Mechanochemical Preparation of Hydrogen-Bonded Adducts Between the Diamine 1,4-Diazabicyclo[2.2.2]octane and Dicarboxylic Acids of Variable Chain Length: An X-ray Diffraction and Solid-State NMR Study

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Abstract: Mechanical mixing of solid dicarboxylic acids of variable chain length $HOOC(CH_2)_nCOOH$ (n = 1–7) with solid 1,4-diazabicyclo[2.2.2]octane generates the corresponding salts or co-crystals of the formula $[N(CH_2CH_2)_3N]$-H-$[OOC(CH_2)_nCOOH]$ (n=1–7). Preparation of the same systems from solution has been instrumental for a full characterization of the mechanochemical products by means of single-crystal and powder-diffraction X-ray analyses, as well as by solid-state NMR. The acid–base adducts, whether involving proton transfer from the COOH group to the N-acceptor, that is having $^{(-)}O\cdots H–N^{(+)}$ interactions, or the formation of neutral O–H···N hydrogen bonds, show a melting point alternation phenomenon analogous to that shown by the neutral carboxylic acids. The carbon chemical shift tensors of the COOH group obtained from the sideband intensity of low speed spinning NMR spectra provide a reliable criterion for assigning the protonation state of the adducts.

Keywords: chemical shift tensor · crystal engineering · hydrogen bonds · mechanochemistry · solid-state NMR

Introduction

Mechanochemical reactions are environmentally friendly and take place when reactants are mixed together in the solid state without the intermediacy of solvents.[1] Reactions of this kind have been known for a long time and may yield products that differ in stoichiometry or topology from those obtained from solution.[2] The success of crystal engineering[3] has attracted renewed interest in solid–solid reactions. Solvent-free reactions can be used for the self-assembly of building blocks without the intermediacy of solvent molecules, thereby circumventing a common problem of crystallization from solution, namely the unforeseen inclusion of solvent molecules in the crystal structure and the problem of crystal *pseudo*-polymorphism.[4] Solvent-free reactions typically need to be mechanically activated by manual grinding or milling. These procedures are commonly exploited with inorganic solids[5] (alloying, milling of soft metals with ceramics, activation of minerals for catalysis, extraction, preparation of cements) and also in the organic chemistry field.[6] More recently, the reactions between molecular systems have begun to be investigated[7] because solvent-free molecular reactions may follow different topochemical routes compared to the same reactions in solution.[8]

Our interest in mechanochemical reactions is twofold. On the one hand, we are seeking new ways to assemble organometallic and organic molecules in the solid state by means of hydrogen-bonding interactions,[9] while on the other hand, we are interested in expanding our understanding of the relationship between crystallization and nucleation, with the aim of learning how to control polymorph formation by non-solution methods.[10] For instance, we have recently reported on the selective hydration of the crystalline material $[Co^{III}(\eta^5\text{-}C_5H_5)_2]^+[Fe(\eta^5\text{-}C_5H_4COOH)(\eta^5\text{-}C_5H_4COO)]^-$ by grinding in air,[10a] on the solid-state complexation of alkali metal cations by grinding the zwitterion $[Co^{III}(\eta^5\text{-}C_5H_4COOH)(\eta^5\text{-}C_5H_4COO)]$ with a number of

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salts,[10b] and on the possibility of direct reaction between the solid organometallic diacid [Fe(η^5-$C_5H_4COOH)_2$] and solid 1,4-diazabicyclo[2.2.2]octane by mechanical mixing of the two components.[10c]

Since the building blocks of choice are organic and organometallic carboxylic acids and nitrogen-containing bases, hydrogen bonds and proton transfer constitute a relevant part of our studies.

The issue of hydrogen bonds is one that still attracts enormous interest[11] and, in spite of the number of studies[12] and the contributions of extremely active groups,[13] there are still several controversial aspects to unravel.[14]

In considering acid-base reactions, a good reason for adopting the solvent-free approach in the case of carboxylic acids and amines is the fact that it avoids the use of solvents that may compete in hydrogen-bond formation (water, alcohols, etc.). Hydrogen-bonding solvents often lead to the formation of crystalline solvates upon crystallization of the acid-base salts or adducts. The possibility of carrying out acid-base reactions directly in the solid state provides a route to anhydrous systems and allows us to ascertain whether solid-state treatment and crystallization from solution lead to the formation of the same phase or to the formation of *pseudo*-polymorphs.

The drawback of the direct preparation of solid phases is inherent to the characterization of the products, which needs to rely on solid-state techniques.[15] Although the most common techniques are based on X-ray diffraction (powder and single-crystal), an unambiguous identification of the hydrogen-bonding interactions requires spectroscopic tools, because of the intrinsic limitations of X-ray diffraction when dealing with hydrogen atom positions.

It is well known that high-resolution solid-state NMR spectroscopy can provide useful information concerning the nature of hydrogen bonding, and it is a general method for evaluating the protonation state of carboxylic acids.[16] This information can be obtained not only from the small but reproducible change in the isotropic chemical shift upon protonation, but also from the value of the chemical shift tensor obtained from the analysis of low spinning speed spectra. For this reason, a comparison between the solid-state ^{13}C NMR data and X-ray diffraction data obtained for crystalline or powdered samples can be particularly useful for obtaining unambiguous information about the proton transfer.

In this paper, we report the results of a systematic investigation of the reaction in solution and in the solid state of a tertiary amine base, namely 1,4-diazabicyclo[2.2.2]octane, **1**, with a series of dicarboxylic organic acid molecules of increasing aliphatic chain length, $HOOC(CH_2)_nCOOH$ (n = 1–7). The aim of this study has been to address the following questions:

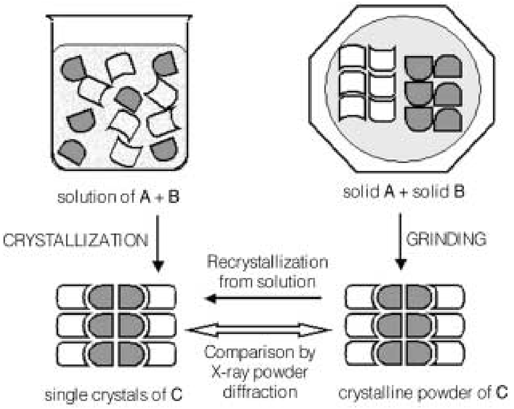
1) Is it possible to react **1** with the diacids in the solid state by mechanical mixing? If so, are the products the same as those that can be obtained by crystallization from solution?
2) Is the hydrogen-bonded chain motif present in crystals of the acids retained upon formation of the products, or is there an alternative preferential packing motif arising from the interaction of the base **1** with the carboxylic acid groups?
3) Since the reaction implies, in terms of supramolecular bonding, a competition between O–H···O interactions (between carboxylic acids) that need to be broken and those of the O–H···N or $^{(+)}$N–H···O$^{(-)}$ types (between the organic acid and base) that need to be formed, what is the rationale for the product formation?
4) Is solid-state NMR a viable alternative to X-ray diffraction for a qualitative characterization of the hydrogen bond between the acid and base as either O–H···N or $^{(+)}$N–H···O$^{(-)}$, which depends critically on the hydrogen atom location?
5) Organic diacids of the type $HOOC(CH_2)_nCOOH$ are known to show melting point alternation[17] depending on whether there is an even or odd number of carbon atoms in the chain; is such a melting point alternation also observed in the corresponding adducts?

