Organic Alloys

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A Supramolecular Approach to Organic Alloys: Cocrystals and Three- and Four-Component Solid Solutions of 1,4-Diazabicyclo[2.2.2]octane and 4-X-Phenols ($X=Cl, CH_3, Br$)

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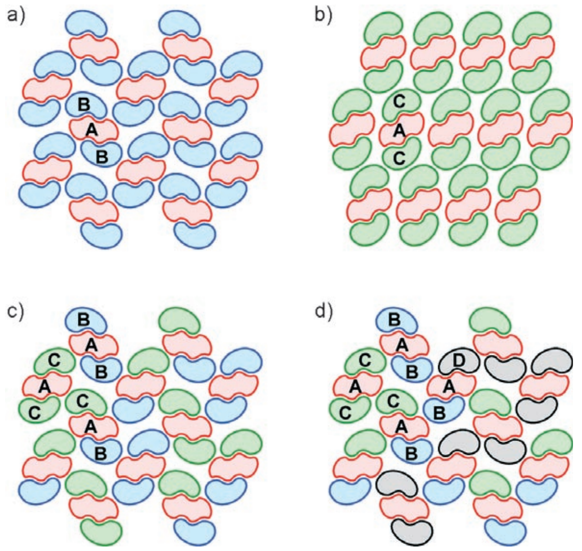
Herein, we describe the preparation of binary cocrystals and ternary and quaternary solid solutions of 1,4-diazabicyclo-[2.2.2]octane (DABCO) and 4-X-phenols ($X=Cl, CH_3, Br$). Multicomponent solids, be they cocrystals or solid solutions, are materials that may exhibit new or superior functionalities relative to the individual components.[1] Though molecular complexes have been studied for a long time,[1–3] the design of cocrystals containing more than two different components remains a challenging task.[4] Except for a few notable contributions,[5] most studies on organic cocrystals led only to the formation of binary organic solids.[1] In contrast, metals and inorganic compounds readily form multicomponent solids in the form of solid solutions.[6] Creating multicomponent solid solutions of organic molecules, however, is challenging because these molecules possess intricate shapes and participate in directional intermolecular interactions.[3] Not surprisingly, most molecule-based solid solutions contain only two components.[7] We describe a supramolecular approach for the preparation of solid solutions that contain three or more organic molecules. The principal advantage of solid solutions is that their properties can be modulated by the gradual modification of the relative ratio of the components.[8]

Scheme 1 shows our approach to the formation of organic alloys. We begin with a trimolecular motif wherein a central molecule (A) is connected to two peripheral molecules (B or C) through similar intermolecular interactions. If the two peripheral molecules are identical, the binary cocrystals AB_2 or AC_2 are formed. If they are different, a ternary cocrystal BAC or a ternary solid solution $A(B_nC_{1-n})_2$ $(0<n<1)$ can be formed, depending on the similarity of the sizes and shapes of the peripheral molecules. Adding another isosteric component (D) can lead to a quaternary solid solution $A(B_nC_mD_p)_2$ $(n+m+p=1, 0<n,m,p<1)$.

We use DABCO as the central molecule and 4-X-phenols ($X=Cl, CH_3, Br$) as the peripheral molecules (Scheme 2). The chloro, methyl, and bromo substituents of the 4-X-phenols have similar shapes and comparable sizes (20, 24, and 28 Å^3),[9] and do not interfere with the O−H···N hydrogen bonding required for the trimolecular assembly. We surmised that the size, shape, and chemical similarity of the 4-X-phenols would enable the formation of solid solutions upon crystallization of DABCO with two or three of the phenols. We call these crystalline materials *supramolecular* solid solutions because their repeat unit is a trimolecular assembly.[10]



Scheme 1. Cocrystals and solid solutions of molecule A with molecules B, C, and/or D, which have similar shapes and sizes. Binary cocrystals a) AB_2 and b) AC_2 adopting different crystal structures. c) A ternary solid solution of A, B, and C adopting the structure of AB_2 (it could as well adopt the AC_2 structure or some other structure). The trimolecular assemblies in (c) may have BAB, CAC, or BAC configurations. The overall composition of the solid solution is $A(B_nC_{1-n})_2$ $(0<n<1)$. d) A quaternary solid solution of A, B, C, and D adopting the structure of AB_2 and having an overall composition of $A(B_nC_mD_p)_2$ $(n+m+p=1, 0<n,m,p<1)$.

