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ARTICLE TYPE

Are gamma amino acids promising tools of crystal engineering? – Multicomponent crystals of baclofen

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Baclofen, (*RS*)-4-amino-3-(4-chlorophenyl)butanoic acid is a slightly water soluble hydrophobic γ-amino acid and primarily used as a muscle relaxant. The crystal structure, thermal analysis and powder X-ray analysis of the multicomponent crystals formed between baclofen and selected monocarboxylic acids (benzoic acid, p-toluic acid and 1-hydroxy-2-naphthoic acid), dicarboxylic acids (oxalic acid and maleic acid) and p-toluene sulfonic acid are presented. Conformation and protonation properties of the baclofen moiety are discussed. Hirshfeld surface analysis is used to analyse the specific intermolecular interactions in the presented structures and their percentage appearance is correlated with the melting points of the multicomponent crystals.

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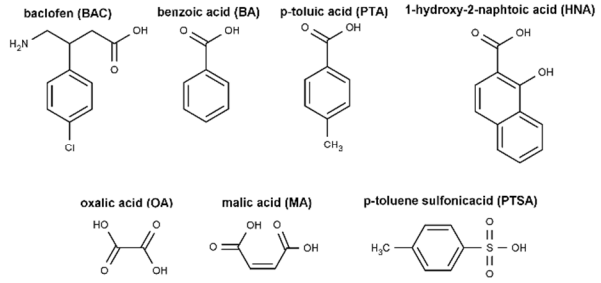
Introduction

Amino acids (AAs) are at the centre of interest of structural chemistry for decades because of their biological importance. Extensive and thorough investigations of their molecular and crystal structures were carried out by many research groups[1], although these systematic works are focused on the α-AAs only because of their biochemical and biological role. Due to the coexistence of a carboxylic acid/carboxylate and a primary amine/ammonium moiety in these compounds, they are popular coformers in cocrystallisation experiments[2]. A recent mini-review summarized their application in salification of active pharmaceutical ingredients to improve the physico-chemical or solid state properties of a given drug substance[3]. Rather less interest has been shown towards the less numerous β and γ-AAs. A fresh search in the Cambridge Structural Database[4] (CSD, v.5.36, November 2014, update May 2015) resulted in less than 100 hits for β-AA and 232 hits for γ-AAs. Undoubtedly the most typical γ-AA is the inhibitory neurotransmitter γ–aminobutyric acid (GABA). Its solvate formation properties[5] and hydrate formation under high pressure[6] have been investigated recently. Gabapentin is a structural analogue of GABA and a widely marketed drug under various brand names to treat pain, epilepsy and bipolar disorder. Its polymorphic behaviour under ambient and non-ambient conditions were investigated[7] and its multicomponent crystals were formed and analysed with carboxylic acids by various research groups[8].

In this work, we present and analyse six multicomponent crystals of another γ–AA, baclofen (BAC), (*RS*)-4-amino-3-(4-chlorophenyl)butanoic acid. BAC is a $GABA_B$ receptor agonist which is commonly used in the treatment of cerebral palsy[9], specific types of neuralgia[10], spinal cord injuries[11] and addictive behaviours, such as opiate addiction[12], eating disorders[13] and early stage of alcoholism[14]. Although it is known that the *R* enantiomer carries the biological activity, the currently available formulations employ the racemic modification. An early work by Chang et al[15] presented the *S* and the *R*-baclofen hydrochloride without 3D coordinates (CSD refcodes CRBMZB and CRBMZC) and later the same group published the 3D coordinates of the *R* enantiomer[16] (CRBMZC10). Almost 30 years passed before a new crystal structure of baclofen, a cocrystal hemihydrate with ferulic acid (RUWGOG) was presented by Zaworotko et al[17].

Baclofen is a slightly water soluble drug (4.3 mg/ml, pH 7.6) hence cocrystallisation was employed to form new solid state forms of the drug and thus alter its physico-chemical properties. A series of organic acids were selected (Scheme 1) with different pKa values, namely benzoic acid (BA), p-toluic acid (PTA), 1-hydroxy-2-naphthoic acid (HNA), oxalic acid (OA) and maleic acid (MA). p-Toluene sulfonic acid (PTSA) was also used in cocrystallisation experiments to test the protonation properties of the zwitterionic compound against sulfonic acid derivatives. Conformation of the polar head of BAC will be discussed with the relevant protonation stages and its involvement in hydrogen bonding. Furthermore, the crystal packing will be analysed by using Hirshfeld surfaces and melting point of the crystals will be correlated to the observed intermolecular interactions. All these analyses aim to understand how γ-AAs may be used for crystal engineering purposes.



Scheme 1 Structural diagram of baclofen (BAC) and the guest compounds: benzoic acid (BA), p-toluic acid (PTA), 1-hydroxy-2-naphthoic acid (HNA), oxalic acid (OA), maleic acid (MA) and p-toluene sulfonic acid (PTSA).

Experimental section

Crystal growth

All chemicals were purchased from Sigma Aldrich and used without further purification. Additional crystallisation conditions are given in the Electronic Supplementary Information.

X-ray crystallography

Intensity data were collected on Nonius Kappa CCD [**BAC•BA** and **(2BAC$^+$)(OA^{2-})**] and Bruker DUO APEX II[18] diffractometers [**BAC•PTA, (BAC$^+$)(MA$^-$)** and **(BAC$^+$)(HNA$^-$)**] with graphite monochromated Mo $K\alpha_1$ radiation (λ = 0.71073 Å) at 173 K. Data reduction and cell refinement were performed using *SAINT-Plus*[19] or COLLECT[20], DENZO and SCALEPACK[21]. The space group was determined from systematic absences by *XPREP*[22]. All the structures were solved using SHELXS-97[23] and refined using full-matrix least squares methods in SHELXL-97[23], within the X-Seed[24] graphical user interface. Non-hydrogen atoms were refined anisotropically. The hydrogen atoms bound to carbon atoms were placed at idealized position and refined as riding atoms. Hydroxyl hydrogen atoms were located in the difference electron density map and refined independently. Diagrams and publication material were generated using *PLATON,*[25] *X-Seed* and *Mercury (3.5)*[26].

