L-Proline 2,5-Dihydroxybenzoic Acid (1/1): A Zwitterion Co-crystal

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The crystal structure of L-proline 2,5-dihydroxybenzoic acid (1/1) (as determined by single-crystal X-ray diffraction), a rare example of a hydrogen-bonded, zwitterion co-crystal with non-linear optical properties, is reported. The colourless crystals are orthorhombic with $a = 5.896(2)$, $b = 11.486(1)$, $c = 18.016(3)$ Å, $Z = 4$, space group $P2_12_12_1$. The complex hydrogen-bond network within the structure is discussed in detail, and the possibilities of using such a material as a model system for theoretical and experimental investigations of hydrogen bonding are addressed.

Most organic crystalline materials can be conveniently grouped together according to the nature of the individual building blocks within the material, *viz.*, molecular solids, salts, co-crystals or zwitterionic compounds. Here we present the crystal structure of a rare example of a newly recognized type of crystalline solid — a co-crystal between a zwitterion (L-proline) and a neutral molecule (2,5-dihydroxybenzoic acid) — a class of materials that we have termed 'zwitterion co-crystals'.

L-Proline 2,5-dihydroxybenzoic acid (1/1), displays second harmonic generation (SHG) comparable to that of α-quartz (as measured by standard powder techniques[1]), and we are currently examining a series of related zwitterion co-crystals for their non-linear optical properties. In each of these co-crystals, one, or both, of the components is chiral, and the neutral component has significant polarizability. To date, we are aware of the crystal structures of only three zwitterion co-crystals incorporating an amino acid; glycine 1,3,5-benzenetricarboxylic acid (1/1) monohydrate,[2] L-glutamine L-pyroglutamic acid (1/1) monohydrate,[3] and L-serine L-ascorbic acid (1/1),[4] two of which are hydrates.

We have previously reported on the development of several novel SHG-active salts with a wide range of desirable chemical and physical properties.[5–7] However, L-proline 2,5-dihydroxybenzoic acid (1/1) comprises a chemical system which, apart from exhibiting non-linear optical properties (guaranteed when one component is chiral), can provide enhanced insight into the nature of hydrogen bonding itself.

Experimental

Synthesis. L-Proline 2,5-dihydroxybenzoic acid (1/1) was prepared by treating equimolar quantities of L-proline (Pro) with 2,5-dihydroxybenzoic acid (dhbaH) in methanol. The product was recrystallized from an aqueous solution to yield translucent, colourless crystals. M.p. 192–193 °C (decomp.). Found: C, 53.2; H, 5.4; N, 5.1%. Calc. for $C_{12}H_{15}NO_6$: C, 53.50; H, 5.57; N, 5.20%.

Structure determination. Data were collected, using a colourless crystal (ca. $0.3 \times 0.25 \times 0.2$ mm), on an Enraf-Nonius CAD4 diffractometer fitted with a cold dinitrogen stream, low temperature attachment, in the θ–2θ mode, with $\Delta\theta = [0.8 + 0.35 \tan(\theta)]°$ and a maximum scan time of 1 min. Cell parameters were obtained from 25 unique reflections. A total of 1284 reflections were measured for $2 < \theta < 25°$ and $+h + k + l$, and 973 unique reflections with $|F^2| > 3\sigma(F^2)$ were used in the refinement, where $\sigma(F^2) = [\sigma^2(I) + (0.04I)^2]^{1/2}/Lp$. There was no crystal decay and no correction was made for absorption. The structure was solved by direct methods using SHELXS-86. All remaining calculations were carried out using the SDP-Plus program system on a MicroVax computer. Non-hydrogen atoms were refined anisotropically by full-matrix least-squares. Hydrogen atoms were located on a difference map. The hydrogen atom vibrational parameters were fixed such that $B_{iso} = 1.3B_{eq}$ for the atom to which they are bonded, but positional parameters were allowed to refine freely. Final parameters were $R = 0.039$,

Table 1. Crystallographic data for L-proline 2,5-dihydroxy-benzoic acid (1/1).