To address the questions posed above, we have investigated the solid-state structures of seven adducts corresponding to the general formula $[N(CH_2CH_2)_3N]$-H-$[OOC(CH_2)_n$-$COOH]$ (n = 1–7) and report herein their characterization by solid-state ^{13}C NMR and by powder and single-crystal X-ray diffraction analysis. For convenience, in the following we refer to the diacids by the total number of carbon atoms in the molecule (C3 corresponding to malonic acid, C4 to succinic acid, etc.), hence the adducts are identified as **1**·C3, **1**·C4, and so on. As shown in the following, the formation of the acid-base product is not necessarily accompanied by proton transfer. The epithet adduct, rather than co-crystal (no proton transfer) or salt (proton transfer), will thus be used to collectively describe the products, stressing the ambiguity in the nature of the hydrogen-bonding interactions linking the base and acid in the solid state (see below). The C–O structural parameters relating to the carboxylic/carboxylate groups will also be used.

Results and Discussion

As mentioned above, our approach is based on comparison of the products obtained directly by grinding together the reactants with those obtained by crystallization from ethanol solution. Mechanochemical treatment of molar equivalents of the dicarboxylic acids of the formula $HOOC(CH_2)_n$-$COOH$ (n = 1, 2, 3, 4, 5, 6, 7) with the base 1,4-diazabicyclo[2.2.2]octane (**1**) generates the 1:1 compounds of the general formula **1**·C*n*. The process is schematically depicted in Scheme 1. If single crystals are obtained, these can be used to determine the solid-state structure in detail and, consequently, to calculate the theoretical powder diffractogram. Comparison of the calculated diffractogram with that measured from the mechanochemical product allows one to establish with confidence whether the same phase or a different one, or a mixture of phases, has been obtained.

In the present case, all seven compounds appear to possess the same structure whether obtained from solution or mechanochemically, although in most cases the 1:1 adduct is



Scheme 1. Schematic representation of the relationship between the grinding process and crystallization from solution.

not the only product of the solid–solid process. In the case of **1**·C7, a second phase has been identified (see below), in that single crystals of the two phases could be quantitatively obtained by crystallization, depending on the speed of this latter process. In the case of **1**·C9, while two pure phases were obtained separately, it was not possible to grow single crystals of the second phase, not even by seeding.[18]

The case of compound **1**·C5 is taken as representative of the series of diffraction experiments carried out for all the compounds. Figure 1 shows a comparison of the powder diffraction pattern calculated on the basis of the single-crystal X-ray data and that measured experimentally from the sample obtained by the grinding process, together with the powder patterns of the reagents.

Structural data for all neutral acids are those reported by Boese[17] and were retrieved from the CSD.[19,20] Relevant hydrogen-bonding parameters for all the compounds are listed in Table 1. To assist the assignment of the interactions as O–H···N or $^{(+)}$N–H···O$^{(-)}$, the C–O structural parameters of the groups involved in the interactions are also listed.

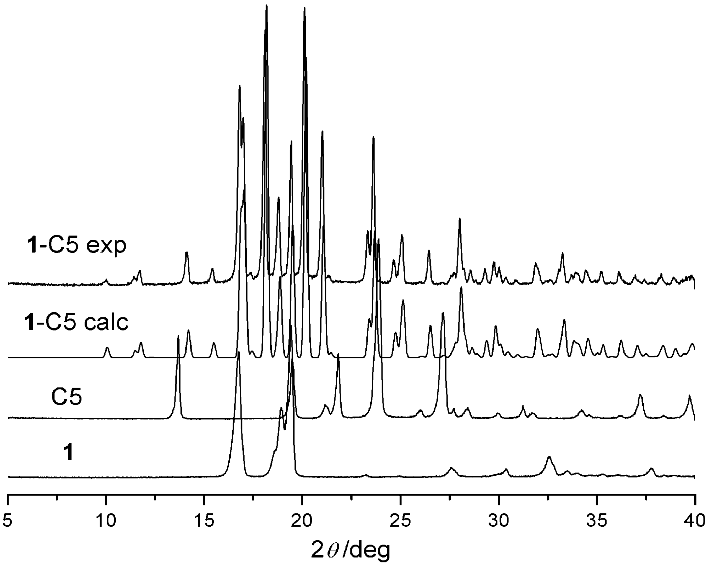


Figure 1. Comparison of the powder diffraction pattern of compound **1**·C5 calculated on the basis of the single-crystal X-ray data with that measured experimentally from the sample obtained by the grinding process, together with the powder patterns of the reagents.

Compound **1**·C3 can be described as consisting of hydrogen-bonded ion pairs (Figure 2), where the monoprotonated $[HN(CH_2CH_2)_3N]^+$ ion forms a charge-assisted $^{(+)}$N–H···O$^{(-)}$ hydrogen bond with the hydrogen malonate anion [N···O 2.703(3) Å]. The remaining OH group forms an intramolecular O–H···O hydrogen bond, which is much shorter [O···O 2.455(3) Å] than the charge-assisted $^{(+)}$N–H···O$^{(-)}$. This observation provides some insight into the relationship between the length of a hydrogen bond and the localization of the ionic charge. Judging purely from the two distances, one gets the impression that the charge is localized on the O-atom forming the intramolecular bond, while the intermolecular one is more likely between a C=O and the N–H$^{(+)}$. It should be mentioned, in passing, that in this crystal, as in all the others of the series, there is a plethora of C-H···O interactions[21] meeting the accepting capacity of the hydrogen-bond acceptors. Although important for the overall stabilization of the crystal structures, these interactions will not be considered in detail.

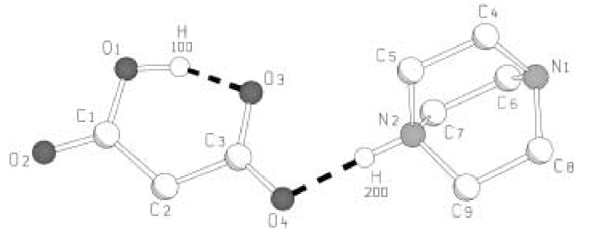


Figure 2. In crystalline **1**·C3, the monoprotonated $[HN(CH_2CH_2)_3N]^+$ cation forms a charge-assisted $^{(+)}$N–H···O$^{(-)}$ hydrogen bond with the hydrogen malonate anion [N···O 2.703(3) Å]. Note the intramolecular O–H···O hydrogen bond [O···O 2.455(3) Å].

The structure of compound **1**·C4 shows the presence of two independent molecules of **1** (one of which shows 80:20 orientational disorder about the N···N axis) and two independent molecules of succinic acid; the units of **1** are inserted into the chains of succinic acid molecules, resulting in chains of alternating units of **1** and the acid [N···O distances in the range 2.556(5)–2.588(4) Å] (Figure 3). Only three of the four hydrogen atoms involved in the interactions could be located (see Experimental Section). To unambiguously characterize the nature of the interactions, the C–O distan-

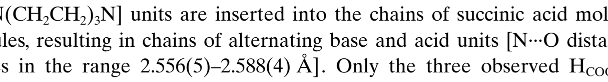


Figure 3. In crystalline **1**·C4, there are two independent molecules of $[N(CH_2CH_2)_3N]$ and two independent molecules of succinic acid; the $[N(CH_2CH_2)_3N]$ units are inserted into the chains of succinic acid molecules, resulting in chains of alternating base and acid units [N···O distances in the range 2.556(5)–2.588(4) Å]. Only the three observed H_{COOH} atoms are shown.