Further details of crystal data[$] and hydrogen bonds are given in Table S1 and Table S2 (ESI) respectively. CCDC 1411558-1411563 contain the supplementary crystallographic data for all structures. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/data_request/cif, by e-mailing data_request@ccdc.cam.ac.uk, or by contacting the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033. DOI:0.1039/b000000x

Powder X-ray diffraction (PXRD) was recorded on a Bruker D2

phaser diffractometer using Cu Kα radiation (λ= 1.54184 Å) generated at 30 kV and 10 mA. Simulated powder patterns of crystal structures were calculated using Mercury and compared with the experimental patterns to confirm bulk phase purity (Fig S1-S6, ESI).

Thermal analysis

Differential Scanning Calorimetry (DSC) was carried out using a Perkin Elmer 6 under a N_2 gas purge (flow rate of 20.0 ml/min). Experiments were conducted over a temperature range of 30 °C to 350 °C. DSCs for multicomponent crystals and their relevant starting materials are shown in Fig. S7-S12 (ESI)

Results and Discussion

Multicomponent crystals of baclofen with monocarboxylic acids

Crystallisation of baclofen (BAC) with benzoic acid (BA) was carried out in 1:1 molar ratio but resulted crystals with unexpected 2:3 stoichiometry (Fig. 1a). As there was no proton transfer, this system is a cocrystal with BAC as a zwitterion. All hydrogen atoms of the amino groups, hydroxyl and carbonyl groups are involved in strong hydrogen bonds and form an extended network of ring systems (Fig. 2) which was described by graph set notation[27] and the metrics are summarized in Table S2. The first level $R_2^2(14)$ motif is formed between two BACs (molecule A) via N1-H11A···O2A and its symmetry generated counterpart. This ring conjuncts with a second level $R_4^4(12)$ motif formed around a centre of inversion constructed by N1-H11A···O2A and N1-H11C···O1A. A second level $R_4^4(22)$ ring forms around a centre of inversion between one BAC (mol B) and one BA (mol E) from the combination of O4E-H7E···O2B with N2-H11D···O3E. The two symmetry independent BACs form a third level $R_4^3(18)$ motif via N1-H11C···O1A, N2-H11E···O1A and N2-H11F···O1B. The main feature of the crystal is the alternation of the hydrogen bonded and the aromatic layers without strong interactions (Fig.3a). This arrangement is typical in the crystal structures of hydrophobic amino acids and discussed in details by Görbitz et al[28]. From [100] direction the crystal packing presents an interesting optical effect, the so called Zöllner illusion, when the packing of the molecules looks antiparallel, however they are indeed parallel, hence the space group is monoclinic (Fig.3b and c).

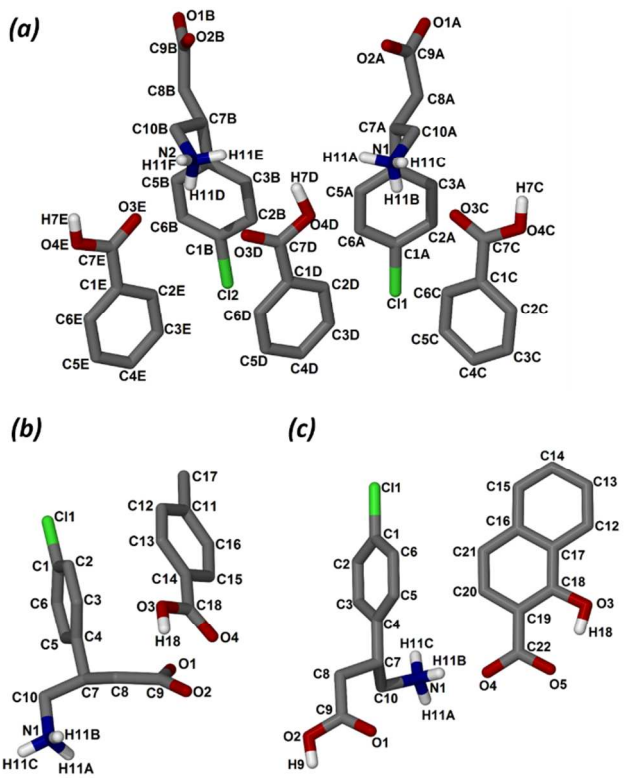


Fig. 1 The asymmetric units of (a) BAC•BA, (b) BAC•PTA and (c) (BAC^+)(HNA^-)with labelled heavy atoms. (Non-essential hydrogen atoms are omitted for clarity.)

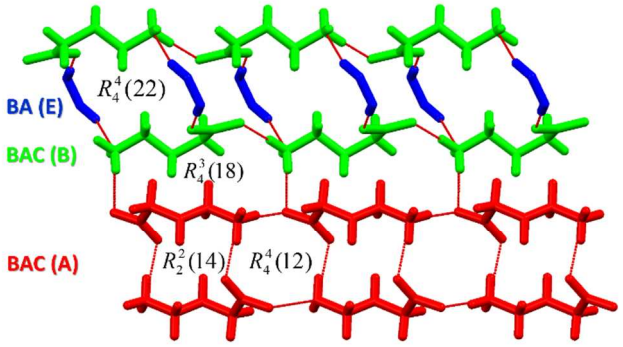


Fig. 2 Hydrogen bonding motifs along the [001] direction in BAC•BA (BAC Molecule A (red), BAC Molecule B (green) and BA Molecule E (blue); hydrophobic groups are omitted)

The asymmetric unit of BAC•PTA cocrystal contains one molecule of BAC and one PTA (Fig.1b) and its structure may be described with a series of hydrogen bonded motifs (Fig. 4a). The two first level $R_2^2(14)$ rings formed around inversions from N1-H11A···O1 or N1-H11B···O2. Also the former hydrogen bond combined with N1-H11C···O2 forms a second level $R_4^4(12)$ ring while the latter builds an $R_4^2(8)$ motif with N1-H11C···O2. The main feature of the crystal is the alternation of the hydrogen bonded/polar layers and the aromatic/hydrophobic layers without strong interactions. In this manner, the BAC•PTA crystal structure shows remarkable similarities with BAC•BA (Fig. 4b).