Formula	$C_{12}H_{15}NO_6$
M_w	269.3
$F(000)$	568
Radiation	MoKα
Wavelength/Å	0.71069
Crystal system	Orthorhombic
a/Å	5.896(2)
b/Å	11.486(1)
c/Å	18.016(3)
U/Å^3	1220.1
Space group	$P2_12_12_1$
Z	4
D_{calc}/g cm^{-3}	1.47
μ(MoKα)/cm^{-1}	1.1

$R' = 0.044$, $\omega = 1/\sigma^2(F)$, $s = 1.5$, 217 variables, (Δ/σ)max = 0.46, $(\Delta\rho)$max,min = $+0.21$, -0.15 Å^{-3} on a final difference map. Crystallographic data are given in Table 1.

In order to verify that the chosen single crystal was representative of the bulk material, the powder X-ray diffraction pattern was simulated from the single-crystal data (using CERIUS 3.2 from Molecular Simulation Inc.) and compared with the experimental powder X-ray diffraction pattern recorded on a bulk sample. The match between simulated and experimental pattern demonstrated that only one structural form of the zwitterion co-crystal was present, thus confirming the structural purity of the sample.[8]
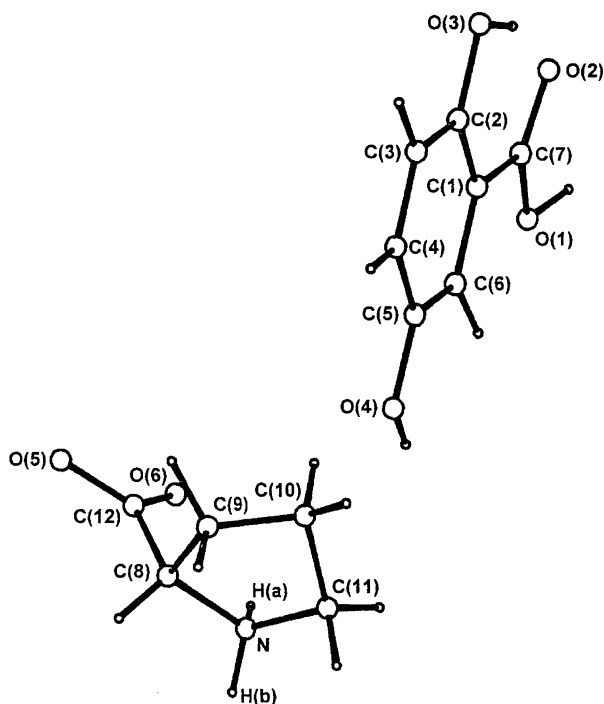

Fig. 1. The geometry of the two components in the zwitterion co-crystal L-proline 2,5-dihydroxybenzoic acid (1/1).

Results and discussion

The low-temperature single-crystal X-ray study revealed that, instead of the formation of a salt [ProH][dhba], a zwitterion co-crystal, Pro·dhbaH, Fig. 1, had formed. Positional parameters are listed in Table 2, bond lengths and angles in Tables 3 and 4.

This structure contains both a zwitterion and a molecule: each of these components have previously been characterized crystallographically, as Pro[9] and dhbaH,[10] respectively. Thus, this co-crystal provides a unique opportunity for a study of the competition between hydrogen-bond donors and acceptors, allowing a comparison of the geometry of specific chemical species in different crystalline environments.

The probability of forming a zwitterion co-crystal involving an amino acid can be estimated by examining the Cambridge Crystallographic Database:[11] the odds are overwhelmingly in favour of making a salt (108 structures) as opposed to a co-crystal (3 structures). This suggests that a delicate chemical/electronic/geometric bal-

Table 2. Fractional atomic coordinates ($\times 10^4$ for C, N, O; $\times 10^3$ for H) and equivalent isotropic thermal parameters Å$^2 \times 10^3$).[a]