Table 1. Relevant hydrogen-bonding parameters and C–O bond lengths for compounds **1**·C3, **1**·C4, **1**·C5, **1**·C6, **1**·C7, **1**·C8, and **1**·C9 as determined by single-crystal X-ray diffraction analysis.

Compound	N–H···O	O–H···O	C–O	C–O in the pure acids[17]
1·C3	N2···O4 2.703(3)	O1···O3 2.455(3)	C1–O1 1.310(3)	1.285
			C1–O2 1.207(3)	1.221
			C3–O4 1.241(3)	1.290
			C3–O3 1.257(3)	1.232
1·C4	N1···O3 2.558(5)	—	C7–O1 1.184(5)	1.309
	N3···O7 2.588(4)	—	C7–O2 1.289(4)	1.218
	O2···N2 2.556(5)	—	C10–O3 1.278(4)	
	O6···N4 2.559(5)	—	C10–O4 1.196(5)	
			C17–O5 1.213(4)	
			C17–O6 1.273(4)	
			C20–O7 1.306(4)	
			C20–O8 1.188(4)	
1·C5	N2···O2 2.697(3)	O4···O1 2.523(3)	C1–O1 1.255(2)	1.308
			C1–O2 1.242(2)	1.229
			C5–O3 1.202(2)	
			C5–O4 1.310(2)	
1·C6	O2···N1 2.594(5)	—	C1–O1 1.203(5)	1.295
	N2···O4 2.557(5)	—	C1–O2 1.298(5)	1.223
			C6–O3 1.235(5)	
			C6–O4 1.264(5)	
1·C7	O2···N2 2.588(4)	—	C1–O1 1.199(5)	1.299
	N1···O4 2.563(4)	—	C1–O2 1.311(5)	1.234
			C7–O3 1.202(4)	
			C7–O4 1.302(4)	
1·C8	O2···N2 2.595(4)	—	C1–O1 1.202(4)	1.295
	O4···N1 2.571(4)	—	C1–O2 1.286(4)	1.230
			C8–O3 1.192(4)	
			C8–O4 1.285(4)	
1·C9	O1···N1 2.548(3)	—	C1–O1 1.295(4)	1.310
	O4···N2 2.605(3)	—	C1–O2 1.186(3)	1.224
			C9–O3 1.186(3)	
			C9–O4 1.295(3)	

ces had to be considered. As shown in Table 1, the C–O distances are consistent with the presence of three carboxylic groups. The fourth carboxylic group might be subject to some disorder, as the C–O distances are in between those observed for pure COOH groups and deprotonated COO^- groups [C–O 1.213(4), 1.273(4) Å].

The structure of compound **1**·C5 is at variance with the packing of **1**·C4 and, as we will see later, also with the packings of the other acid derivatives with an even number of carbons in the chain. Monodeprotonation of glutaric acid leads to the formation of hydrogen glutarate anions connected through $^{(-)}$O–H···O$^{(-)}$ interactions (Figure 4). The interanion O···O distance of 2.523(3) Å is slightly longer than the distances usually found in crystals of hydrogen dicarboxylate anions, although comparable with the mean value observed for [COOH]···[COO^-] interactions (2.533(3) Å).[11,19] The monoprotonated units of **1** are linked along the side of the anionic chain through $^{(+)}$N–H···O$^{(-)}$ interactions, with an N···O distance of 2.697(3) Å. No interchain linking is observed. The uncoordinated N-acceptor site does not seem to interact with any other donor.

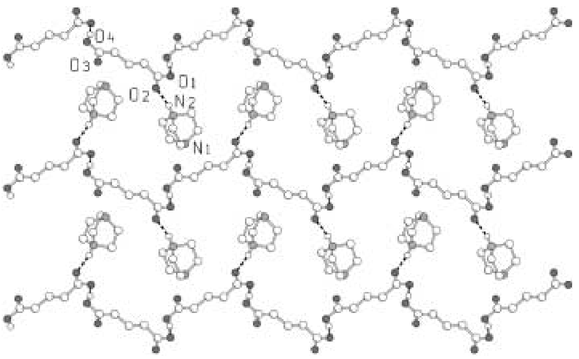


Figure 4. In crystalline **1**·C5, monodeprotonation of glutaric acid leads to the formation of chains of hydrogen glutarate anions joined by $^{(-)}$O–H···O$^{(-)}$ interactions [2.523(3) Å]. The monoprotonated base units are linked along the side of the anionic chain through N–H$^{(+)}$···O$^{(-)}$ interactions of 2.697(3) Å.

The structure of the product of the reaction of **1** and adipic acid, **1**·C6, is shown in Figure 5. The A/B/A/B alternation observed in **1**·C4 is restored on going to adipic acid; the unit of **1** is inserted into the original chains of acid mole-

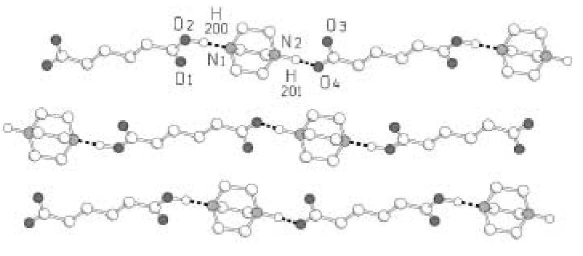


Figure 5. In crystalline **1**·C6, A/B/A/B alternation is observed, as in the case of **1**·C4. Monoprotonated base units and hydrogen adipate anions are held together along the chains by two types of hydrogen bonds, a short one involving the protonated N–H group and the deprotonated COO^- group [N···O 2.557(5) Å], and a longer one involving the protonated carboxylic group [N···O 2.594(5) Å].

cules, and no interchain linking is observed. In terms of hydrogen bonds, the situation is not much different from that shown in Figure 2. However, judging from the X-ray data and from the information that could be obtained from the experimental Fourier map, the compound can be described as a salt, as proton transfer from a carboxylic group to an adjacent nitrogen atom along the chain is observed. This is in agreement with the solid-state NMR data (see below). Units of monoprotonated **1** and hydrogen adipate anions are held together along the chains by two types of hydrogen bonds, a short one involving the protonated N–H group and the deprotonated $\mathrm{COO^-}$ group [N···O 2.557(5) Å] and a longer one involving the protonated carboxylic group [N···O 2.594(5) Å]. Both the metrics of the $\mathrm{COO^-/COOH}$ groups and the difference in the N···O distances confirm that the negative charge is essentially localized on the carboxylate group.

The product of the reaction of **1** with pimelic acid, **1**·C7, is an extremely hygroscopic material: in order to collect single-crystal data, the crystal of **1**·C7 had to be immersed in oil and cooled to 230 K. The same behaviour was observed with the mechanochemically prepared powder used for X-ray diffraction, though it was possible to measure the powder pattern in air at room temperature. A series of X-ray powder diffraction measurements showed that the grinding experiment only leads to formation of the 1:1 adduct, **1**·C7, although traces of unreacted acid were also detectable. When the reaction is conducted in solution, however, the nature of the crystalline material varies according to the crystallization conditions. Slow crystallization yields only crystals of **1**·C7, while rapid removal of the solvent in a rotary evaporator leads to the formation of a mixture of the 1:1 adduct and a 3:2 (three pimelic acid moieties to two base **1** units) adduct.[22]

Compound **1**·C9 is also hygroscopic, though not as severely as compound **1**·C7. The mechanochemical product was found to consist of **1**·C9, even though the powder diffractogram also showed the presence of an unidentified phase and of some unreacted acid.

