Novel additive effect of inclusion crystals on polymorphs–cholic acid crystals having different hydrogen-bonded networks with the same organic guest

Kazunori Nakano, Kazuki Sada and Mikiji Miyata*

Material and Life Science, Faculty of Engineering, Osaka University, Yamadaoka, Suita, Osaka 565, Japan

Addition of a third component enables cholic acid to form polymorphic inclusion crystals with different hydrogen-bonded networks with the same organic guest, indicating a novel additive effect on polymorphs.

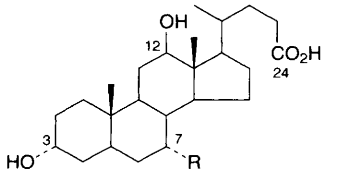
It is well known many organic molecules form polymorphic crystals.[1] With inclusion crystals, host molecules change their association modes to fit guest molecules, indicating that the host assemblies are guest-dependent polymorphs.[2] Multifunctional hosts, such as cholic acid **1**, can exhibit diversible modes in the form of different hydrogen-bonded networks.[3] Previous studies indicated that such a host having hydrogen-bonding groups has a unique hydrogen-bonded network that accepts an organic guest.† Some reports[4] involve inclusion crystals having the same guests but in different host–guest ratios.‡ To the best of our knowledge, there is only one report of an organic guest inducing inclusion crystals with different hydrogen-bonded networks with the same host–guest ratio.[5]. Here we report a novel example that **1** can form inclusion crystals of different hydrogen-bonded networks with the same organic guest when a third component is added to the solution containing both host and guest components.

Most of the inclusion crystals can be obtained preferentially by direct recrystallization from liquid guests (Method A). This method cannot be used for guests where the hosts are highly or sparingly soluble. These guests required us to find third components which either do not form inclusion crystals or form very unstable ones (Method B).[6] These third components can also be used in Method A. These two different methods raises the question as to whether the crystals obtained by Method A are the same as those obtained by Method B or not.

We earlier reported that butanols can be used as the third component for obtaining the inclusion compounds of **1** with aromatic hydrocarbons.[6] We have re-examined the formation of the compounds in the presence of a third component. More than 100 analogues of **1** with various organic substances were examined by X-ray powder diffraction method. The polymorphic inclusion crystals mentioned above were found only when we used propionitrile, acrylonitrile, methacrylonitrile and acetic acid as guests in the presence of the third component. The former three exhibited the real polymorphs in the same host–guest ratios, whilst with acetic acid there was a guest-dependent polymorph in different host–guest ratios.

First, we describe the case of nitriles as guests. Only propionitrile, acrylonitrile and methacrylonitrile of aliphatic nitriles were shown to give two kinds of crystals by means of X-ray powder diffraction. In the case of acrylonitrile, the crystals were prepared as follows. Method A consisted of dissolution of **1** (30 mg) into acrylonitrile (5.6 ml). On cooling the inclusion crystals **a** were obtained in 1 : 1 host–guest ratio, as determined by thermogravimetry and ^{1}H NMR spectroscopy. Method B involved addition of acryronitrile (1.0 ml) into a saturated butan-1-ol solution of **1** (0.4 ml). On standing at room temperature inclusion crystals **b** in 1 : 1 host–guest ratio were obtained. These crystals have different sharp absorption peaks in the hydroxy stretching region in the IR spectra, indicating different hydrogen-bonded networks. This was verified by single-crystal X-ray structural analysis. Crystals **a**§ belong to the same space group (orthorhombic, $P2_12_12_1$) as those of **1** without guests, Fig. 1(*a*).[7] The host molecules form a crossing structure with helical networks of OH[C(3)]···OH-[C(12)]···O = C-OH[C(24)]···OH[C(7)]···OH[C′(3)], Fig. 2(*a*). According to Etter *et al.*,[8] the network is defined as $R^4_4(10)$. On the other hand, crystals **b**§ belong to the same space group (monoclinic, $P2_1$) as those of the compounds of **1** with benzene,[6] acetophenone[3a] and γ-valerolactone.[3b] The host molecules form a bilayered structure with cyclic networks of OH[C(3)]···OH[C(12)]···O = C-OH[C(24)]···OH[C(7)]···OH-[C(3)], Fig. 2(*b*). The network is shown as $C^4_4(10)$. In this way the crystals have different networks in spite of having the same guest. Other nitriles, such as acetonitrile, butyronitrile, crotononitrile, isobutyronitrile and valeronitrile form only the latter 1 : 1 crystals with bilayered structures even in the presence of the third component.