	x	y	z	U_{eq}[a]
O(1)	2703(4)	8058(2)	5414(1)	32(1)
O(2)	−300(5)	8498(2)	6105(1)	40(1)
O(3)	−2217(4)	6874(2)	6889(2)	47(2)
O(4)	4965(5)	4017(2)	6176(1)	36(1)
O(5)	2388(4)	191(2)	5023(1)	28(1)
O(6)	4474(4)	1795(2)	4885(1)	31(1)
N	8007(5)	1046(2)	5639(1)	24(1)
C(1)	1273(6)	6603(3)	6208(2)	26(2)
C(2)	−429(6)	6204(3)	6677(2)	32(2)
C(3)	−306(7)	5071(3)	6953(2)	35(2)
C(4)	1499(7)	4365(3)	6783(2)	30(2)
C(5)	3229(6)	4760(3)	6318(2)	26(2)
C(6)	3115(6)	5879(3)	6030(2)	23(2)
C(7)	1154(6)	7793(3)	5905(2)	27(2)
C(8)	5962(6)	266(3)	5623(2)	23(2)
C(9)	5207(6)	193(3)	6446(2)	28(2)
C(10)	6069(7)	1318(3)	6778(2)	33(2)
C(11)	8385(7)	1452(3)	6429(2)	35(2)
C(12)	4165(6)	820(3)	5131(2)	23(2)
H(Na)	767(7)	172(4)	526(2)	
H(Nb)	923(7)	66(4)	544(2)	
H(01)	257(8)	894(4)	533(3)	
H(03)	−175(8)	760(4)	666(3)	
H(04)	593(8)	432(4)	587(2)	
H(3)	−158(8)	480(4)	723(2)	
H(4)	162(7)	358(4)	702(2)	
H(6)	444(7)	615(4)	581(2)	
H(8)	634(7)	−48(4)	542(2)	
H(9a)	591(8)	−49(4)	668(2)	
H(9b)	341(8)	9(4)	646(2)	
H(10a)	619(7)	136(4)	732(2)	
H(10b)	511(8)	197(4)	663(2)	
H(11a)	899(8)	227(4)	638(2)	
H(11b)	967(9)	96(4)	663(2)	

[a] U_{eq} is defined as one third of the trace of the orthogonal U_{ij} tensor.

Table 3. Bond lengths (Å), with estimated standard deviations in parentheses.

O(1)–C(7)	1.307(4)	O(1)–H(O1)	1.03(4)
O(2)–C(7)	1.233(4)	O(3)–C(2)	1.360(4)
O(3)–H(O3)	0.96(5)	O(4)–C(5)	1.357(4)
O(4)–H(O4)	0.87(5)	O(5)–C(12)	1.287(4)
O(6)–C(12)	1.219(4)	N–C(8)	1.503(4)
N–C(11)	1.514(4)	N–H(Na)	1.05(4)
N–H(Nb)	0.92(4)	C(1)–C(2)	1.390(5)
C(1)–C(6)	1.405(5)	C(1)–C(7)	1.474(5)
C(2)–C(3)	1.395(5)	C(3)–C(4)	1.372(5)
C(3)–H(3)	0.96(5)	C(4)–C(5)	1.397(5)
C(4)–H(4)	1.00(4)	C(5)–C(6)	1.387(5)
C(6)–H(6)	0.93(4)	C(8)–C(9)	1.552(5)
C(8)–C(12)	1.520(5)	C(8)–H(8)	0.96(4)
C(9)–C(10)	1.512(5)	C(9)–H(9a)	0.99(4)
C(9)–H(9b)	1.07(4)	C(10)–C(11)	1.511(6)
C(10)–H(10a)	0.99(4)	C(10)–H(10b)	0.98(4)
C(11)–H(11a)	1.01(5)	C(11)–H(11b)	1.02(5)

ance must be achieved between the components in a co-crystal, and hence, a zwitterion co-crystal may constitute a flexible and sensitive system for theoretical investigations of the relationship between charge, geometry and hydrogen-bond acceptor/donor strength. This system also provides an opportunity to initiate an investigation of the required pK_a difference ($\Delta pK_a = |pK_a^{base} - pK_a^{acid}|$) necessary for the formation of a zwitterion co-crystal. For uncharged species, earlier guidelines[12] predict salt formation when $\Delta pK_a > 3.8$ (comparing hydrogen-bond donor and hydrogen-bond acceptor), and formation of a co-crystal when $\Delta pK_a < 3.8$, but these benchmarks may be significantly different when one component is a zwitter-

ion. The pK_a difference between the two components in this co-crystal is 1.02 (proline 1.95; 2,5-dihydroxybenzoic acid 2.97) which means that the formation of this co-crystal is consistent with previous, empirical, guidelines.