In terms of crystal structure, compounds **1**·C7, **1**·C8, and **1**·C9 share the same features: the reaction with the base **1** leads to the insertion of units of **1** in between acid molecules, with the formation of chains of the A/B/A/B type similar to those observed for **1**·C4 and **1**·C6. However, contrary to these latter compounds, proton transfer does not seem to take place and the adducts formed by **1** with pimelic, suberic, and azelaic acids ought to be described as co-crystals on the basis of the diffraction data. The structural features are shown in Figure 6, Figure 7, and Figure 8, respectively. In terms of N···O distances, one may note the values of 2.588(4) and 2.563(4) Å in **1**·C7, and of 2.595(4) and 2.571(4) Å in **1**·C8. In compound **1**·C9, on the other hand, one of the two hydrogen atoms along the chain is located almost at the midpoint of the shorter of the two N···O bonds [N···O 2.548(3) Å], while in the longer N···O hydrogen bond [2.605(3) Å] the hydrogen atom is closer to the oxygen of the carboxylic group.

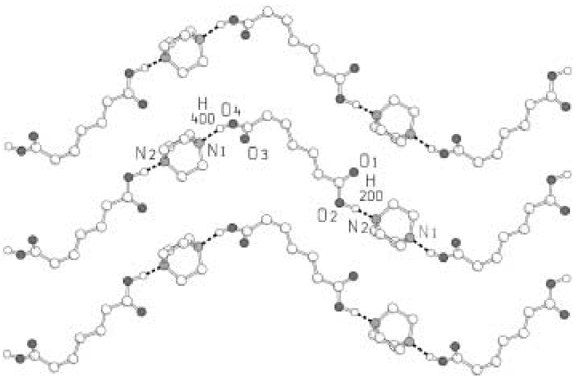


Figure 6. In crystalline **1**·C7, the A/B/A/B sequence generates a wavy pattern. The N···O distances are 2.588(4) and 2.563(4) Å, respectively.

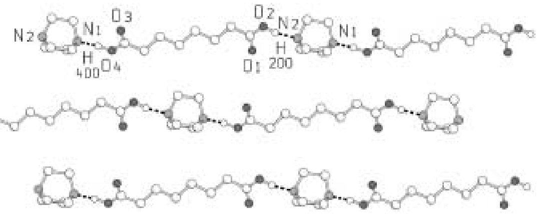


Figure 7. In crystalline **1**·C8, the A/B/A/B sequence generates a straight linear pattern (compare with Figure 4). The N···O distances are 2.595(4) and 2.571(4) Å, respectively.

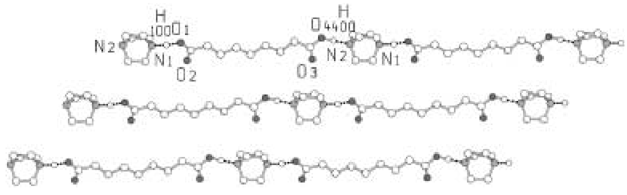


Figure 8. In crystalline **1**·C9, the A/B/A/B sequence generates a straight linear pattern as in the cases of **1**·C4, **1**·C6, and **1**·C8. Note how one of the two hydrogen atoms along the chain is located almost midway along the shorter of the two N···O bonds [N···O 2.548(3) Å], while in the longer distance N···O hydrogen bond [2.605(3) Å] the hydrogen atom is closer to the oxygen of the carboxylic group.

Hydrogen bonding interactions and melting points: Table 1 shows that all N···O distances within the N···H···O interactions in **1**·C4, **1**·C6, **1**·C7, **1**·C8, and **1**·C9 fall within a narrow range [2.548(3)–2.605(3) Å], *irrespective of the ionic or neutral nature of the interaction*s. To put this observation into context, the CSD has been searched for neutral COOH···N and $\mathrm{COO^{(-)}\cdots HNR_3^{(+)}}$ interactions (where N bears three singly-bonded carbon atoms); the results are shown in the histograms of Figure 9.

On comparing the two distributions, it can be seen that the location of the charge has no appreciable effect on this type of interaction. This is at variance with cases of charge assistance involving amines, amides, and bis(amidine)s,[23] which show a marked shortening of the N···O distances when the N atom is loaded with a proton transferred from a carboxylic group. It may also be noted that the N···O separations in compounds **1**·C4, **1**·C6, **1**·C7, **1**·C8, and **1**·C9 fall on the short side of the histograms, thus representing cases of very short N···O hydrogen bonds.

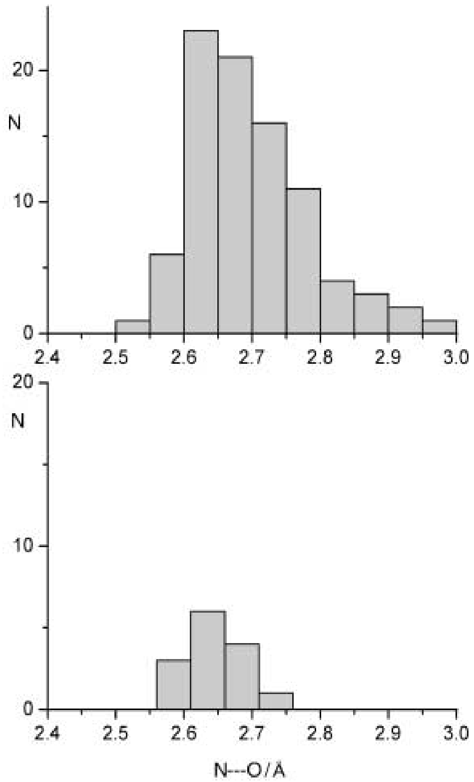


Figure 9. Comparison of the distributions of N···O distances for (top histogram) neutral $\mathrm{COO^{(-)}\cdots HNR_3^{(+)}}$ and (bottom histogram) COOH···N interactions (the N atom bears three singly-bonded carbon atoms).

N···O distances are appreciably longer in compounds **1**·C3 and **1**·C5 than in all the other compounds [2.703(3) and 2.697(3) Å for **1**·C3 and **1**·C5, respectively]. The reason for this lies in the presence of a $\mathrm{COOH\cdots{}^{(-)}OOC}$ intramolecular interaction within the malonate anion in **1**·C3, and in the presence of a chain of hydrogen-bonded glutarate anions in **1**·C5, that is, in a competition for the use of the hydrogen-bonding acceptor $\mathrm{COO^{(-)}}$ group. Similar considerations apply to most observations on the right-hand side of the top histogram.

