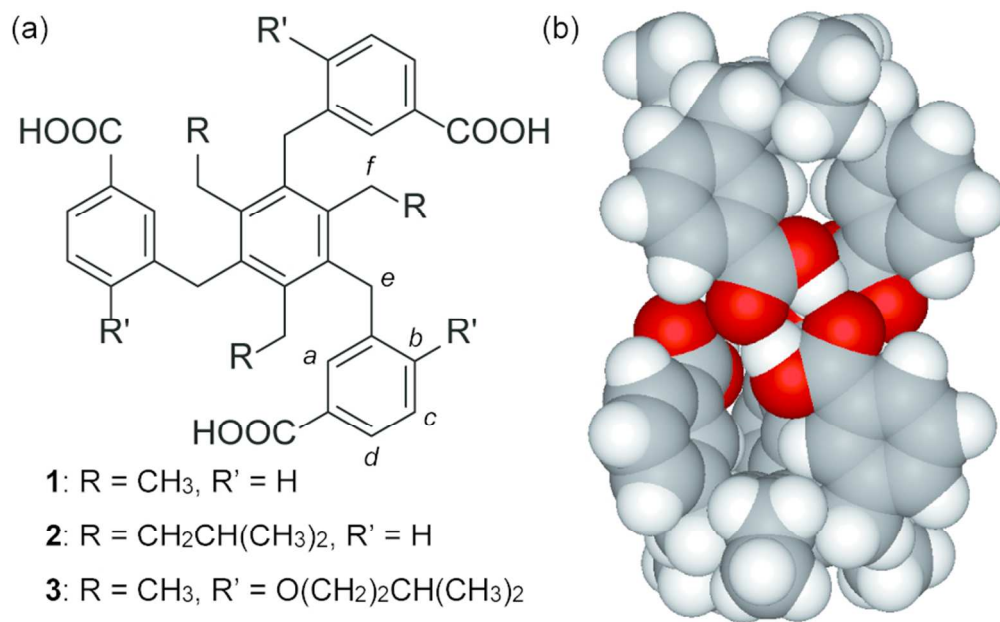
159x101mm (150 x 150 DPI)
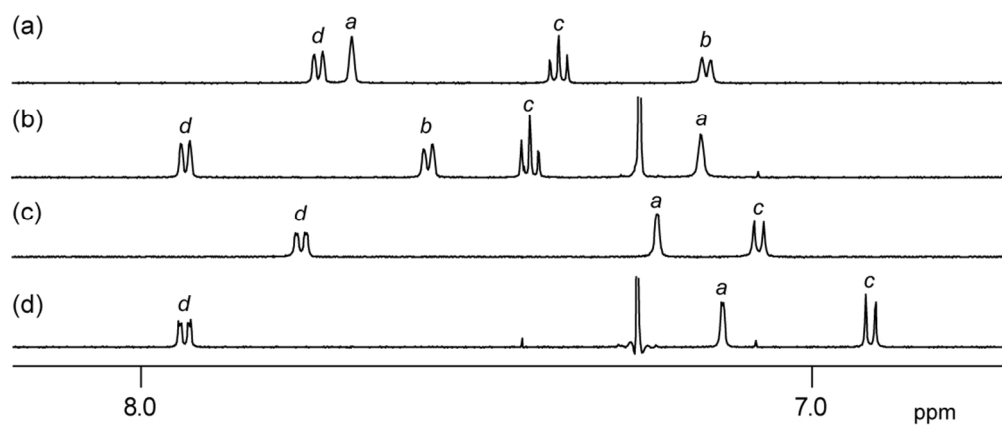
194x80mm (150 x 150 DPI)

124x176mm (150 x 150 DPI)

194x84mm (150 x 150 DPI)

115x176mm (150 x 150 DPI)