The large number of potential hydrogen-bond donors (five) and hydrogen-bond acceptors (six) present in Pro·dhbaH, forms the framework for an extensive, and complex, hydrogen-bonded network throughout the crystal; two of the six unique hydrogen bonds are intramolecular, Table 5.

2,5-Dihydroxybenzoic acid is known to be dimorphic, and in both reported polymorphs neighbouring molecules display the head-to-head, dimeric arrangement which is common for most carboxylic acids. These dimeric units are then stacked in columns in either a parallel or anti-parallel fashion.[9] The molecular conformation of dhbaH in these structures compares well with that found in Pro·dhbaH. However, in the co-crystal, there are no hydrogen bonds between adjacent carboxylic acids; the head-to-head arrangement has been disrupted in favour of a hydrogen bond from the carboxylic proton to an oxygen on the L-proline zwitterion, $r[O(1)-H(O1)\cdots O(5)''']$ 2.557(4) Å. This proton, H(O1), is clearly associated more strongly with the benzoic acid moiety, $r[O(1)-H(O1)]$ 1.03(4) Å, than with the proline residue, $r[H(O1)\cdots O(5)]$ 1.54(4) Å. This, then, provides convincing evidence that the material is, in fact, a zwitterion co-crystal rather than a salt.

This ability of proline to disrupt the head-to-head hydrogen-bonding of the carboxylic acid suggests that the surplus charge residing on its formally negatively charged

Table 4. Bond angles (°), with estimated standard deviations in parentheses.

C(7)–O(1)–H(O1)	106(3)	C(2)–O(3)–H(O3)	98(3)
C(5)–O(4)–H(O4)	111(3)	C(8)–N–C(11)	108.7(3)
C(8)–N–H(Na)	106(2)	C(8)–N–H(Nb)	109(3)
C(11)–N–H(Na)	114(2)	C(11)–N–H(Nb)	114(3)
H(Na)–N–H(Nb)	105(3)	C(2)–C(1)–C(6)	120.1(3)
C(2)–C(1)–C(7)	119.8(3)	C(6)–C(1)–C(7)	120.1(3)
O(3)–C(2)–C(1)	122.9(3)	O(3)–C(2)–C(3)	117.9(3)
C(1)–C(2)–C(3)	119.2(3)	C(2)–C(3)–C(4)	120.8(3)
C(2)–C(3)–H(3)	117(3)	C(4)–C(3)–H(3)	122(3)
C(3)–C(4)–C(5)	120.5(3)	C(3)–C(4)–H(4)	119(2)
C(5)–C(4)–H(4)	120(2)	O(4)–C(5)–C(4)	117.4(3)
O(4)–C(5)–C(6)	123.3(3)	C(4)–C(5)–C(6)	119.3(3)
C(1)–C(6)–C(5)	120.1(3)	C(1)–C(6)–H(6)	123(3)
C(5)–C(6)–H(6)	115(3)	O(1)–C(7)–O(2)	122.1(3)
O(1)–C(7)–C(1)	115.7(3)	O(2)–C(7)–C(1)	122.3(3)
N–C(8)–C(9)	104.1(3)	N–C(8)–C(12)	108.8(3)
N–C(8)–H(8)	111(2)	C(9)–C(8)–C(12)	112.3(3)
C(9)–C(8)–H(8)	113(2)	C(12)–C(8)–H(8)	108(2)
C(8)–C(9)–C(10)	103.6(3)	C(8)–C(9)–H(9a)	110(2)
C(8)–C(9)–H(9b)	108(2)	C(10)–C(9)–H(9a)	111(2)
C(10)–C(9)–H(9b)	115(2)	H(9a)–C(9)–H(9b)	109(3)
C(9)–C(10)–C(11)	103.1(3)	C(9)–C(10)–H(10a)	117(3)
C(9)–C(10)–H(10b)	111(3)	C(11)–C(10)–H(10a)	110(3)
C(11)–C(10)–H(10b)	109(3)	H(10a)–C(10)–H(10)	106(4)
N–C(11)–C(10)	103.1(3)	N–C(11)–H(11a)	105(3)
N–C(11)–H(11b)	106(2)	C(10)–C(11)–H(11a)	117(3)
C(10)–C(11)–H(11b)	118(3)	H(11a)–C(11)–H(11)	107(4)
O(5)–C(12)–O(6)	125.6(3)	O(5)–C(12)–C(8)	114.9(3)
O(6)–C(12)–C(8)	119.5(3)		