The behaviour with respect to proton transfer is thus an intriguing feature of this class of compounds. Even though there is no appreciable difference in N···O distances between salts and co-crystals, it seems that the lighter acids (with an ambiguity in the case of compound **1**·C6, but see below) tend to protonate **1**, while the heavier acids do not. Cases of proton retention are known, and even some cases in which both situations are observed (see Conclusion). For instance, we have reported that the organometallic zwitterion $[\mathrm{Co^{III}}(\eta^5\text{-}\mathrm{C_5H_4COOH})(\eta^5\text{-}\mathrm{C_5H_4COO})]$ reacts with formic acid vapour to yield crystalline $[\mathrm{Co^{III}}(\eta^5\text{-}\mathrm{C_5H_4COOH})(\eta^5\text{-}\mathrm{C_5H_4COO})]\cdot[\mathrm{HCOOH}]$. Both the C–O distances within the HCOOH moiety and ^{13}C CPMAS NMR data indicate that the formic acid molecule retains its acidic hydrogen.[24]

The saltlike or co-crystal nature of the adducts does not correlate with the melting points of the solid materials. The melting temperatures of compounds **1**·C3 to **1**·C9, determined by DSC measurements on pure samples, are shown in Figure 10. The melting points of the corresponding dicarboxylic acids are also shown for comparison. The alternation of melting points depending on the even or odd number of carbon atoms is a well-known fact, which has recently been rationalized by Boese et al.[17] on the basis of twist and non-twist molecular conformations of odd- and even-numbered chains, respectively.

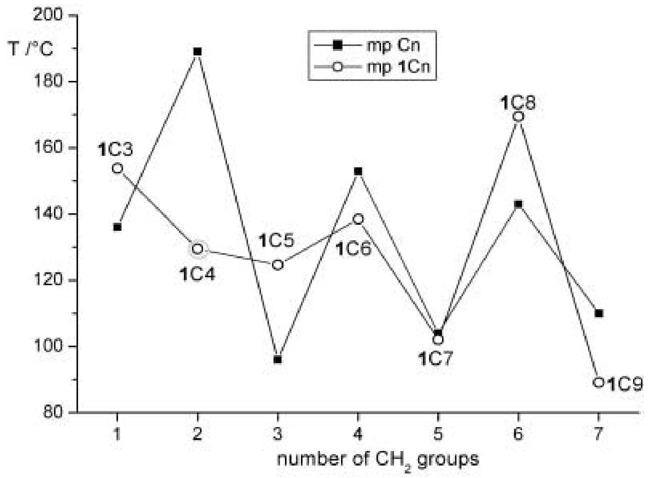


Figure 10. Comparison between melting point alternation of dicarboxylic acids and of the **1**·C3 to **1**·C9 adducts. The melting points of **1**·C7 and **1**·C9 refer to the pure 1:1 adducts. [Note that the melting point of **1**·C4, though reported in the plot, actually corresponds to the melting point of an uncharacterized form, resulting from two subsequent and very close phase transition processes].

However, in the case of compounds **1**·C3 to **1**·C9, one might have expected possible differences to be correlated with the ionic or molecular nature of the crystals rather than with the length of the carbon atom chains. Figure 10 shows that, while there is no relationship with the extent of proton transfer, the melting points roughly follow an alternating trend reminiscent of that of the parent acids. This is quite surprising in view of the great differences in packing arrangements within the family **1**·C3 to **1**·C9. Unfortunately, the melting point data set for **1**·C3 to **1**·C9 is incomplete, since the melting point temperature of the structurally determined **1**·C4 phase could not be obtained. Repeated DSC measurements on pure **1**·C4 showed that the compound undergoes two very close solid–solid phase transitions (at 57 and 62 °C) to a high-temperature phase that melts at 130 °C. It is worth noting, however, that crystalline **1**·C4 shows the presence of disorder involving one of the two independent units of **1** (see Experimental Section). Even though further studies are necessary to clarify this behaviour, it seems that the two phase transitions might be associated with the onset of a rotational motion involving the units of base **1**.

Solid-state NMR investigation of the protonation state: Solid-state ^{13}C NMR studies of protonated and deprotonated carboxylates in amino acids have shown that the orientation and values of the principal elements of the nuclear shielding tensor (δ_{11}, δ_{22}, δ_{33}) change significantly with the protonation state of the carboxylic groups.[25] Several studies dealing with this approach have been published[26] and the topic has been reviewed by Veeman.[27]

The change in magnitude and orientation of the chemical shift associated with the localization of the intermolecular hydrogen bond may represent a possible tool in assigning the protonation or deprotonation state of carboxylic groups if one considers the following points:

1) δ_{11} lies in the plane of symmetry of the group and, in the case of carboxylate, is directed along the C–C axis (or bisector of the O–C–O angle), while for the carboxylic acid is directed perpendicularly to the C=O moiety. This element is a nice indicator of the degree of protonation of the acid, and changes from 242 ± 4 ppm (deprotonated form) to 257 ± 4 ppm (protonated form) in the case of amino acids;[25]
2) δ_{22}, perpendicular to δ_{11} in the plane containing the carbon and oxygen atoms, is the most sensitive parameter with values in the range of 177 ± 10 ppm for the deprotonated form and 155 ± 20 ppm for the protonated form;[25]
3) δ_{33}, the most shielded tensor, is perpendicular to the plane of symmetry of the group, and is usually not very sensitive to the structural changes neither to the O–H···O distance;
4) δ_{iso} (where $\delta_{iso} = (\delta_{11} + \delta_{22} + \delta_{33})/3$) shows a reproducible increase in shielding upon protonation, but unfortunately this information is intrinsically limited by the fact that the changes in δ_{11} and δ_{22} are in opposite directions, while δ_{33} is not particularly influenced.

It is also interesting to consider the difference between δ_{11} and δ_{22}, since this parameter represents a reliable indicator of the relative delocalization of the π charge between the two C–O bonds. As the proton moves away from the oxygen atom, the lengths of the two C–O bonds move towards similar values, increasing the delocalization of the π electrons; (δ_{11}–δ_{22}) shows values of around 131 ppm for the COOH group and of around 34 ppm for the COO^- group in the reported examples of amino acids[25].

The principal values of the chemical shift tensor were extracted by computer simulation of the spectrum obtained at low speeds by using the Herzfeld–Berger method[28].

As an example, the ^{13}C CPMAS NMR spectrum (carboxylic region) of **1**·C5 recorded at a spinning speed of 1160 Hz is depicted in Figure 11: the computer simulation of the pattern associated with the isotropic peak at $\delta = 176.5$ ppm affords the three components of the chemical shift tensors ($\delta_{11} = 256.4$, $\delta_{22} = 167.1$, $\delta_{33} = 105.9$ ppm), which can be readily assigned to a COOH group that forms an O–H···O bond with another acid molecule. On the other hand, the chemical shift tensor components found for the peak at $\delta = 181.8$ ppm ($\delta_{11} = 238.1$, $\delta_{22} = 198.3$, $\delta_{33} = 109.1$ ppm) indicate the presence of a carboxylate group bonded to **1**. In the aliphatic region (not shown in Figure 11), the presence of four resonances assigned to the CH_2 of **1** ($\delta = 45.7$ and $\delta = 44.0$ ppm) and to the CH_2 of the dicarboxylic acid ($\delta = 34.9$ and $\delta = 21.4$ ppm), respectively, is in agreement with two different environments for the interaction of the carboxylic groups. The chemical shifts of the ^{13}C resonances and the values of the tensor components of the carboxylic groups of the seven adducts are reported in Table 2.