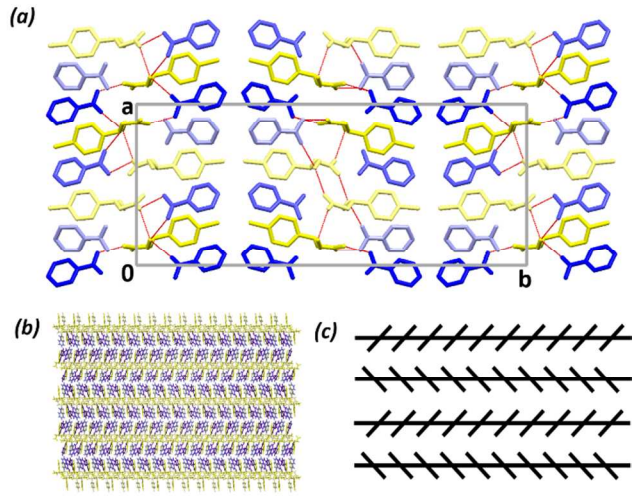


Fig. 3 (a) Crystal packing of BAC•BA down [001]. The symmetry independent baclofen molecules are coloured with light yellow and yellow and the symmetry independent benzoic acids are coloured with three shades of blue.(b) Zöllner illusion in the [001] direction and its graphical representation with seemingly antiparallel lines (c).

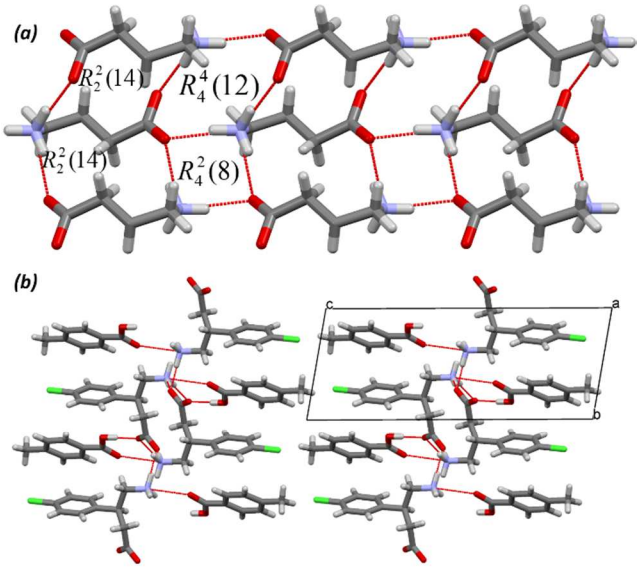


Fig. 4 (a) Hydrogen bonding motifs (hydrophobic groups are omitted) and (b) crystal packing of BAC•PTA viewed down [100].

The crystallisation of BAC with HNA resulted in the formation of crystals with 1:1 stoichiometry. The ΔpKa value (Table 2) for these compounds (1.1) suggests an equal probability of cocrystal or salt formation. The single crystal X-ray analysis revealed that the carboxylic proton of the HNA was transferred to the BAC, therefore the crystal is a salt (Fig. 1c).

The hydrogen bonding may be described with two second level ring motifs. The N1-H11A···O5 and N1-H11C···O5 hydrogen bonds form $R_4^2(8)$ motif around an inversion and joins $R_4^4(12)$ ring formed by N1-H11B···O4, N1-H11A···O5 and their symmetry generated counter parts. Similarly to the previously discussed BAC cocrystals, the main structural feature is the alternation of the hydrogen bonded polar and hydrophobic layers (Fig. 5b)

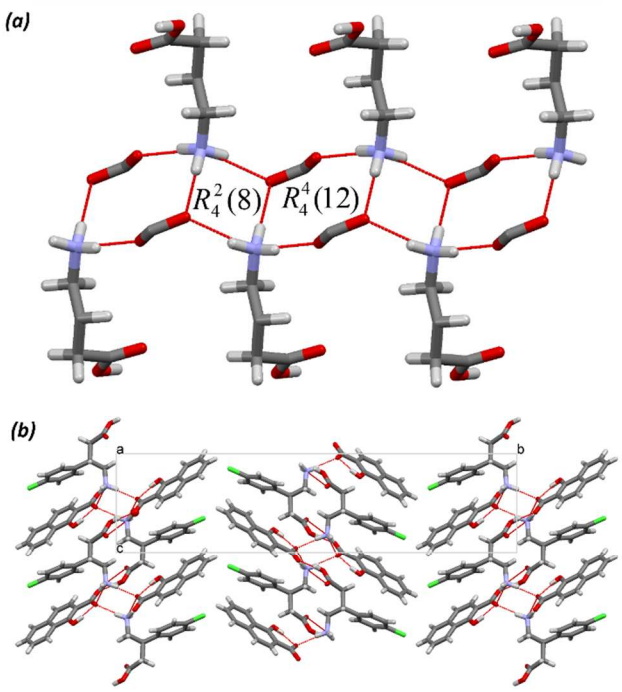


Fig. 5 (a) Hydrogen bonding motifs along the [100] direction (hydrophobic groups are omitted) and (b) crystal packing of (BAC^+)(HNA^-) down [100].