Table 5. Geometry of the hydrogen bonds in L-proline 2,5-dihydroxybenzoic acid (1/1).[a]

D—H···A	r(D—H)/Å	r(H···A)/Å	r(D···A)/Å	$\angle$(DH···A)/°
N—H(a)···O(6)	1.05(4)	2.00(4)	2.632(4)	115(3)
N—H(a)···O(6)'	1.05(4)	2.03(4)	2.790(4)	127(3)
N—H(b)···O(5)"	0.92(4)	2.08(4)	2.978(4)	165(4)
O(1)—H(O1)···O(5)'''	1.03(4)	1.54(4)	2.557(3)	167(4)
O(3)—H(O3)···O(2)	0.96(5)	1.68(5)	2.599(4)	158(5)
O(4)—H(O4)···O(5)'	0.86(5)	1.91(4)	2.745(4)	162(4)

[a] Symmetry elements: (') $^{1}/_{2}+x$, $^{1}/_{2}-y$, $1-z$; (") $1+x$, y, z; (''') x, $1+y$, z.

Table 6. Semiempirical (AM1) Mulliken charge on Pro and dhba.

Proline (zwitterion)		2,5-Dihydroxybenzoic acid	
Atom	Charge	Atom	Charge
N	−0.04	O(2)	−0.39
O(5)	−0.54	O(1)	−0.31
O(6)	−0.45	O(3)	−0.25
		O(4)	−0.25

oxygen atom, O(5), (owing to its zwitterionic nature) gives rise to a more stable hydrogen bond than that formed by the formally neutral oxygen atom of –C(O)OH. The basis of this assessment is supported by semiempirical calcu-

lations carried out on the two components. The geometries of Pro (in its zwitterionic form) and dhbaH were optimized using the AM1 algorithm, and the fractional charges were obtained from a Mulliken population analysis. The results, Table 6, show that both carboxylate oxygens on proline, O(5) and O(6), carry more negative charge than does the carbonyl oxygen, O(2), of dhbaH.

Within experimental error, the conformation of the zwitterion in Pro·dhbaH displays no significant difference compared with that found in the relatively poorly determined crystal structure of L-proline.[10] However, the zwitterions give rise to different hydrogen-bonded aggregates in Pro·dhbaH and in Pro. In the latter, the zwitterions form infinite hydrogen-bonded sheets constructed from two cross-linking hydrogen-bonded chains, Fig. 2;
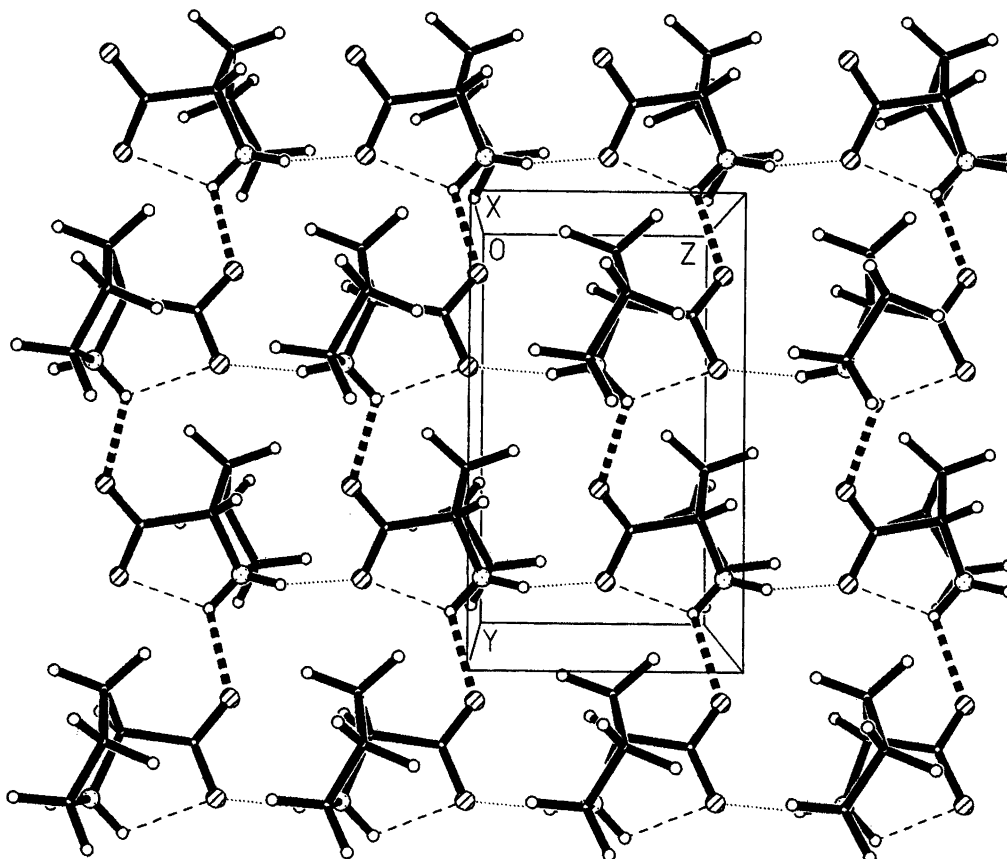

