

Absolute Ordered Cluster Formation of an *o*-Bisguanidinobenzene–Benzoic Acid Complexes

Masatoshi KAWAHATA,^a Kazuaki SHIKII,^b Hiroko SEKI,^b Tsutomu ISHIKAWA,^{*c} and Kentaro YAMAGUCHI^{*a}

^aFaculty of Pharmaceutical Sciences at Kagawa Campus, Tokushima Bunri University; 1314-1 Shido, Sanuki, Kagawa 769-2193, Japan; ^bChemical Analysis Centre, Chiba University; 1-33 Yayoicho, Inage-ku, Chiba 263-8522, Japan; and ^cGraduate School of Pharmaceutical Sciences, Chiba University; 1-33 Yayoicho, Inage-ku, Chiba 263-8522, Japan.

Received October 24, 2005; accepted November 8, 2005; published online November 11, 2005

Stoichiometry-controlled complexation of *o*-phenylenebis(*N,N'*-dimethyl-*N,N'*-ethylene)guanidine (BG) and benzoic acid (BA), which is forming 1:1, 1:2, 1:3, and 1:4 BG+BA systems, was observed in solution by using cold-spray ionization mass spectrometry CSI-MS and pulsed field gradient PFG NMR diffusion and in the solid state by X-ray structure analysis.

Key words guanidine chemistry; acid-base system; cluster; cold-spray ionization mass spectrometry; pulsed field gradient NMR

The creation of desired molecular complex by controlling the cluster formation attracted considerable interest in the field of supramolecular chemistry.^{1–3} Recently, some of the authors reported hydrogen-bonded stoichiometry-controlled complexation of *o*-phenylenebis(*N,N'*-dimethyl-*N,N'*-ethylene)guanidine (BG) and benzoic acid (BA) in the crystalline state.⁴ Although the cluster formation remains the most important step to generate supramolecular systems, detailed observation of this phenomenon in solution is generally difficult.

NMR is one of the most effective methods to elucidate the dynamic nature of organic molecules in solution.^{5,6} Other instrumental analysis including MS and X-ray help to reveal the role of hydrogen bond formation in solution. Recently, we have reported the structure analysis of many steroid compounds in solution.⁷ The formation in solution of large-scale aggregated chain structures or clusters, through intermolecular hydrogen bonds, was confirmed by cold-spray ionization CSI-MS and PFG NMR.^{7–9}

Herein we report the structure analysis of BG+*n*BA (*n*=1–4) in solution by CSI-MS and PFG NMR analysis. The results obtained in solution are compared with in the crystal structure of the corresponding molecular-ratio-dependent-complexes.

The X-ray crystal structures of BG+3BA and the previously reported complex BG+*n*BA (*n*=1, 2, 4) are presented.⁴ The BG+*n*BA (*n*=1–4) crystals, including BG itself, are prepared by standard procedure.⁴

In the cases of BG+BA (1:1) (Fig. 1, left) and BG+2BA (1:2) (Fig. 1, right), only one guanidyl groups in BG is involved in hydrogen bonding with BA (red and orange dotted line for 1:1 and 1:2, respectively). Additionally in the 1:2 system, a second BA (pink), interacts with BA (orange) through hydrogen bond (pink dotted line). Interestingly, BG+3BA (1:3),¹⁰ shown in Fig. 2, exhibits a combined structure of 1:1 and 1:2 complexes. The left part (blue BG

and red BA) corresponds to the 1:1 system whereas the right part comes from the 1:2 system (light blue BG and two BAs). Three strong hydrogen bonds are observed in this system: C–O⋯H–N (O⋯N distance 2.54 Å red dotted line in the left part), C–O⋯H–N (O⋯N distance 2.73 Å orange dotted line) and C–O–H⋯O=C (O⋯O distance 2.50 Å pink dotted line in the right). The crystal structure of BG+4BA (1:4), which possesses C₂ symmetry, is presented in Fig. 3. Two strong hydrogen bonds (red dotted line) in addition to T-shaped C–H-π interactions (orange dotted line) are clearly observed between BG and BA.

The structures of the BG+*n*BA system in solution are studied by means of CSI-MS and PFG NMR. Conventional electrospray ionization ESI-MS shows no ion peak corresponding to the complexes observed in the solid state. The ion peak of [BA–H][–] in the negative mode and [BG+H]⁺ in the positive mode are detected. However, the molecular-ratio-dependent-complexes are clearly observed by CSI-MS measurement,¹¹ see Fig. 4. In all system, the negative ion [BA–H][–] is attached the neutral BG+*n*BA complexes, giving rise to the [(BG+*n*BA)+(BA–H)][–] signal. The molecular ion peak of 1:*n* systems [(BG+*n*BA)+(BA–H)][–] (*n*=1; *m/z* 543, 2; *m/z* 665, 3; *m/z* 787, 4; *m/z* 909) are unambiguously observed.