We next studied the case of acetic acid. Method A yielded 1 : 1 inclusion crystals **c**,§ which have crossing structures, Fig. 1(*c*), with helical hydrogen-bonded networks involving the carboxyl groups of the guest, Fig. 2(*c*). On the other hand, using



1 R = OH
2 R = H

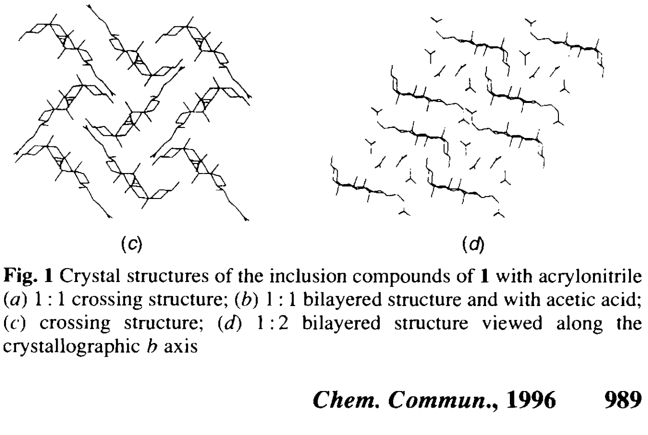


Fig. 1 Crystal structures of the inclusion compounds of **1** with acrylonitrile (*a*) 1 : 1 crossing structure; (*b*) 1 : 1 bilayered structure and with acetic acid; (*c*) crossing structure; (*d*) 1 : 2 bilayered structure viewed along the crystallographic *b* axis

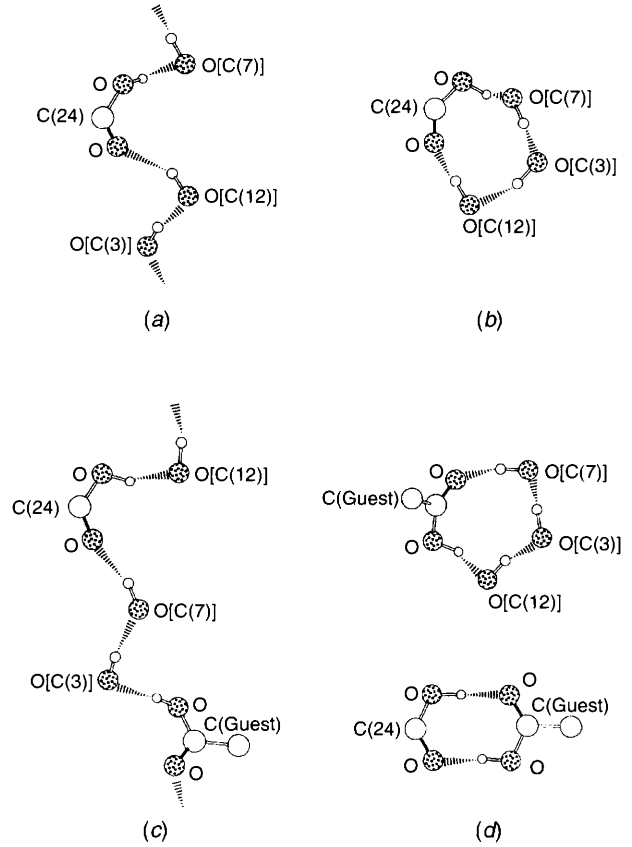


Fig. 2 Schematic representation for the hydrogen-bonding networks: the inclusion compounds of **1** with acrylonitrile (*a*) 1 : 1 crossing structure; (*b*) 1 : 1 bilayered structure and with acetic acid; (*c*) 1 : 1 crossing structure; (*d*) 1 : 2 bilayered structure

Method B with cyclohexane as the third component yielded 1 : 2 inclusion crystals **d**,§ which have a bilayered structure, Fig. 1(*d*), with two kinds of cyclic hydrogen-bonded networks involving the guest groups, Fig. 2(*d*). It can be seen from a comparison of Figs. 2(*b*) and (*d*) that the carboxylic group of the host replaces the corresponding group of the guest. The replaced group of the host forms another cyclic network with another carboxylic group of the guest. The host molecule sidechain leans towards the lipophilic side, resulting in the formation of such networks.[9]

In contrast, we did not obtain polymorphic crystals of deoxycholic acid **2** with various organic guests in the presence of the third component. The reason for this is that **2** cannot form the multiple and flexible hydrogen-bonded networks because of the lack of a hydroxy group at the C-7 position.

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

Footnotes

† There are such cases for hydrates. For example, **1** employs two crystal forms, monoclinic $(P2_12_12_1)$[10] and hexagonal $(P6_5)$.[11] Compound **2** forms tetragonal $(P4_12_12)$ and hexagonal $(P6_5)$ crystals.[12]

‡ These do not satisfy the definition of polymorphs, because their repeating units are different.[13]