Fig. 2. An infinite sheet (in the b—c plane) in L-proline,[10] formed by hydrogen-bonds between adjacent zwitterions. Symmetry equivalent hydrogen bonds have similar labels. Only one layer is shown, and there are no hydrogen bonds parallel with a.
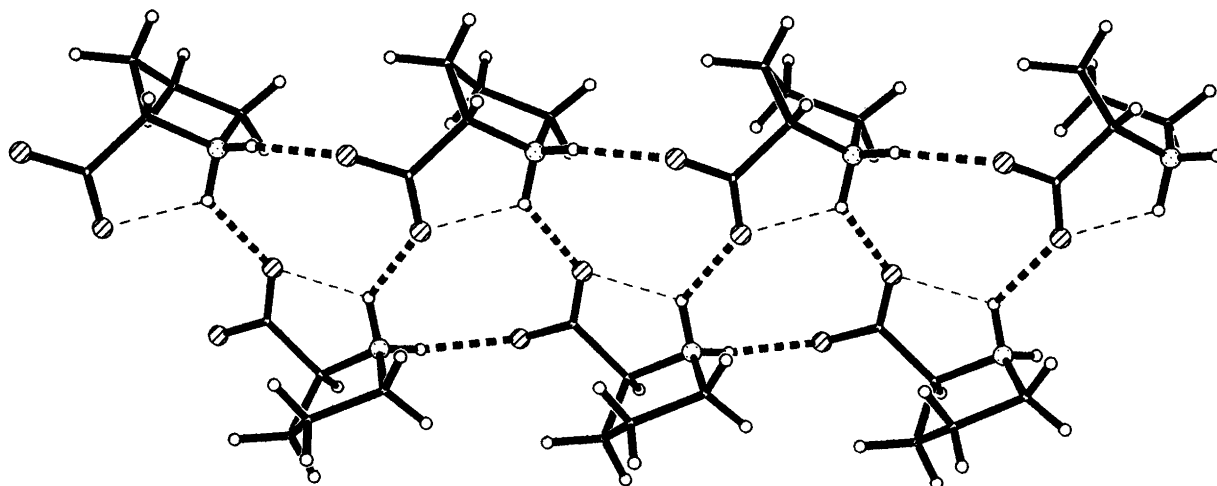
Fig. 3. A column of infinite chains, parallel to *a*, formed by hydrogen-bonded zwitterions in Pro · dhbaH. Dashed lines indicate intramolecular hydrogen bonds.

there are no hydrogen bonds between adjacent sheets. In Pro · dhbaH, the zwitterions give rise to columns of infinite, double chains, parallel to *a*, created by two N–H···O hydrogen bonds, $r[\text{N}\cdots\text{O(6)}']$ 2.790(4), $r[\text{N}\cdots\text{O(5)}]$ 2.978(4) Å, Fig. 3. These columns are then cross-linked in the *b–c* plane by the acid molecules, Fig. 4.