Multicomponent crystals of baclofen with dicarboxylic acids

The asymmetric unit of ($2BAC^+$)(OA^{2-}) contains one molecule of BAC and half molecule of OA (Fig. 6a). Both of the carboxylic protons from the OA were transferred to two BACs, therefore the crystal is a molecular salt. The polar hydrogen bonded layer may be described by a second level $R_4^4(22)$ ring formation around an inversion from N1-H11B···O4 and O2-H9···O3 hydrogen bonds and a third level $R_3^3(11)$ motif via N1-H11A···O1, N1-H11B···O4 and O2-H9···O3 hydrogen bonds (Fig. 7a). The overall packing of the alternating polar and hydrophobic layers is similar to the previous structures (Fig. 7b).

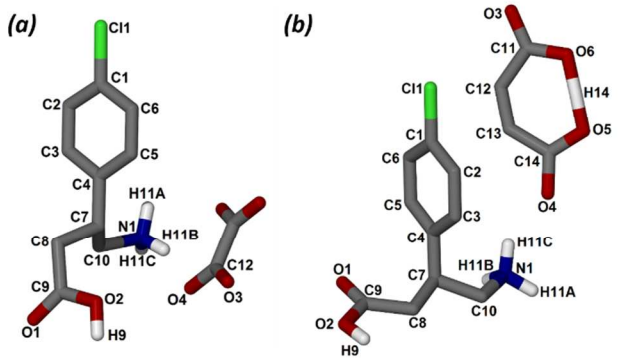


Fig. 6 (a) Asymmetric unit with labelled atoms for (a) ($2BAC^+$)(OA^{2-}) and (b) (BAC^+)(MA^-) (non-essential H atoms are omitted).

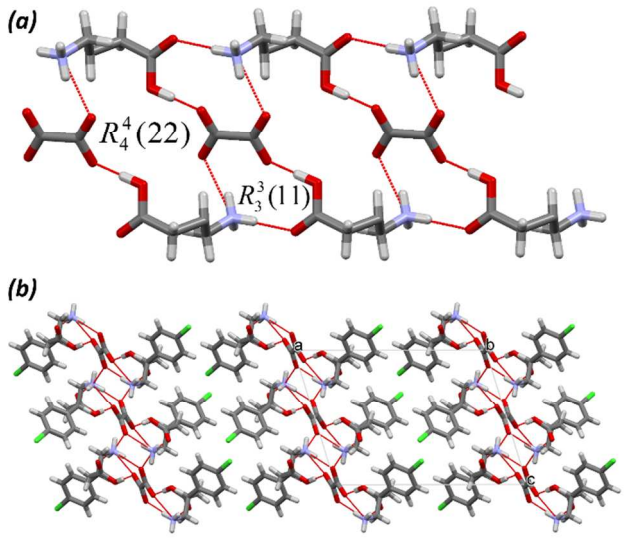


Fig. 7. (a) Hydrogen bonding motifs along the [001] direction (hydrophobic groups are omitted) and (b) crystal packing of $(2BAC^+)(OA^{2-})$ view down [010].

$(BAC^+)(MA^-)$ contains one molecule of BAC and one molecule of MA in the asymmetric unit (Fig. 6b) and is the only compound crystallized in a chiral space group. The structure was solved for the *S* enantiomer of BAC with Flack parameter -0.03(5) therefore the absolute structure given by the structure refinement is correct. One of the carboxylic protons was transferred from the MA moiety to the BAC, therefore the crystal is a molecular salt. The H14 hydroxyl proton of the MA forms an intramolecular hydrogen bond and it is positioned at equal distance from O5 and O6 atoms. The main packing motif in the crystal is the hydrogen bonded 2D net of molecules in an off-set brick type arrangement (Fig. 8) and this feature may be described by the $R_6^5(32)$ ring formed from pairs of N1-H11A···O3, N1-H11C···O4 and O2-H9···O4 hydrogen bonds. Interesting to note that this packing significantly differs from other maleate salts of amino acids recently discussed[29]. Arkhipov et al. noted that the discussed hydrophobic α-AA maleate salts contain $C_2^2(12)$ chains of hydrogen bonds and have layered structures. None of these features appear in the $(BAC^+)(MA^-)$ salt.

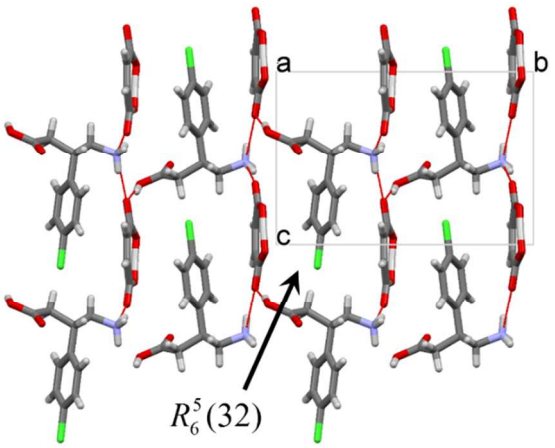


Fig. 8 Hydrogen bonded off-set brick type net of $(BAC^+)(MA^-)$.

Multicomponent crystal of baclofen with p-toluene-sulfonic acid

BAC cocrystallized with PTSA in a 1:1 ratio including isopropanol in the crystal. Proton transfer occurred thus the crystal is a solvate of a molecular salt. The IPA is disordered in two positions in 89:11 ratio. The main packing motif in the crystal is the hydrogen bonded structure in [010] direction (Fig. 9a) built from alternating $R_4^4(12)$ and $R_6^6(26)$ rings. The former contains N1-H11A···O5, N1-H11C···O3 hydrogen bonds and their symmetry related pairs, while the latter is formed by N1-H11B···O5, O2-H1···O6, O6-H6A···O3 hydrogen bonds around a centre of inversion.