Single crystals of binary cocrystals and of ternary and quaternary solid solutions (having equimolar ratios of phenols) suitable for X-ray diffraction were grown from benzene solutions (Table 1; Scheme 2).[11] The binary cocrystals **ClCl** and **MeMe** are isostructural;[12] Figure 1a shows the structure of **ClCl**. The unit cell of **MeMe** is larger than that of **ClCl**, in accordance with the larger size of the methyl groups relative to the chloro groups. As expected, each DABCO molecule binds to two phenol molecules through O−H···N hydrogen bonds. This trimolecular assembly is situated on an inversion center; that is, the two phenol molecules are symmetry-related. The packing of these assemblies in three dimensions

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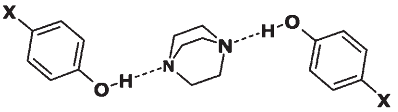
Supporting information for this article (IR and ^1H NMR spectroscopic, DSC, and X-ray diffraction data, along with structural analyses and additional packing diagrams) is available on the WWW under http://www.angewandte.org or from the author.



ClCl : X = Cl
MeMe : X = CH_3
BrBr : X = Br
binary cocrystals

ClMe : X = nCl + (1-n)CH_3 0 < n < 1
ClBr : X = nCl + (1-n)Br 0 < n < 1
MeBr : X = $n CH_3$ + (1-n)Br 0 < n < 1
ternary solid solutions

ClMeBr : X = ⅓CH_3 +⅓Cl +⅓Br
quaternary solid solution

Scheme 2. Chemical structures and compositions of cocrystals and solid solutions of DABCO with one, two, or three different 4-X-phenols (X = Cl, CH_3, Br).

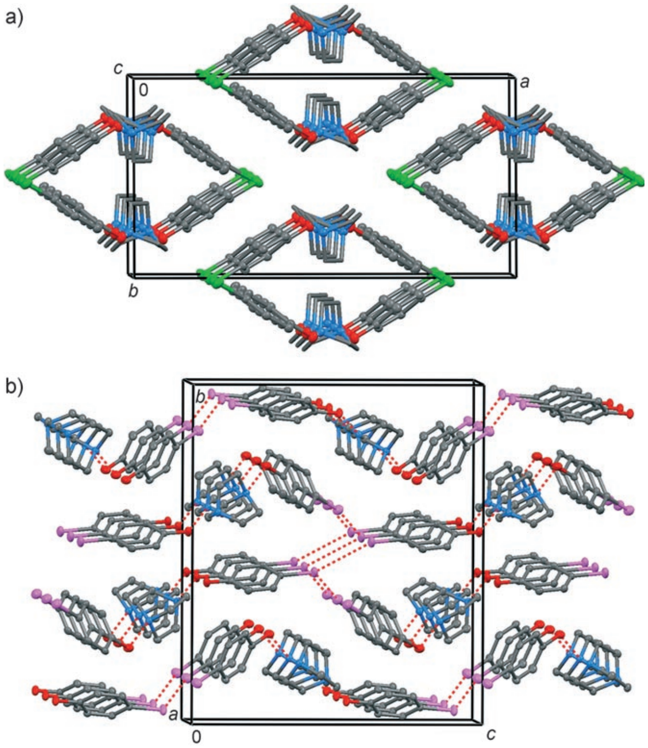


Figure 1. Crystal structures of a) **ClCl** and b) **BrBr**. In (b), dashed lines show the O–H···N hydrogen bonds and the Br···Br contacts. Note that the overall structures of the two cocrystals are different. C gray, N blue, O red, Cl green, Br pink; H omitted.

is governed by C–H···O, C–H···π, and van der Waals interactions.

In the crystal structure of **BrBr** (Table 1, Figure 1 b), the hydrogen-bonded trimolecular assembly is located on a general position; that is, the two phenol molecules are not related by symmetry. These assemblies are extended into interconnected chains through type-I and type-II Br···Br interactions.[13] It is probable that **BrBr** crystallizes in a different structure to accommodate these interactions. Despite the marked differences in the structures of **ClCl**/**MeMe** and **BrBr**, the trimolecular assemblies in all the cocrystals adopt similar conformations (Figure 2). Noting this similarity and the similarities in the molecular structures of the phenols, we attempted the preparation of the ternary solid solutions **ClMe**, **ClBr**, and **MeBr** (Scheme 2).