In order to clarify and communicate the differences between the two extended proline assemblies, both hydrogen-bond aggregates were encoded using the methodology developed by Etter and co-workers.[13] A graph set is specified using the pattern designator (G), its degree (n) and the number of donors (d) and acceptors (a); $G_d^a(n)$. *G*, the descriptor referring to the pattern of hydrogen bonding, can be *S* (intramolecular bond), *C* (infinite chain), *R* (intermolecular ring), or *D* (non-cyclic dimers

and other finite structures) and the parameter *n* refers to the number of atoms in a ring, or the repeat unit of a chain. Graph sets are assigned initially to motifs (a hydrogen-bonded set constructed by only one type of hydrogen bond), and then to the first-level network. The first-level network is a sequential listing of all the relevant motifs, e.g., if the array contains four different hydrogen bond types, then the first-level network is a combination of four motifs. Higher-level networks are assigned to sets generated by combinations of several different hydrogen-bond types. The resulting first-level graph set for the proline aggregates in both Pro and Pro · dhbaH is $N_1 = C_1^1(5)C_1^1(5)S_1^1(5)$, which demonstrates the similarities between the two aggregates; both aggregates contain two intermolecular and one intramolecular hydrogen bond. The second-level graph sets, however, reveal the differ-
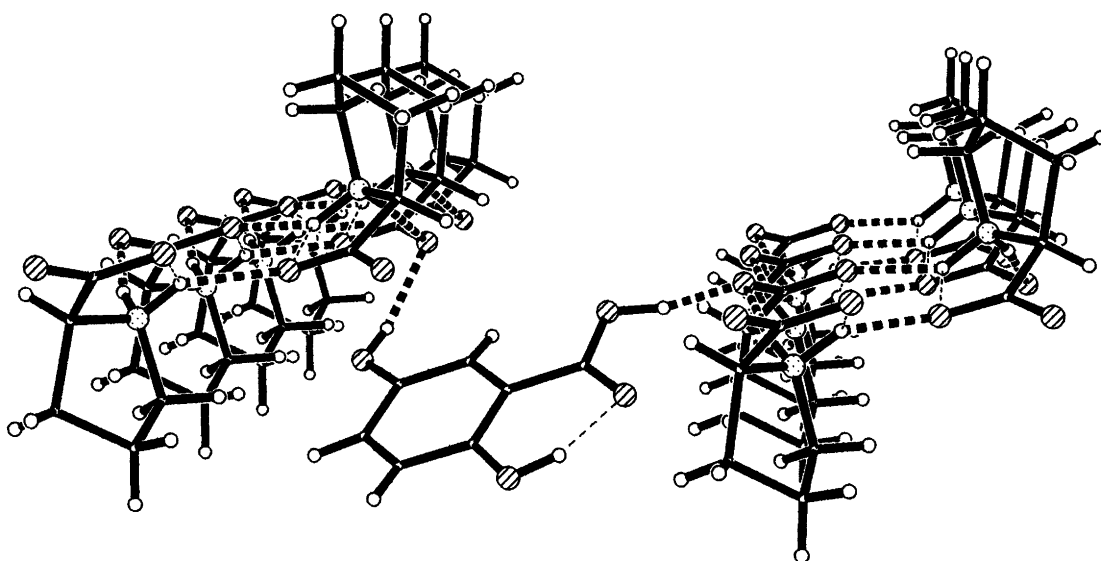

Fig. 4. Cross-linking of infinite columns of zwitterions by the carboxylic acid in Pro · dhbaH. Only one molecule of dhbaH is shown, for clarity.

ences between the two aggregates; $N_2 = C_1^2(3)C_2^2(6)C_2^2(6)$ for Pro·dhbaH and $N_2 = C_1^2(4)C_2^1(4)C_2^2(6)$ for Pro. Although the second-level graph set for both compounds contains three chains, the length and directionality of these chains result in two different structural aggregates; an infinite sheet for Pro and isolated double chains in Pro·dhbaH.

Zwitterion co-crystals form a family of materials which could be the basis for several, very different, structural and theoretical examinations. The molecular conformation, electron distribution, packing patterns and recognition ability of a zwitterion can be examined in the presence of another chemical species *without* significantly altering its overall electronic charge (as would be the case if the zwitterion were incorporated into an ionic material). Consequently, by preparing new zwitterion co-crystals it should be possible to examine the behaviour of, for example, amino acids in a variety of structural environments which, in turn, may throw new light on the chemical and physical properties of amino acids and other zwitterionic compounds.

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