The salt formation between BAC and PTSA is not surprizing because the compounds have the largest differences between their pKa values (6.7). It is worthwhile to mention that this structure exclusively included the solvent of crystallisation. This observation may be related to the strong hydrogen bond acceptance of the sulfonic acid group and was observed in unpublished crystal structures of BAC with PTSA and 4-chlorobenzenesulfonic acid.[30] In both cases, the water of crystallisation was included in the crystal structure. Based on the figures presented in the source, the overall packing of the baclofen:4-chlorobenzenesulonate hydrate structure (Fig. 4.9 in ref. 22) show similarities with $(2BAC^+)(OA^{2-})$ structure (Fig. 7b), while the $(BAC^+)(PTSA^-)\bullet H_2O$ (Fig. 4.6 in ref. 22) packing resembles the isopropanol inclusion (Fig. 9b).

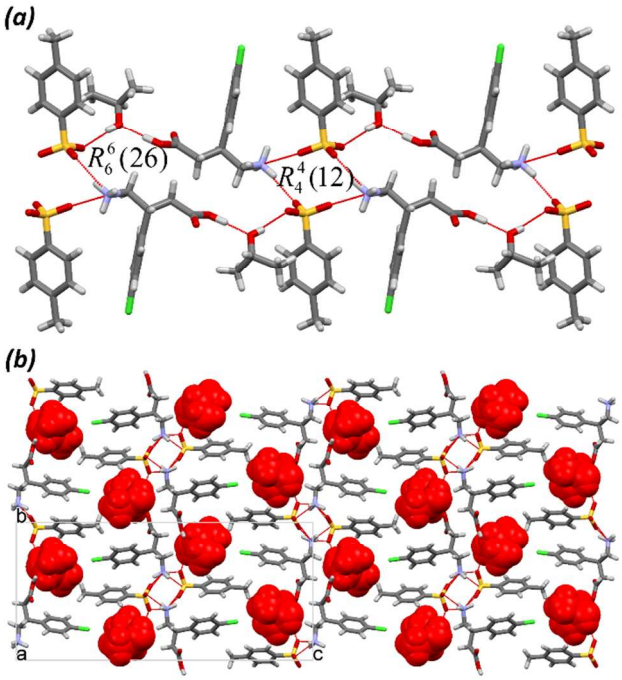


Fig. 9 (a) Hydrogen bonding in $(BAC^+)(PTSA^-)\bullet IPA$ down [100] and (b) crystal packing down [100]. The included isopropanol molecules are with red space filling model.

Conformational comparison of baclofen molecules

The source of the conformational freedom of baclofen lies in the four torsion angles presented in Fig. 10a. The rotation of the –

CH_2-COOH/ -–CH_2-COO^- moiety may be described by τ1, while the rotation of the –COOH/-COO^- with τ2. The movement of the –NH_2/ –NH_3^+ group is defined by τ3 and the aromatic ring rotation relative to the amino acid functionality with τ4. The previously described six baclofen crystal structures contain seven different conformations of baclofen. All structures crystallized in achiral space groups with the exception of (BAC^+)(MA^-) which structure was solved with the *S* enantiomer; therefore the torsion angles were measured on the *S* enantiomers in all crystal structures. In case of molecular salts, the carboxylate oxygen atoms are indistinguishable; therefore for the measurement of τ1 the smaller torsion angle was recorded. Also, the tilt of the aromatic ring (τ4) was described with the smaller torsion angle. The superimposed baclofen molecules are shown in Fig. 10b and the related torsion angles are summarized in Table 1. The CSD (v.5.36 November 2014, update May 2015) contains only 4 structures of baclofen. Two of them (CRBMZB and CRBMZC2) are the structures of *S* and *R*-baclofen hydrochloride respectively, but no 3D coordinates are presented therefore the molecular structure cannot be interpreted. The structure of the *R*-enantiomer was recollected at a later stage with 3D coordinates (CRMBZC10). One inclusion compound of baclofen with ferulic acid hemihydrate has been also published (ROWGOG) with 3D coordinates. The torsion angles of these baclofen molecules are also included in Table 1 for comparison. The very few structures cannot be a base of a statistical analysis, however it is interesting to note that the torsion angles are clustered. τ1 values are typically ~+165° or ~+65°, thus this suggests two preferred conformation for the –CH_2-COOH/ -–CH_2-COO^- moiety. τ2 variations show almost free rotation of the –COOH/-COO^- group; values vary from +5° to +34° and -17° to -58°. The –NH_2/ –NH_3^+ group shows less freedom of movement and the measured angles are close to ~-65° or ~-170°. The tilt of the aromatic ring shows the smallest variation. All torsion angles vary between -37° and -74° with the exception of BAC•PTA. To summarize, baclofen presents acceptable torsional flexibility in the available crystal structures and this can be one of the reason of the successful cocrystallisations.

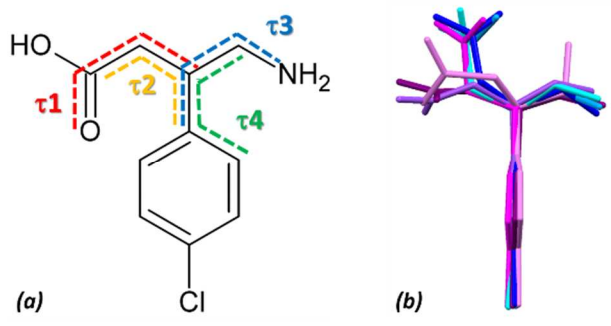


Fig. 10 Graphical explanation of the discussed torsion angles of baclofen (a) and the superimposed 7 baclofen molecules from structures BAC•BA (molecule A: dark blue, molecule B: blue), BAC•PTA (violet), (BAC^+)(HNA^-) (magenta), (2BAC^+)(OA^{2-}) (cyan), (BAC^+)(MA^-) (purple) and (BAC^+)($PTSA^-$)•IPA (lilac).

Table 1 Related torsion angles of baclofen measured on the S enantiomer in all the structures.