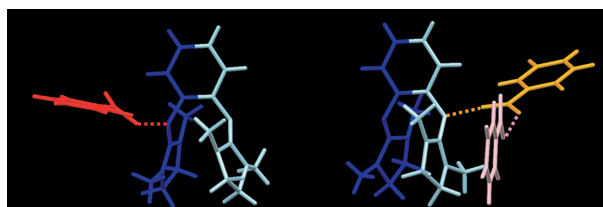


Fig. 1. Crystal Structure of BG+*n*BA (*n*=1, Left and *n*=2, Right)

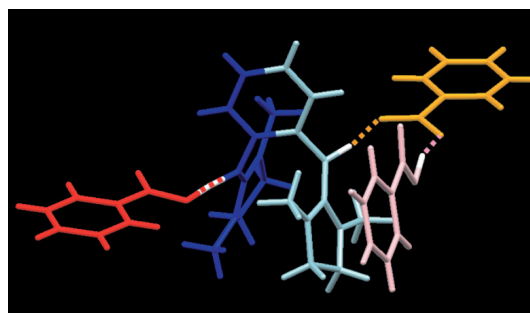


Fig. 2. Crystal Structure of BG+3BA

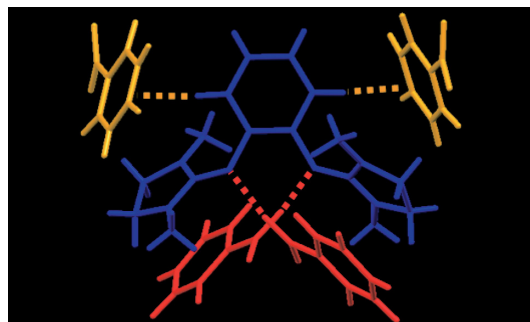


Fig. 3. Crystal Structure of BG+4BA

* To whom correspondence should be addressed. e-mail: yamaguchi@kph.bunri-u.ac.jp

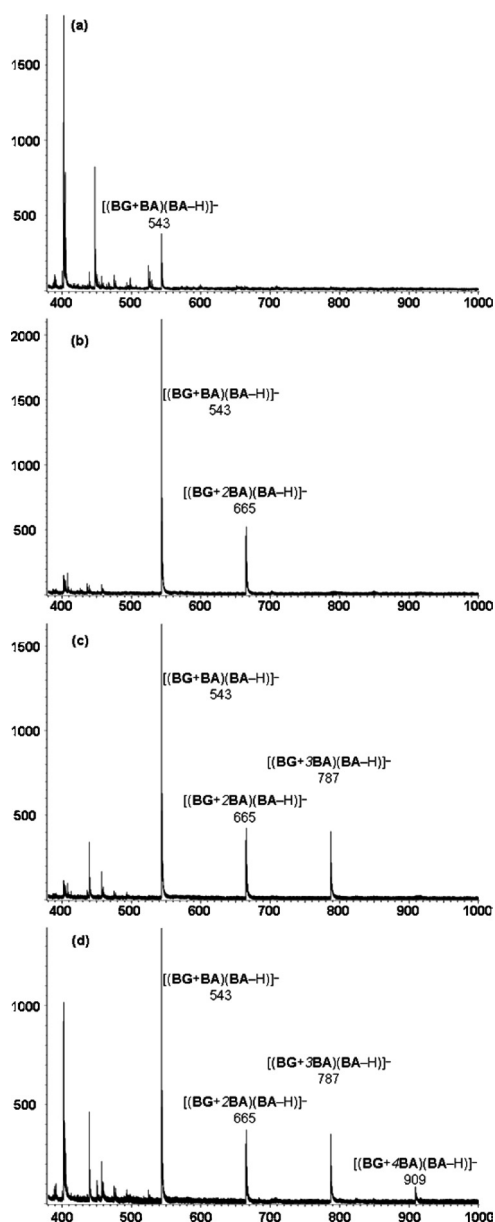


Fig. 4. CSI-MS Spectra of BG+nBA Complexes

(a) $n=1$, (b) $n=2$, (c) $n=3$, (d) $n=4$.