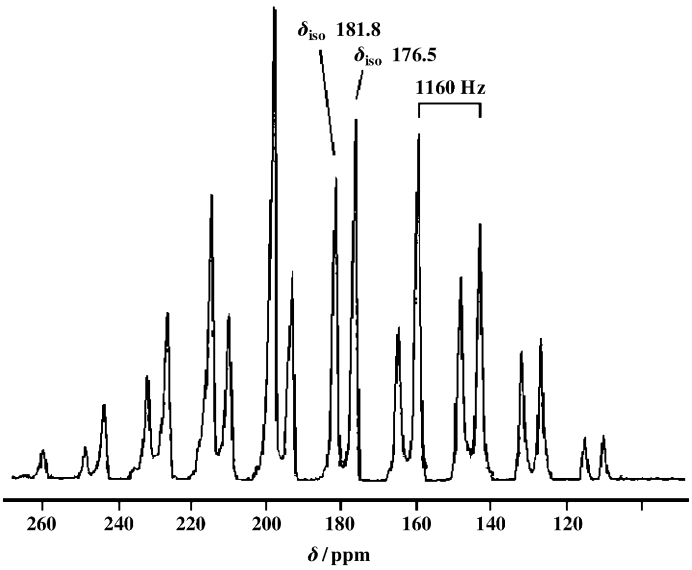


Figure 11. ^{13}C CP-MAS NMR spectrum (carboxylic region) of **1**·C5, recorded at 67.94 MHz at a spinning speed of 1160 Hz.

Table 2. Chemical shift for compounds **1**·C3 to **1**·C9 and tensor elements for carboxyl groups.

Compound	δ_{iso} [ppm]	δ_{11} [ppm]	δ_{22} [ppm]	δ_{33} [ppm]
1·C3	178.8 (COO···HN)	240.7	186.8	108.8
	174.1 (COOH···O)	250.7	166.1	105.4
	CH_2 base: 45.0			
	CH_2 acid: 38.5			
1·C4	175.8 (COOH···N)	252.1	161.5	113.8
	CH_2 base: 44.7			
	CH_2 acid: 31.1			
1·C5	181.8 (COO···HN)	238.1	198.3	109.1
	176.5 (COOH···O)	256.4	167.1	105.9
	CH_2 base: 45.7, 44.0			
	CH_2 acid: 34.9, 21.4			
1·C6	177.0 (COOH···N)	253.2	160.5	117.1
	CH_2 base: 44.3			
	CH_2 acid: 35.4, 27.3, 24.4			
1·C7	177.4 (COOH···N)	251.3	159.4	121.5
	CH_2 base: 44.4			
	CH_2 acid: 35.4, 31.4, 25.2, 24.0			
1·C8	176.5 (COOH···N)	251.4	160.3	117.9
	CH_2 base: 45.1			
	CH_2 acid: 35.7, 31.9, 27.2			
1·C9	176.4 (COOH···N) 248.7	159.7	120.8	
	181.0[a]			
	179.0[b]			
	CH_2 base: 44.7			
	CH_2 acid: 37.5, 35.9, 33.9, 33.2, 31.1, 29.9, 25.2			

[a] Unreacted acid. [b] Uncharacterized phase.

Compounds **1**·C4, **1**·C7, and **1**·C8 exhibit approximately the same δ_{11} and δ_{22} values, and they are in agreement with the values reported in the literature for COOH groups.[25] **1**·C3 shows two isotropic resonances in the carboxylic region, which can be readily assigned to an intramolecular O–H···O bond for the protonated group ($\delta = 174.1$ ppm) and an intermolecular N–H···O bond for the deprotonated carboxyl signal at lower field ($\delta = 178.8$ ppm). The ^{13}C

CPMAS NMR spectrum of **1**·C9 (Figure 12) shows three isotropic peaks in the carboxylic region at $\delta = 176.4$, 179.0, and 181.0 ppm, attributable to the known **1**·C9, to an unidentified product, and to unreacted azelaic acid, respectively, in agreement with the powder X-ray data. The δ_{11} and δ_{22} values obtained for the most intense resonance ($\delta = 176.4$) allow the characterization of the known phase as a molecular co-crystal without proton transfer, whereas the partial overlapping of the two smaller peaks ($\delta = 179.0$ and 181.0 ppm) prevents an exact evaluation of the three components of the nuclear shielding for the second unidentified resonance.

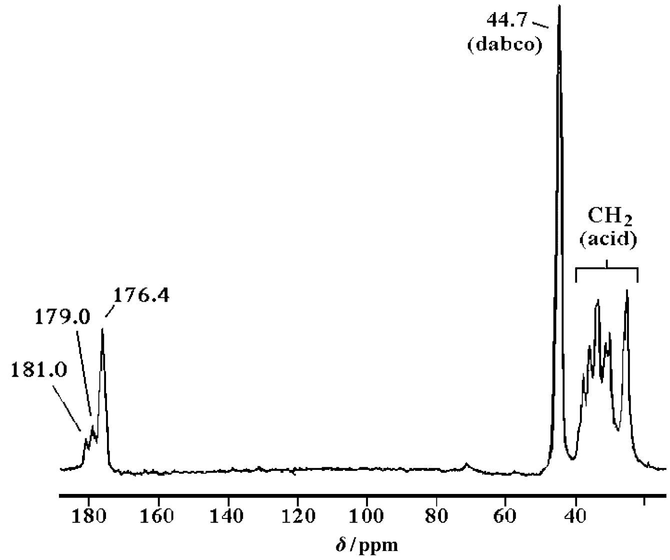


Figure 12. ^{13}C CP-MAS NMR spectrum of **1**·C9 (67.94 MHz) obtained at 7100 Hz.

A discrepancy between the NMR and X-ray data is found in the case of **1**·C6. The ^{13}C NMR spectrum shows only one peak at $\delta = 177.0$ ppm, while from the X-ray structure one would expect the presence of two signals due to the two different environments. This behaviour probably arises because the carboxylic protons are viewed as being in a dynamic situation on the NMR time scale, but rigid when observed by X-ray techniques.

Figure 13 displays the tensor elements for **1**·C3, **1**·C4, **1**·C5, **1**·C7, **1**·C8, and **1**·C9 (main phase) as a function of the difference between the C–O and C═O bond lengths obtained from the crystallographic data for each compound. It should be noted that there are eight signals because two different signals for the carboxylic groups were found for **1**·C3 and **1**·C5. Examination of the dependence of tensor elements as a function of this structural parameter shows that the data are in nice agreement with the diffraction study and the previously published trends. Moreover, by solid-state NMR techniques, it is possible to define **1**·C4, **1**·C7, **1**·C8, and **1**·C9 as molecular co-crystals (no proton transfer), while **1**·C3 and **1**·C5 can be classified as ionic crystals (proton transfer). The occurrence of proton transfer does not seem to be associated with the solid-state reactions, since NMR measurements carried out on ground single crystals (obtained from solvents) and on mechanochemical products yielded the same results.

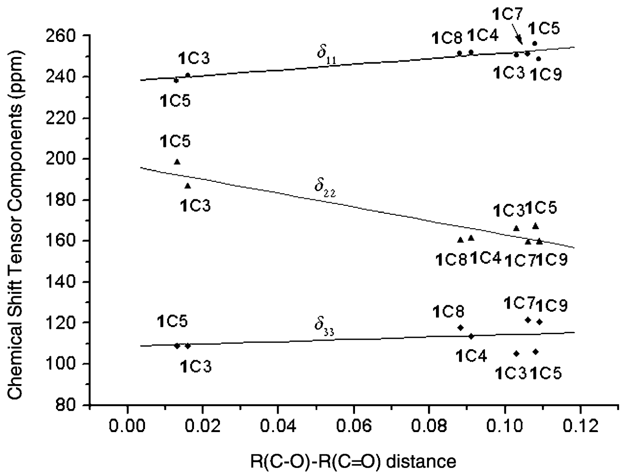


Figure 13. Chemical shift tensor components for compounds **1**·C3, **1**·C4, **1**·C5, **1**·C7, **1**·C8, and **1**·C9, plotted as a function of the difference between C–O and C═O bond lengths obtained from the crystallographic data.