S enantiomer in compounds	τ1 /° -CH_2COOH/-CH_2COO^-	τ2 /° -COOH/-COO^-	τ3 /° -NH_2/-NH_3^+	τ4 /° (aromatic tilt)
BAC•BA *Molecule A*	**+164**	**+5**	**-57**	**-74**
BAC•BA *Molecule B*	**+168**	**+17**	**-57**	**-72**
BAC•PTA	**+83**	**-20**	**-175**	**+86**
(BAC^+)(HNA^-)	**+167**	**-39**	**-61**	**-37**
(2BAC^+)(OA^{2-})	**+165**	**-58**	**-67**	**-55**
(BAC^+)(MA^-)	**+68**	**+11**	**-64**	**-57**
(BAC^+)($PTSA^-$)•IPA	**+64**	**+31**	**-75**	**-68**
CRBMZC10*	**-84**	**+17**	**+168**	**+63**
RUWGOG *Molecule 1*	**+51**	**+34**	**-176**	**-70**
RUWGOG *Molecule 2*	**+72**	**+6**	**-168**	**-43**

**Angles were measured on the R enantiomer because the structure is chiral and were evaluated with the opposite values to generate a theoretical S enantiomer for clustering.*

Protonation stages of baclofen

The pKa of the amino group is 9.79 and for the carboxylic acid 3.89 in baclofen (ΔpKa= 5.90).[31] Therefore, baclofen is likely to be in the zwitterionic form in the range of the pH scale used in this work. Applying the 'quantitated' pKa rule by Cruz-Cabeza[32] for the formation of the crystals, clearly salt formation was expected for the PTSA crystal. Hence the ΔpKa values for the other combinations are between -1 and 4, the outcome of the crystallisation can be either a cocrystal or a molecular salt. Every increase in one ΔpKa difference increases the probability of the salt formation. The ΔpKa values for the crystal formation between BAC and the acids BA and PTA are on the lower range of the scale (-0.2 and -0.4, respectively) thus the formation of cocrystals are expected. Combining BAC with HNA, OA or MA more likely result in salts because the ΔpKa values are closer to 4 (1.1, 2.5 and 2.0 respectively) (Table 2).

It is important to note that the pKa value of a compound is dependent on the solvent used. The crystallisations conducted were carried out mainly in 1:1 ethanol/methanol:water. The pKa value for a carboxylic acid measured in a 1:1 alcohol:water mixture increases by ca. 1 unit[33] thus the calculated ΔpKa values are acceptable estimates.

As a result of the cocrystal/molecular salt formation the baclofen moieties are in two protonation stages‡, namely z(0) in BAC•BA and BAC•PTA and c(1) in the remaining structures. These protonation stages are common for hydrophobic amino acids.

Table 2 Calculated pKa values for BAC and the guest compounds: BA, PTA, HNA, OA, MA and PTSA; the ΔpKa values between BAC and the acids; and the observed protonation state of BAC in the crystals

compound	-COOH[1]	-NH_2	-COOH[2]	-SO_3H	ΔpKa	Salt/Cocrystal
BAC	3.9	9.8			-	
BA	4.1				-0.2	cocrystal; z(0)
PTA	4.3				-0.4	cocrystal; z(0)
HNA	2.8				1.1	salt; c(1)
OA	1.4		4.1		2.5	salt; c(1)
MA	1.9		6.1		2.0	salt; c(1)
PTSA				-2.8	6.7	salt; c(1)

Hirshfeld surface analysis

Hirshfeld surface analysis[34] was conducted on all baclofen moieties found in the prepared crystals to map their intermolecular interactions with a more sophisticated method than a simple geometrical hydrogen bond analysis. The 3D Hirshfeld surfaces are demonstrated with a 2D representation, the so called fingerprint plot (Fig. 11). The visual comparison of the two molecules for BAC•BA did not display significant differences; both molecules show strong hydrogen bonding interactions which are represented by the symmetrical spikes labelled ① on Fig. 11. Fingerprint plots of BAC•PTA and $(2BAC^+)(OA^{2-})$ are very similar to BAC•BA in that the main feature of the plot is the symmetrical spikes related to hydrogen bond donor and acceptor functions of the molecule. All the remaining figures present slightly different hydrogen bond donor-acceptor behaviour hence the spikes are asymmetrical. This is due to the fact that the baclofen is protonated in these salt structures and therefore acts more likely as a hydrogen bond donor than an acceptor. However, $(2BAC^+)(OA^{2-})$ is a salt also but the hydrogen bonding ability of the BAC is more similar to the cocrystals because of the different stoichiometry. The plot of $(BAC^+)(HNA^-)$ is distorted compared to the previous ones and show the 'chicken wings' feature, ② which is typical in crystals with $C_{aromatic}\cdots H$ interactions. A similar feature can be found on the plot of $(BAC^+)(PTSA^-)$•IPA. It is interesting to note that $(BAC^+)(MA^-)$ does not show this motif hence the packing is significantly different from all the other crystals and lacks of the hydrophobic layers.

Numerical comparison of the structures was conducted and the relevant intermolecular interactions of the baclofen moieties are presented in Table 3. The O···H interactions vary from 29%, $(2BAC^+)(OA^{2-})$ to 38% $(BAC^+)(MA^-)$. The C···H % represent the C-H···π interactions in the crystals and its highest values were measured in $(BAC^+)(HNA^-)$ and BAC•PTA. Indeed, subtle edge-to-face C-H···π interactions can be found in these two structures (Fig. S13 a and b). The % of C···C interactions is the highest in $(BAC^+)(MA^-)$ and for Molecule A in BAC•BA. These distances are informative typically about the π···π interactions. In the structure of $(BAC^+)(MA^-)$ the maleic acid sp2 carbons overlap with the aromatic ring of BAC while in BAC•BA the BAC moiety is off-set with BA (Molecule D) (Fig. S13 c and d). The highest value for H···H interactions were measured for $(BAC^+)(PTSA^-)$•IPA. The Hirshfeld surface was calculated with the main component of the disorder isopropanol left in the structure therefore this % should be treated with caution. The Cl···H and the Cl···C interactions are the highest % in $(2BAC^+)(OA^{2-})$, 18% and 4% respectively. The sigma hole, the electron deficient tip of the Cl is pointing towards neighbouring aromatic rings of BAC and its negative 'belt' is aligned with the π system of another BAC. (Fig. S13 e).