In the cases of 1:2, 1:3 and 1:4, other ion peak(s) corresponding to lower stoichiometric systems $[(BG+nBA-mBA)+(BA-H)]^-$ ($n=2-4$, $m=1-n-1$) are observed. Therefore, CSI-MS measurements give a direct observation on the formation of ordered clusters in solution.

To confirm this unprecedented phenomenon in solution, we performed diffusion study by pulsed field gradient PFG NMR.¹²⁻¹⁴ The D values of the complexes BG+nBA ($n=1-4$) including BG and BA itself, obtained by PFG NMR measurements are shown in Table 1. The observed D value decreases in accordance with the increasing number of

Table 1. Diffusion Coefficient of BG+nBA Complexes (10 °C, 1 mm in CD_2Cl_2)

Compound	Diffusion coefficient (D) ($\times 10^{-10} m^2/s$)
BG	13.0
BG+BA (1 : 1)	11.6
BG+2BA (1 : 2)	10.0
BG+3BA (1 : 3)	9.7
BG+4BA (1 : 4)	9.4
BA	22.3

attached BA (n). The pure BG and BA solutions exhibit a large D value which is dependent of their molecular weight. This result clearly supports the ordered formation of the complexes in solution as observed by CSI-MS.

In consequence, stoichiometry-controlled absolute ordered cluster formation of BG and BA was confirmed by CSI-MS, PFG NMR and X-ray crystallography. These results give experimental evidence that desired molecular complex in solution as well as in the solid state by simple mixing acid and base components can be obtained. Investigation on the formation of other acid-base systems is in progress.

References and Notes

- Desiraju G. R., *J. Mol. Struct.*, **656**, 5—15 (2003).
- Bond A. D., Jones W., "Supramolecular Organization and Materials Design," ed. by Jones W., Rao C. N. R., Cambridge University Press, Cambridge, 2002, pp. 391—443.
- Jones W., "Organic Molecular Solids, Properties and Applications," CRC Press, New York, 1997, pp. 181—194.
- Kawahata M., Yamaguchi K., Ishikawa T., *Cryst. Growth Des.*, **5**, 373—377.
- Seki H., Nakagawa M., Hashimoto A., Hino T., *Chem. Pharm. Bull.*, **41**, 1173—1176 (1993).
- Dell'Erba C., Gasparrini F., Grilli S., Lunazzi L., Mazzanti A., Novi M., Pierini M., Tavani C., Villani C., *J. Org. Chem.*, **67**, 1663—1668 (2002).
- Shikii K., Seki H., Sakamoto S., Sei Y., Utsumi H., Yamaguchi K., *Chem. Pharm. Bull.*, **53**, 792—795 (2005).
- Shikii K., Sakamoto S., Seki H., Utsumi H., Yamaguchi K., *Tetrahedron*, **60**, 3487—3492 (2004).
- Yamaguchi K., *J. Mass Spectrom.*, **38**, 473—490 (2003).
- BG+3BA (1 : 3) complex: $C_{37}H_{42}N_6O_6$, $M=666.77$, monoclinic, $a=17.041(2)$, $b=8.7317(13)$, $c=24.014(3)$ Å, $\beta=106.665(3)^\circ$, $V=3423.2(9)$ Å³, $T=150$ K, space group $P2_1/c$ (no. 14), $Z=4$, μ (Mo- $K\alpha$)=0.089 mm⁻¹, 20016 reflections measured, 7769 unique ($R_{int}=0.0698$), 458 parameters refined, $R1(F)=0.0575$, $wR(F^2)=0.1867$ (all data). CCDC 282493.
- CSI-MS measurements were performed using a time-of-flight mass spectrometer (JEOL JMS-T100) equipped with an orthogonal CSI source. Typical measurement conditions are as follows: acceleration voltage, 2.0 kV; needle voltage, 1.4 kV; orifice voltage, 193 V; resolution 6000; spray temperature, -25 °C.
- The diffusion experiments were carried out on a JEOL JNM ECA-700 spectrometer, used with bipolar-pulse-pair stimulated-echo (BPP-STE) pulse sequence in the standard measurement condition. The self-diffusion coefficient D were measured after 1 h at 10 °C for stabilization and by using 3 mm I.D. sample tube due to the decrease of the solution thermal convection.
- Tanner J. E., *J. Magn. Reson.*, **52**, 2523—2526 (1970).
- Wu D., Chen A., Johnson C. S., *J. Magn. Reson. Series A*, **115**, 260—264 (1995).