We crystallized the three solid solutions with varying proportions of the corresponding phenols and characterized them using powder X-ray diffraction (Figure 3), as well as IR and ^{1}H NMR spectroscopy (see the Supporting Information). We also determined the crystal structures of the members of the ternary solid solutions containing DABCO and the two respective phenols in a 1:1:1 proportion (Table 1; 50Cl-50Me, 50Cl-50Br, and 50Me-50Br in Figure 3). In these structures, the X sites of the 4-X-phenol molecules are occupied by an approximately equal mixture of the two substituents (Cl/CH_3, Cl/Br, or CH_3/Br).

The 50Cl-50Me member of the ternary **ClMe** solid solution is isostructural to **ClCl** and **MeMe**; the volume of its unit cell lies between those of **ClCl** and **MeMe** (Table 1). Powder X-ray diffraction analysis of the **ClMe** solid solution shows a gradual change of the structure

Table 1: Structural data for binary cocrystals and solid solutions of DABCO with one, two, or three 4-X-phenols (X = Cl, CH_3, Br).

Compound[a]	Space group	a [Å]	b [Å]	c [Å]	β [°]	V [Å^3]	O···N[b] [Å]
ClCl	$C2/c$	17.987	9.256	11.241	101.85	1831.7	2.68
MeMe	$C2/c$	18.351	9.179	11.254	102.73	1849.0	2.70
BrBr	$P2_1/n$	6.456	18.577	15.914	91.05	1908.2	2.65/2.69
ClMe	$C2/c$	18.178	9.202	11.260	102.36	1839.8	2.68
ClBr	$P2_1/c$	18.231	9.165	11.354	94.88	1890.2	2.65/2.70
MeBr	$P2_1/n$	6.443	18.559	15.884	91.36	1898.7	2.66/2.70
ClMeBr[c]	$P2_1/n$	6.443	18.442	15.778	91.59	1874.0	–

[a] See Scheme 2 for compositions. For **ClMe**, **ClBr**, and **MeBr**, the crystal structures of the 50Cl-50Me, 50Cl-50Br, and 50Me-50Br members (n = 0.5) of the solid solutions were determined. [b] The O···N distance(s) of the symmetry-independent O–H···N hydrogen bond(s); not determined for **ClMeBr**. [c] Crystal structure not determined.

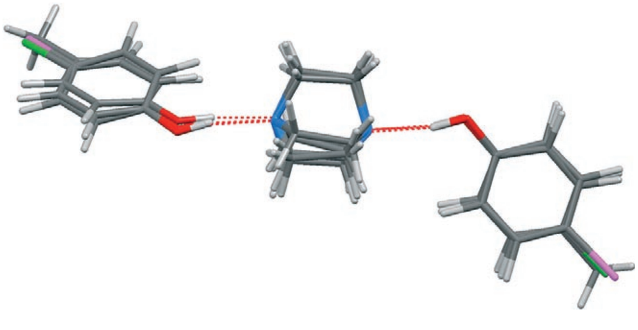


Figure 2. Superposition of the trimolecular assemblies in the binary cocrystals **ClCl**, **MeMe**, and **BrBr**. Dashed lines show the O–H···N hydrogen bonds. C gray, H white, N blue, O red, Cl green, Br pink.