Although there is a some spread in the δ_{11}, δ_{22}, and δ_{33} values among the deprotonated and protonated forms, there is a remarkable agreement between NMR and crystallographic data if one considers the well-separated regions of the plot in which the carboxylic and carboxylate groups fall. This is also more evident if the $\delta_{11}-\delta_{22}$ values are reported as a function of the difference between the C–O and C═O bond lengths obtained from the crystallographic data, as shown in Figure 14.

Again, we have found the usual bimodal distribution for the protonated and deprotonated forms. A similar trend can also be obtained if one compares the δ_{22} values with the O···N distance in **1**·C3, **1**·C4, **1**·C5, **1**·C7, **1**·C8, and **1**·C9 (main phase) (see Supporting Information): δ_{22} values shift linearly downfield with increasing O···N distance. It is worth noting that an opposite trend has recently been found by

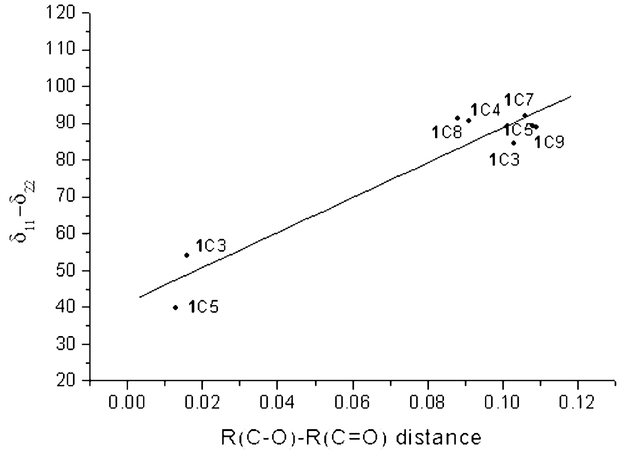


Figure 14. Difference between δ_{11} and δ_{22} for compounds **1**·C3, **1**·C4, **1**·C5, **1**·C7, **1**·C8, and **1**·C9, plotted as a function of the difference between C–O and C═O bond lengths obtained from the crystallographic data.

Ando and co-workers in peptides involved in hydrogen bonding.[29] However, in their case the groups involved were the amide C=O and the amide N–H. The lack of a precise location of the hydrogen atom by neutron diffraction data prevented further correlation between the structural parameters and the chemical shielding tensors obtained by solid-state NMR spectroscopy.

Conclusion

In this study we have investigated the formation of the acid–base adducts **1**·C3 to **1**·C9 between dicarboxylic acids of variable carbon chain length (from three to nine) and the base 1,4-diazabicyclo[2.2.2]octane. All compounds have been obtained by both solid–solid grinding and by crystallization from solutions in ethanol. Crystallization from solvents has allowed the determination of the single-crystal X-ray structures of **1**·C3 to **1**·C9, which, in turn, have been used to identify the mechanochemical products by comparing calculated and measured X-ray powder diffractograms. Melting points for all species (with the caveat mentioned for compound **1**·C4) have been measured by DSC. The carbon chemical shift tensors of the COOH group obtained from the sideband intensity of low speed spinning NMR spectra have been used to assess the protonation state of the products.

The results of single-crystal X-ray structure determinations have allowed the identification of two major supramolecular motifs, namely the A/B/A/B chain whereby the base is inserted into the carboxylic chain of the parent diacid, and the A/A/A/A chain with lateral bonds to the base B. In all cases, the interaction between A and B implies hydrogen bonds of the O···H···N type; whether the proton remains on the donor O-atom or is transferred to the acceptor N-atom, or adopts an intermediate geometry, is difficult to establish with confidence on the basis of the X-ray diffraction data. We have shown that this issue can be successfully addressed by measuring the carbon chemical shift tensors of the COOH group from the sideband intensity of low speed spinning solid-state NMR spectra, which resolve the crystallographic ambiguities regarding the H-atom positions.

In fact, on the basis of the diffraction data, compounds **1**·C3, **1**·C5, and **1**·C6 ought to be described as salts (that is, proton transfer from the acid to the base has occurred), whereas **1**·C4, **1**·C7, **1**·C8, and **1**·C9 are better described as co-crystals (that is, no proton transfer has occurred). When this information is evaluated in the light of the solid-state NMR experiments, we find that there is substantial agreement between the results of the two techniques, except in the case of compound **1**·C6, which probably shows proton motion on the NMR time scale.

This correlation may be useful in studies of ionic hydrogen bonds because it is often necessary to know whether or not proton transfer from a donor to an acceptor has occurred. What is more, the proton transfer process along a hydrogen bond, whether associated with a phase transition or not, may imply the transformation of a molecular crystal into a molecular salt. Wilson[30] has discussed, on the basis of an elegant neutron diffraction study, the migration of the proton along an O–H···O bond in a co-crystal of urea and phosphoric acid (1:1), whereby the proton migrates towards the mid-point of the hydrogen bond as the temperature is increased, becoming essentially centred at $T = 335$ K. Mootz and Wiechert,[31] on the other hand, have isolated two crystalline materials composed of pyridine and formic acid having different compositions. In the 1:1 co-crystal, the formic acid molecule retains its proton and transfer to the basic N atom on the pyridine does not take place (hence molecules are linked by neutral O–H···N interactions). In the 1:4 co-crystal, however, one formic acid molecule releases its proton to the pyridine molecule establishing $^{(+)}$N–H···O interactions. Many analogous situations that may be encountered in crystal engineering studies of hydrogen-bonded systems may be better appreciated if a combination of X-ray diffraction analysis and solid-state NMR experiments were to be used.

Incidentally, it is worth noting that the melting points of compounds **1**·C3 to **1**·C9, investigated in this work, do not correlate with the salt-like or co-crystal nature of the adducts, but rather with the even- or odd-numbered carbon chain length, in spite of the substantial differences in supramolecular arrangements in the crystals of the adducts with respect to those of the parent diacids, for which melting point alternation is a well-known and rationalized phenomenon.

Experimental Section

General: All reactants were purchased from Aldrich and were used without further purification. Reagent grade solvents and doubly-distilled water were used. In all cases, correspondence between the structure of the solid residue and that obtained by single-crystal X-ray diffraction was ascertained by comparing measured X-ray powder diffractograms with those calculated on the basis of the single-crystal experiments.

Solid-state syntheses: All the adducts were prepared by solid-state synthesis. Equimolar quantities of **1** and the dicarboxylic acid were manually ground in an agate mortar. The 1:1 adduct could always be easily identified in the reaction mixture, although in most cases the X-ray powder diffractogram showed the presence of varying amounts of additional products and/or traces of unreacted acid.

Solution synthesis of 1·[HOOC(CH$_2$)$_n$COOH] ($n = 1$–7):

1·C3: Malonic acid, HOOC(CH$_2$)COOH, (520 mg, 5 mmol), was dissolved in 99% EtOH (25 mL), and then **1** (560 mg, 5 mmol) was added. The suspension was stirred at 50 °C until complete dissolution. The solution was allowed to cool slowly to room temperature overnight, yielding colourless crystals of **1**·C3 suitable for X-ray diffraction analysis.