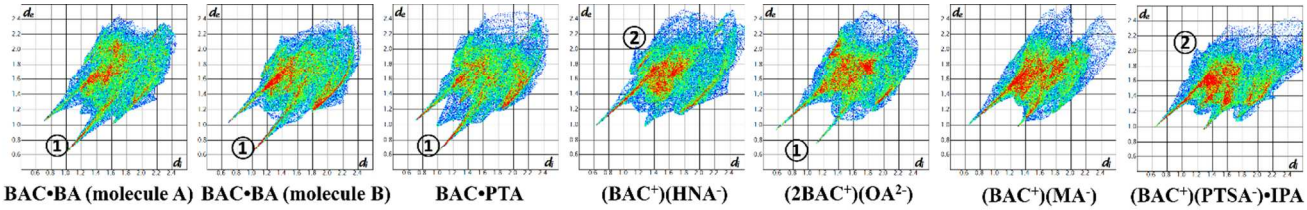


Fig. 11 Fingerprint plots of Hirshfeld surfaces generated for baclofen moieties in the analysed multicomponent crystals.

Table 3 Various intermolecular interactions of the baclofen moieties in the analysed crystal structures. (Their highest values are with bold.)

	BAC•BA (A)	BAC•BA (B)	BAC•PTA	$(BAC^+)(HNA^-)$	$(2BAC^+)(OA^{2-})$	$(BAC^{+)}(MA^-)$	$(BAC^+)(PTSA^-)$•IPA
O···H (%)	35	36	33	29	29	**38**	34
C···H (%)	16	16	**19**	**19**	10	6	14
C···C (%)	**3**	1	1	2	1	**3**	1
H···H (%)	31	31	31	34	33	30	**37**
Cl···H (%)	13	13	13	13	**18**	13	14
Cl···Cl (%)	1	0	1	0	1	0	0

Melting points of multicomponent baclofen crystals

The melting points of the baclofen crystals are summarized in Table 4 with the addition of the calculated Packing Indices (PI) and densities for clarity. It is clearly seen that the cocrystal/molecular salt formation of baclofen resulted in crystals with lower melting points than baclofen itself (MP_{BAC}= 205.5ºC). The values of the melting point, the PI and the density do not necessarily correlate. The lowest melting BAC•BA (98.1ºC) has the same PI as BAC•PTA whose melting point is 166.7ºC. Also the melting point of $(2BAC^+)(OA^{2-})$ is almost identical to that of BAC•PTA, namely but its PI and density are one of the highest values, 72.8% and 1.502 $g.cm^{-3}$, respectively. However, $(BAC^+)(MA^-)$ has the highest melting point (180.1ºC), the highest PI (73.7%) and calculated density (1.517 $g.cm^{-3}$).

The crystal structure of pure baclofen is unknown therefore its high melting point cannot be discussed with features of the intermolecular interactions. It is interesting to note that the nature

of the structure, namely being a cocrystal or molecular salt has no influence on the melting point. The two highest melting compounds are salts, (BAC^+)(MA^-) and (BAC^+)($PTSA^-$)•IPA, but the cocrystal BAC•PTA has virtually the same melting point as (BAC^+)(HNA^-) and ($2BAC^+$)(OA^{2-}) salts. BAC•BA has the lowest melting point of all the compounds and this can be justified with the unusual stoichiometry of the crystal.

The % of the various intermolecular interactions was aligned with the melting point of the crystals (Fig. 12), however there was no correlation found between them. It is worth noting that if the BAC•BA structure were excluded from the results, the correlation between the % O···H interactions and the melting points is 0.9023 (Fig.12 blue background region). This value does not show a linear correlation between the O···H interactions and MP but suggests a kind of dependence.

Table 4 Melting points of BAC and its multicomponent crystals

	MP (°C)	PI (%)	Density (g.cm^{-3})
BAC	205.4	-	-
BAC•BA	**98.1**	68.9	1.359
BAC•PTA	166.7	68.9	1.349
(BAC^+)(HNA^-)	166.4	68.8	1.386
($2BAC^+$)(OA^{2-})	165.4	72.8	1.502
(BAC^+)(MA^-)	**180.1**	**73.7**	**1.517**
(BAC^+)($PTSA^-$)•IPA *	169.5	-	1.393

** Packing Index cannot be calculated because of disordered structure.*

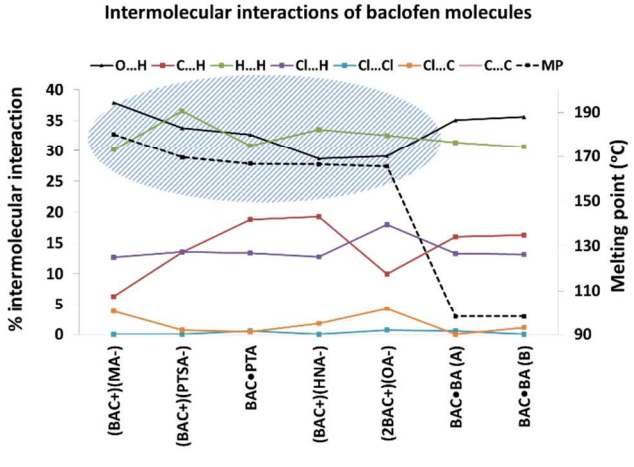


Fig. 12 Various intermolecular interactions and the melting points of multicomponent crystals of BAC.