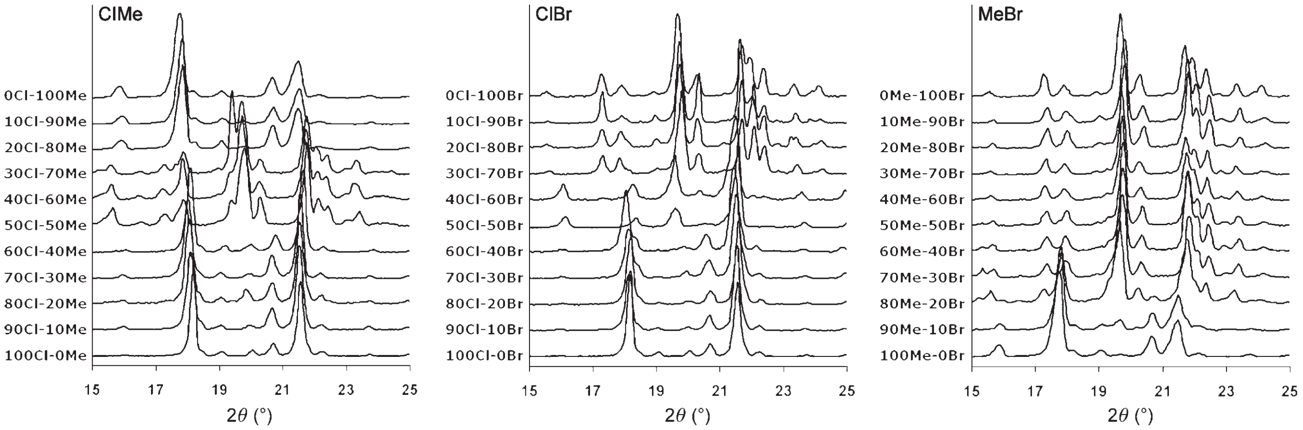


Figure 3. Powder X-ray diffraction patterns of the **ClMe**, **ClBr**, and **MeBr** solid solutions. They are labeled such that the total phenol content is 100%; for example, 60Cl-40Br corresponds to DABCO·2 (0.6 chlorophenol·0.4 bromophenol).

from 100Cl-0Me (**ClCl**) to 0Cl-100Me (**MeMe**). The additional peaks present in the patterns of 50Cl-50Me–30Cl-70Me suggest that **ClMe** may also adopt the **BrBr** structure in this composition range. 50Cl-50Br adopts a similar structure, albeit with reduced symmetry ($P2_1/c$; Table 1; Figure S3), yet the volume of its unit cell is close to that of **BrBr**, indicating the presence of bromine in the crystal. The **ClBr** solid solution adopts the **ClCl** structure or the lower-symmetry 50Cl-50Br structure from 100Cl-0Br (**ClCl**) to 40Cl-60Br; from 30Cl-70Br to 0Cl-100Br (**BrBr**), it adopts the **BrBr** structure (Figure 3). In contrast to 50Cl-50Br, 50Me-50Br adopts the structure of **BrBr** (Table 1). Figure 3 shows that the **MeBr** solid solution adopts the **MeMe** structure only from 100Me-0Br (**MeMe**) to 90Me-10Br. From 80Me-20Br to 0Me-100Br (**BrBr**), it adopts the structure of **BrBr**. The Supporting Information provides further structural comparisons between the three solid solutions.

The X-ray diffraction methods used herein provide useful, yet limited, structural information for solid solutions. Single-crystal X-ray diffraction affords the structure of the repeat unit as an average of millions of such units. Consequently, we cannot distinguish which of the following compositions the ternary solid solutions possess: i) a mixture of binary AB_2 and AC_2 motifs randomly distributed throughout the crystal; ii) a mixture of randomly distributed AB_2, AC_2, and BAC motifs; or iii) ternary BAC motifs randomly disordered over two orientations, such that B and C are superposed in the average structure. We can, however, ascertain from these X-ray diffraction studies that the repeat unit is indeed a trimolecular assembly and that the solid solutions each contain three different components in variable proportions.

Figure 4 shows the differential scanning calorimetry (DSC) results for the ternary **ClBr** solid solution. The corresponding DSC results for the **ClMe** and **MeBr** solid solutions are given in the Supporting Information (Figure S9). The melting point of the **ClBr** solid solution gradually decreases from 100Cl-0Br (**ClCl**) to 40Cl-60Br, and then increases to 0Cl-100Br (**BrBr**). This behavior illustrates that solid solutions offer the unique ability to modulate the physical properties of materials in an almost continuous fashion.

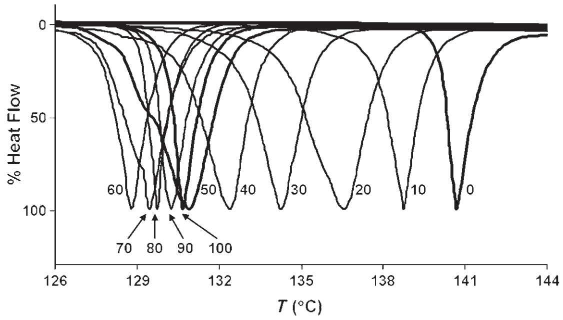


Figure 4. DSC traces of the **ClBr** solid solution. They are labeled with the percentage of bromophenol in the total phenol content; for example, 10 corresponds to 90Cl-10Br, that is, DABCO·2 (0.9 chlorophenol·0.1 bromophenol).