1·C4: Succinic acid, HOOC(CH$_2$)$_2$COOH, (590 mg, 5 mmol), was dissolved in 99% EtOH (25 mL), and then **1** (560 mg, 5 mmol) was added. The suspension was stirred at 50 °C until complete dissolution. The solution was allowed to cool slowly to room temperature overnight, yielding colourless crystals of **1**·C4 suitable for X-ray diffraction analysis.

1·C5: Glutaric acid, HOOC(CH$_2$)$_3$COOH, (1.33 g, 10 mmol), was dissolved in 99% EtOH (25 mL), and then **1** (1.12 g, 10 mmol) was added. The suspension was stirred at 50 °C until complete dissolution. The solution was allowed to cool slowly to room temperature overnight, yielding colourless crystals of **1**·C5 suitable for X-ray diffraction analysis.

1·C6: Adipic acid, HOOC(CH$_2$)$_4$COOH, (1.46 g, 10 mmol), was dissolved in 99% EtOH (25 mL), and then **1** (1.12 g, 10 mmol) was added. The suspension was stirred at 50 °C until complete dissolution. The solution was allowed to cool slowly to room temperature overnight, yielding colourless crystals of **1**·C6 suitable for X-ray diffraction analysis.

1·C7: Pimelic acid, HOOC(CH_2)$_5$COOH, (1.60 g, 10 mmol), was dissolved in 99% EtOH (25 mL) and then **1** (1.12 g, 10 mmol) was added. The suspension was stirred at 50 °C until complete dissolution. The solution was allowed to cool slowly to room temperature overnight, yielding colourless crystals of **1**·C7 suitable for X-ray diffraction analysis.

1·C8: Suberic acid, HOOC(CH_2)$_6$COOH, (1.74 g, 10 mmol), was dissolved in EtOH (25 mL), and then **1** (1.12 g, 10 mmol) was added. The suspension was stirred at 50 °C until complete dissolution. The solution was allowed to cool slowly to room temperature overnight, yielding colourless crystals of **1**·C8 suitable for X-ray diffraction analysis.

1·C9: Azelaic acid, HOOC(CH_2)$_7$COOH, (1.88 g, 10 mmol), was dissolved in 99% EtOH (25 mL), and then **1** (1.12 mg, 10 mmol) was added. The suspension was stirred at 50 °C until complete dissolution. The solution was allowed to cool slowly to room temperature overnight, yielding colourless crystals of **1**·C9 suitable for X-ray diffraction analysis.

Crystal structure determination: Crystal data of all the compounds were collected on a Nonius CAD4 diffractometer equipped with an Oxford Cryostream liquid-N_2 device. Crystal data and details of the measurements are summarized in Table 3. For all of the compounds, graphite-monochromated $Mo_{K\alpha}$ radiation, $\lambda = 0.71073$ Å, was used. SHELX97[32a] was used for structure solution and refinement based on F^2. Non-hydrogen atoms were refined anisotropically. Hydrogen atoms bound to carbon atoms were placed in calculated positions. All H_{COOH} and H_{NH} atoms in **1**·C3, **1**·C5, **1**·C7, **1**·C8, and **1**·C9 were located and refined, while in **1**·C6 they were located, but not refined; in compound **1**·C4, only three of the four H_{COOH} atoms were located, and were not refined. SCHAKAL99[32b] was used for the graphical representation of the results. The program PLATON[32b] was used to calculate the hydrogen-bonding interactions reported in Table 2.

For all the compounds discussed in this paper, powder diffractograms were measured from the samples obtained by grinding or milling. These diffractograms were compared with those calculated on the basis of the structures determined by single-crystal X-ray diffraction analysis, as described above. The diffraction patterns of solid 1,4-diazabicyclo[2.2.2]octane and of all the acids were also measured in order to check whether the reaction was quantitative.

CCDC-205687–CCDC-205693 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336033; or e-mail: deposit@ccdc.cam.ac.uk).

Solid-state NMR measurements: All spectra were recorded on a Jeol GSX 270 spectrometer equipped with a Doty probe operating at 67.8 MHz for ^{13}C NMR and at 270 MHz for ^{1}H NMR. A standard cross-polarization pulse sequence was used, with a contact time of 3.5 ms, a 90° pulse of 4.5 µs, recycle delays of 10 s, and 600–2000 transients. All spectra were recorded at room temperature at different spinning speeds. Cylindrical 6 mm o.d. zirconia rotors with a sample volume of 120 µL were employed. For all samples, the magic angle was carefully adjusted from the ^{79}Br spectrum of KBr by minimizing the linewidth of the spinning sideband satellite transitions. The principal components of the chemical shift tensors were extracted by computer simulation (HBA-graphical Herzfeld-Berger analysis, written by K. Eichele) of the spinning sideband patterns obtained at low speed using the algorithm developed by Herzfeld and Berger.[28] The errors in the evaluation of the chemical shift tensor were estimated to be less than 4 ppm by repeating the calculation at different spinning speeds.

Acknowledgements

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Table 3. Crystal data and details of measurements for compounds **1**·C3 to **1**·C9.

compound	**1**·C3	**1**·C4	**1**·C5	**1**·C6	**1**·C7	**1**·C8	**1**·C9
formula	$C_9H_{16}N_2O_4$	$C_{10}H_{18}N_2O_4$	$C_{11}H_{20}N_2O_4$	$C_{12}H_{22}N_2O_4$	$C_{13}H_{24}N_2O_4$	$C_{14}H_{26}N_2O_4$	$C_{15}H_{28}N_2O_4$
M_r	216.24	230.26	244.29	258.32	272.34	286.37	300.39
T [K]	293	293	293	293	203	233	233
system	monoclinic	monoclinic	monoclinic	triclinic	orthorhombic	monoclinic	monoclinic
space group	$P2_1/c$	$P2_1/c$	$P2_1/n$	$P\bar{1}$	$P2_12_12_1$	$P2_1/n$	$P2_1/c$
a [Å]	8.374(3)	6.763(2)	10.275(4)	7.045(1)	6.710(1)	10.462(5)	6.982(2)
b [Å]	12.434(3)	35.198(9)	12.456(3)	9.000(3)	8.255(2)	15.833(5)	8.598(2)
c [Å]	10.710(2)	9.856(7)	10.681(5)	11.456(2)	27.250(6)	10.617(3)	28.148(6)
α [°]	90	90	90	84.80(2)	90	90	90
β [°]	112.31(2)	101.52(4)	113.88(3)	74.12(2)	90	118.24(3)	93.00(2)
γ [°]	90	90	90	78.26(2)	90	90	90
V [Å^3]	1031.7(5)	2299(2)	1250.0(8)	683.5(3)	1509.4(5)	1549(1)	1687.4(7)
Z	4	8	4	2	4	4	4
$\mu(Mo_{K\alpha})$ [mm^{-1}]	0.110	0.103	0.099	0.094	0.088	0.089	0.085
$2\theta_{max}$/°	50	50	50	50	50	50	50
measured reflns.	1914	4217	2316	2527	1551	2874	3005
unique reflns.	1809	3984	1399	2398	1504	2721	2940
refined parameters	145	315	163	163	181	190	198
GoF on F^2	0.993	0.875	1.010	1.031	0.998	1.000	1.014
$R1$ [on F, $I > 2\sigma(I)$]	0.0357	0.0690	0.0392	0.0755	0.0554	0.0533	0.0550
$wR2$ (on F^2, all data)	0.1092	0.2356	0.1197	0.2455	0.1564	0.1782	0.1751

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