Conclusions

In summary, the cocrystallisation of baclofen with the selected mono- and dicarboxylic acids was successful and resulted in four molecular salts: (BAC^+)(HNA^-), ($2BAC^+$)(OA^{2-}), (BAC^+)(MA^-) and (BAC^+)($PTSA^-$)•IPA, and two cocrystals: BAC•BA and BAC•PTA. The hydrogen bonding of the polar moiety of the BAC shows subtle variation as the result of the freedom of motion of these groups thus the prediction of the formation of the kind of hydrogen bonds are challenging. Similarly to α-AAs, the protonation stage of the BAC moiety varies and this property contributes successfully to the formation of hydrogen bonds with compounds with different acid strength. The packing arrangement of all the crystals (with the exception of the maleate salt) resembles the packing observed in pure hydrophobic α-AAs; namely the hydrogen bonded layers formed by the polar heads and coformers' acid functional groups alternate with the hydrophobic aromatic layers. Even though the melting points of the BAC crystals, their PI and density do not correlate, the % the O···H interactions show a kind of dependence with the melting points of the crystals.

To answer the question raised in the title, the γ-AAs, which are not often used, have H-bond properties that are similar to the α-AAs, provided that they contain hydrophobic functional groups.

γ-AAs with adequate molecular flexibility can accommodate coformer molecules in a similar manner even with variable molecular size and their structural flexibility and strong hydrogen bonding properties make them a promising crystal engineering tool. These conclusions are based on a few examples available currently and needs revision in the future once an adequate amount of structural information is available.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Details of crystal growth, crystallographic data and refinement, hydrogen bond matrics, pxrd results, and Hirshfeld surfaces. See DOI: 10.1039/b000000x/

§ Crystal data for **BAC•BA**: CCDC 1411558, $C_{41}H_{42}Cl_2N_2O_{10}$, M= 793.67, monoclinic, $P2_1/c$ (No.14), a= 14.910(3) Å, b= 35.478(7) Å, c= 7.4293(15) Å, β= 99.21(3)°, V= 3879.3(14) Å^3, Z=4, R1 [I>2.0 σI]= 0.0430, wR2 (all data)= 0.1068, N_{ref}= 7879, N_{par}= 533 and S=1.029; **BAC•PTA**: CCDC 1411562, $C_{18}H_{20}ClNO_4$, M= 349.80, triclinic, *P*-1 (No.2), a= 6.1768(12) Å, b= 7.5101(15) Å, c= 19.092(4) Å, α= 79.43(3)°, β= 82.90(3)°, γ= 84.25(3)°, V= 861.2(3) Å^3, Z=2, R1 [I>2.0 σI]= 0.0385, wR2 (all data)= 0.1045, N_{ref}= 4103, N_{par}= 223 and S=1.044; **(BAC^+)(HNA^-)**: CCDC 1411559, $C_{21}H_{20}ClNO_5$, M= 401.83, monoclinic, $P2_1/c$ (No.14), a= 6.6251(13) Å, b= 34.490(7) Å, c= 8.4698(17) Å, β= 95.75(3)°, V= 1925.6(7) Å^3, Z=4, R1 [I>2.0 σI]= 0.0424, wR2 (all data)= 0.1065, N_{ref}= 4260, N_{par}= 274 and S=1.022; **($2BAC^+$)(OA^{2-})**: CCDC 1411561, $C_{11}H_{13}ClNO_4$, M= 258.67, monoclinic, $P2_1/c$ (No.14), a= 15.035(3) Å, b= 7.2113(14) Å, c= 11.025(2) Å, β= 106.86(3)°, V= 1143.9(4) Å^3, Z=4, R1 [I>2.0 σI]= 0.0353, wR2 (all data)= 0.0979, N_{ref}= 2618, N_{par}= 171 and S=1.046; **(BAC^+)(MA^-)**: CCDC 1411560, $C_{14}H_{16}ClNO_6$, M= 329.73, monoclinic, $P2_1$ (No.4), a= 5.7206(11) Å, b= 13.677(3) Å, c= 9.6377(19) Å, β= 106.78(3)°, V= 722.00(2) Å^3, Z=2, R1 [I>2.0 σI]= 0.0330, wR2 (all data)= 0.0807, N_{ref}= 3605, N_{par}= 220 and S=1.047; **(BAC^+)($PTSA^-$)•IPA**: CCDC 1411563, $C_{20}H_{28}ClNO_6S$, M= 445.94, monoclinic, $P2_1/c$ (No.14), a= 5.4900(11) Å, b= 13.400(3) Å, c= 28.910(6) Å, β= 90.90(3)°, V= 2126.5(7) Å^3, Z=4, R1 [I>2.0 σI]= 0.0680, wR2 (all data)= 0.1444, N_{ref}= 5211, N_{par}= 284 and S=1.059.

‡ The code of type x(N) is used to define each protonation state of a given amino acid, where x= a, z or c for and anionic, zwitterionic or cationic polar head and N defines the overall charge on the molecule.

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Are gamma amino acids promising tools of crystal engineering? – Multicomponent crystals of baclofen

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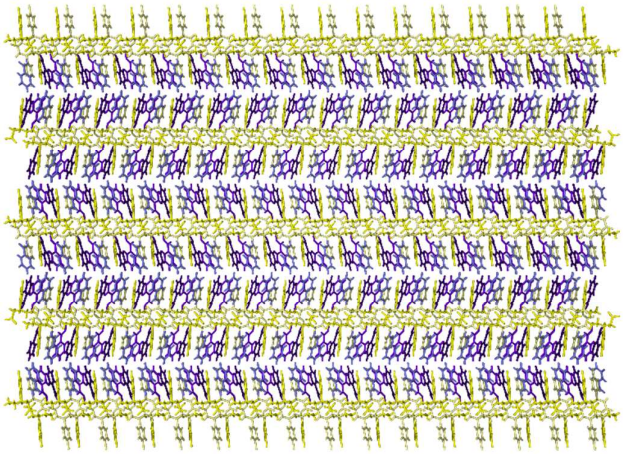

The crystal structure, thermal analysis and powder X-ray analysis of the multicomponent crystals formed between baclofen and selected monocarboxylic acids, dicarboxylic acids and p-toluene sulfonic acid are presented.