The utility of the supramolecular approach to solid solutions (Scheme 1) is exemplified by our synthesis of **ClMeBr**, one member of a quaternary solid solution (Scheme 2, Table 1, Figures S11–S14), from DABCO and three different 4-X-phenols in equimolar proportions. The volume of the unit cell of **ClMeBr** (1874 Å^3) is close to the average of the unit-cell volumes of **ClCl**, **MeMe**, and **BrBr** (1863 Å^3). From the unit-cell dimensions (Table 1) and the powder X-ray diffraction pattern (Figure S14), it is apparent that **ClMeBr** adopts the structure of **BrBr**. The melting point of quaternary **ClMeBr** is distinct from those of the corresponding binary cocrystals and the ternary solid solutions (Figure S13). Note that **ClMeBr** belongs to a four-component solid solution prepared on the basis of a three-component supramolecular assembly. These results show that our approach to solid solutions is an effective method to create truly multicomponent organic alloys.

The advantage of the supramolecular approach shown in Scheme 1 is that any target molecule capable of forming hydrogen bonds can, in principle, be complexed with a set of molecules to form solid solutions. The physical properties of the solid solutions can be finely tuned by changing the nature and relative ratios of the different components. This approach should be applicable to all the situations in which binary systems are currently used, but it may find distinctive use in pharmaceutical form selection.[14] We are currently preparing five-component organic alloys, and ternary and higher-order solid solutions involving pharmaceuticals, using the new approach developed in this work.

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[6] Solid solutions of metals or alloys are easy to form because of the spherical shape of the components and the isotropic nature of their intercomponent interactions.

[7] For an exception, see: K. Sada, K. Inoue, T. Tanaka, A. Epergyes, A. Tanaka, N. Tohnai, A. Matsumoto, M. Miyata, *Angew. Chem.* **2005**, *117*, 7221–7224; *Angew. Chem. Int. Ed.* **2005**, *44*, 7059–7062. Note, however, that the multicomponent solid solutions in this work are based on ionic components.

[8] For example, solid solutions of insulin and a lipophilically modified insulin derivative show superior in vivo therapeutic properties; see: M. L. Brader, M. Sukumar, A. H. Pekar, D. S. McClellan, R. E. Chance, D. B. Flora, A. L. Cox, L. Irwin, S. R. Myers, *Nat. Biotechnol.* **2002**, *20*, 800–804. In this paper, homogeneous mixtures of insulin and its derivative are described as cocrystals. We note that these mixtures, though crystalline, are in fact members of a solid solution.

[9] A. I. Kitaigorodsky, *Molecular Crystals and Molecules*, Academic Press, New York, **1973**.

[10] In contrast, the repeat units in traditional solid solutions of organic compounds are single molecules, for example, anthracene and acridine (see ref. [3] for more examples).