§ *Crystal data* for (**a**) **1**-acrylonitrile (1 : 1) (−65 °C), $C_{24}H_{40}O_5 + C_3H_3N$, $M = 461.64$, orthorhombic, $P2_12_12_1$, $a = 16.882(3)$, $b = 17.619(2)$, $c = 8.497(1)$ Å, $V = 2527.5(5)$ Å^3, $Z = 4$, $D_c = 1.213$ g cm^{-3}. For (**b**) **1**-acrylonitrile (1 : 1) (−65 °C), $C_{24}H_{40}O_5 + C_3H_3N$, $M = 461.64$, monoclinic, $P2_1$, $a = 12.183(2)$, $b = 7.878(1)$, $c = 14.300(3)$ Å, $\beta = 104.16(1)°$, $V = 1330.8(4)$ Å^3, $Z = 2$, $D_c = 1.152$ g cm^{-3}. For (**c**) **1**-acetic acid (1 : 1) (−65 °C), $C_{24}H_{40}O_5 + C_2H_4O_2$, $M = 468.63$, orthorhombic, $P2_12_12_1$, $a = 13.831(3)$, $b = 15.363(5)$, $c = 12.400(3)$ Å, $V = 2634(1)$ Å^3, $Z = 4$, $D_c = 1.181$ g cm^{-3}; For (**d**) **1**-acetic acid (1 : 2) (−65 °C), $C_{24}H_{40}O_5 + C_4H_8O_4$, $M = 528.68$, monoclinic, $P2_1$, $a = 13.353(2)$, $b = 8.189(2)$, $c = 13.993(1)$ Å, $\beta = 112.175(8)°$, $V = 1416.9(1)$ Å^3, $Z = 2$, $D_c = 1.239$ g cm^{-3}. Intensity data were collected on a Rigaku AFC-7R diffractometer with graphite-monochromatized Mo-Kα radiation. 3303, 3433, 3407 and 3491 reflections for the crystals **a**, **b**, **c** and **d** were unique. 1378, 1566, 2126 and 2280 observed reflections with $[|F_o| > 3\sigma(|F_o|)]$ were used for further calculations after Lorenz and polarization corrections, respectively. Both the structures were solved by direct methods (SHELXS86) and refined by full-matrix least-squares. For the crystal **a**, all non-hydrogen atoms of the host molecules were refined anisotropically, whilst the acrylontrile molecule was refined isotropically with geometrical constraints. For the crystals **b**, **c** and **d**, all non-hydrogen atoms were refined anisotropically. C–H groups were located in the calculated positions and O–H group positions were obtained from difference Fourier syntheses. The final R values are 0.089, 0.055, 0.051 and 0.051 respectively. All calculations were performed using TEXSAN crystallographic software package of the Molecular Structure Corporation. Atomic coordinates, thermal parameters, and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, *Chemical Communications*, 1996, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/21.

References

1 J. D. Dunitz and J. Bernstein, *Acc. Chem. Res.*, 1995, **28**, 193; J. D. Dunitz, *Acta. Crystallogr., Sect. B*, 1995, **51**, 619.
2 E. Weber, in *Inclusion Compounds*, ed. J. L. Atwood, J. E. D. Davies and D. D. MacNicol, Academic Press, 1991, vol. 4, ch. 5, pp. 188–262; M. P. Bym, C. J. Curtis, I. Goldberg, Y. Hsiou, S. I. Khan, P. A. Sawin, S. K. Tendick and C. E. Strouse, *J. Am. Chem. Soc.*, 1991, **113**, 6549.
3 (*a*) K. Miki, A. Masui, N. Kasai, M. Miyata, M. Shibakami and K. Takemoto, *J. Am. Chem. Soc.*, 1988, **110**, 6594; (*b*) K. Miki, N. Kasai, M. Shibakami, K. Takemoto and M. Miyata, *J. Chem. Soc., Chem. Commun.*, 1991, 1757; (*c*) M. Shibakami, M. Tamura and A. Sekiya, *J. Am. Chem. Soc.*, 1995, **117**, 4499; (*d*) J. L. Scott, *J. Chem. Soc., Perkin Trans. 2*, 1995, 495.
4 F. Toda, Y. Tagami and T. C. W. Mak, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 1189; K. Hamada, M. Ohhira, T. Fujisawa and F. Toda, *Acta. Crystallogr., Sect. C*, 1992, **48**, 1969; A. T. Ung, R. Bishop, D. C. Craig, I. G. Dance and M. L. Scudder, *Tetrahedron*, 1993, **49**, 639.
5 M. D. Hollingsworth, B. D. Santarsiero and K. D. M. Harris, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 649.
6 K. Nakano, K. Sada and M. Miyata, *Chem. Lett.*, 1994, 137.
7 K. Miki, N. Kasai, M. Shibakami, S. Chirachanchai, K. Takemoto and M. Miyata, *Acta. Crystallogr., Sect. C*, 1990, **46**, 2442.
8 M. C. Etter and J. C. MacDonald, *Acta. Crystallogr., Sect. B*, 1990, **46**, 256; J. Bernstein, R. E. Davis, L. Shimoni and N. Chang, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1555.
9 L. Leiserowitz, *Acta. Crystallogr., Sect. B*, 1976, **32**, 775.
10 L. Lessinger, *Cryst. Struct. Commun.*, 1982, **11**, 1787
11 L. Lessinger and B. W. Low, *J. Crystallogr. Spectrosc. Res.*, 1993, **23**, 85.
12 E. Giglio, in *Inclusion Compounds*, ed. J. L. Atwood, J. E. D. Davies and D. D. MacNicol, Academic Press, 1984, vol. 2, ch. 7, pp. 207–229
13 B. D. Sharma, *J. Chem. Educ.*, 1987, **64**, 404.

Received, 27th October 1995; Com. 5/07089I