[11] Single-crystal X-ray diffraction data were collected on a Bruker SMART CCD diffractometer using $Mo_{K\alpha}$ radiation. All the structures were solved by direct methods and refined on F^2 by least-squares methods using the program SHELXL-97. Crystal data for **ClCl**: $C_{18}H_{22}Cl_2N_2O_2$, $M_r = 369.28$, monoclinic, $a = 17.987(5)$, $b = 9.256(2)$, $c = 11.241(3)$ Å, $\beta = 101.848(4)°$, $V = 1831.7(8)$ Å^3, $T = 193$ K, space group $C2/c$ (no. 15), $Z = 4$, $\rho_{calcd} = 1.339\ g\,cm^{-3}$, $\mu(Mo_{K\alpha}) = 0.367\ mm^{-1}$, 1739 reflections of 2138 unique reflections with $I > 2\sigma(I)$, $2.31 < \theta < 27.86°$, $R_1 = 0.045$, $wR_2 = 0.125$. Crystal data for **MeMe**: $C_{20}H_{28}N_2O_2$, $M_r = 328.44$, monoclinic, $a = 18.351(4)$, $b = 9.1788(19)$, $c = 11.254(2)$ Å, $\beta = 102.729(3)°$, $V = 1849.0(7)$ Å^3, $T = 193$ K, space group $C2/c$ (no. 15), $Z = 4$, $\rho_{calcd} = 1.180\ g\,cm^{-3}$, $\mu(Mo_{K\alpha}) = 0.076\ mm^{-1}$, 1243 reflections of 1633 unique reflections with $I > 2\sigma(I)$, $2.28 < \theta < 25.02°$, $R_1 = 0.065$, $wR_2 = 0.150$. Crystal data for **BrBr**: $C_{18}H_{22}Br_2N_2O_2$, $M_r = 458.20$, monoclinic, $a = 6.4556(15)$, $b = 18.577(4)$, $c = 15.914(4)$ Å, $\beta = 91.048(4)°$, $V = 1908.2(8)$ Å^3, $T = 193$ K, space group $P2_1/n$ (no. 14), $Z = 4$, $\rho_{calcd} = 1.595\ g\,cm^{-3}$, $\mu(Mo_{K\alpha}) = 4.261\ mm^{-1}$, 3254 reflections of 4495 unique reflections with $I > 2\sigma(I)$, $1.69 < \theta < 27.89°$, $R_1 = 0.037$, $wR_2 = 0.082$. Crystal data for **ClMe** (50Cl-50Me): $C_{19}H_{25}ClN_2O_2$, $M_r = 348.86$, monoclinic, $a = 18.178(3)$, $b = 9.2020(14)$, $c = 11.2597(17)$ Å, $\beta = 102.356(2)°$, $V = 1839.8(5)$ Å^3, $T = 193$ K, space group $C2/c$ (no. 15), $Z = 4$, $\rho_{calcd} = 1.259\ g\,cm^{-3}$, $\mu(Mo_{K\alpha}) = 0.221\ mm^{-1}$, 1483 reflections of 1629 unique reflections with $I > 2\sigma(I)$, $2.29 < \theta < 25.02°$, $R_1 = 0.068$, $wR_2 = 0.164$. Crystal data for **ClBr** (50Cl-50Br): $C_{18}H_{22}BrClN_2O_2$, $M_r = 413.74$, monoclinic, $a = 18.231(7)$, $b = 9.165(4)$, $c = 11.354(5)$ Å, $\beta = 94.877(6)°$, $V = 1890.2(13)$ Å^3, $T = 193$ K, space group $P2_1/c$ (no. 14), $Z = 4$, $\rho_{calcd} = 1.454\ g\,cm^{-3}$, $\mu(Mo_{K\alpha}) = 2.328\ mm^{-1}$, 3351 reflections of 4409 unique reflections with $I > 2\sigma(I)$, $1.12 < \theta < 27.90°$, $R_1 = 0.060$, $wR_2 = 0.172$. Crystal data for **MeBr** (50Me-50Br): $C_{19}H_{25}BrN_2O_2$, $M_r = 393.32$, monoclinic, $a = 6.4429(13)$, $b = 18.559(4)$, $c = 15.884(3)$ Å, $\beta = 91.36(3)°$, $V = 1898.7(7)$ Å^3, $T = 193$ K, space group $P2_1/n$ (no. 14), $Z = 4$, $\rho_{calcd} = 1.376\ g\,cm^{-3}$, $\mu(Mo_{K\alpha}) = 2.178\ mm^{-1}$, 3138 reflections of 4465 unique reflections with $I > 2\sigma(I)$, $1.69 < \theta < 27.88°$, $R_1 = 0.048$, $wR_2 = 0.114$. **ClMeBr**: Only cell parameters are reported herein (Table 1); a full structural analysis will be published elsewhere. CCDC-628798 (**ClCl**), CCDC-628799 (**MeMe**), CCDC-628800 (**BrBr**), CCDC-628801 (**ClMe**), CCDC-628802 (**ClBr**), and CCDC-628803 (**MeBr**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[12] The crystal structure of **MeMe** was previously determined at 295 K; see: M. Takama, M. Yasui, S. Harada, N. Kasai, K. Tanaka, F. Toda, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 567–568.

[13] Type-I contact: Br···Br 3.658 Å, C–Br···Br 158.0°; type-II contact: Br···Br 3.632 Å, C–Br···Br 160.5, 119.1°; V. R. Pedireddi, D. S. Reddy, B. S. Goud, D. C. Craig, A. D. Rae, G. R. Desiraju, *J. Chem. Soc. Perkin Trans. 2* **1994**, 2353–2360.

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