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Polymorphism and molecular conformations of non-protonated α-amino acids

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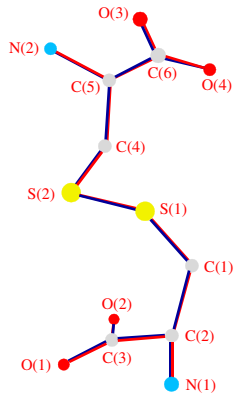
The stereochemistry of non-protonated α-amino acids was examined using the data available in the literature for polymorphic crystals of those substances. The object of the study was to ascertain the extent to which such molecules are capable of exhibiting substantial changes in their geometry. We have found that, in the currently available data base, there are two domains: those exhibiting small (or nearly negligible) variations in conformations and those exhibiting medium to disturbingly large internal divergences in stereochemical parameters. Given the information provided by the authors, on how the crystals were obtained, it is impossible to arrive at any useful conclusions on the relationship between crystal preparation and the resulting stereochemistry of the molecules present in that polymorph.

In order to obtain the information necessary to establish the nature of the molecules present in polymorphs of amino acids, we searched the Cambridge Crystallographic Data Centre CSD File,[1] which can be scanned in a number of different ways. The following criteria were used in order to accept an entry in our data bank:

(*a*) The data contained crystallographic coordinates and no erroneous information was detected by the CSD checking routine.

(*b*) The *R*-factors were reasonably small. Here, a decision must be made given that many of the structures listed in the CSD file are from different periods, including the serious problem associated with the technological transfers from film to diffractometer data and onto CCD measurements. Moreover, the recent availability of routine data collection at low temperatures posed an additional problem, even when no phase transitions occurred.

(*c*) When several structures were listed in the CSD file, the space group remained common and the cell constants did not vary appreciably, the best structure was selected for that polymorph. Does this mean older structures with relatively large *R*-factors should be eliminated for consideration, even if no

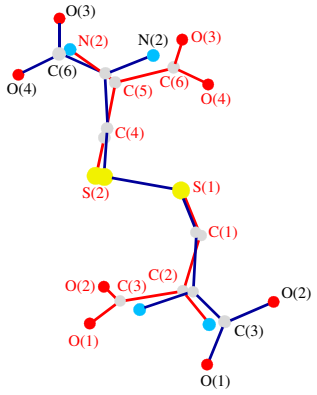


Mean deviation of the atoms/Å:

S(1)···S(1)	0.000000
S(2)···S(2)	0.022547
O(1)···O(1)	0.014197
O(2)···O(2)	0.020533
O(3)···O(3)	0.020896
O(4)···O(4)	0.023701
N(1)···N(1)	0.030294
N(2)···N(2)	0.019566
C(1)···C(1)	0.025557
C(2)···C(2)	0.022036
C(3)···C(3)	0.035500
C(4)···C(4)	0.044506
C(5)···C(5)	0.033284
C(6)···C(6)	0.043664

Figure 1 Old hexagonal L-cystine **1** (red, space group $P6_122$, REFCODE = LCYSTI10)[2] *vs.* newer hexagonal L-cystine **2** (blue, space group $P6_122$, REFCODE = LCYSTI14).[3] The same polymorph was studied by two groups, forty years apart. The comparison was made in order to estimate the differences that could occur in the quality of X-ray structures because of changes in data collection and processing methods. In this case, it is clear the differences are not very significant.

alternatives are available? To test this issue, Figure 1 shows the stereochemistry of hexagonal L-cystine as reported in a room temperature film study of 1959 [$R(F) = 12.3\%$[2]] *vs.* that reported in a 1999 diffractometric study,[3] at 110 K, for which the $R(F)$ factor was 1.4%. From the data displayed in the attached table, the distance between chemically equivalent atoms is not seriously affected by the precision differences in the two studies. Nonetheless, we know this is not always the case. Therefore, in cases where it was necessary to compare data of different precision, or not make any comparison at all, we opted for accepting the imperfection of the resulting comparisons, unless the discrepancies were totally unacceptable.



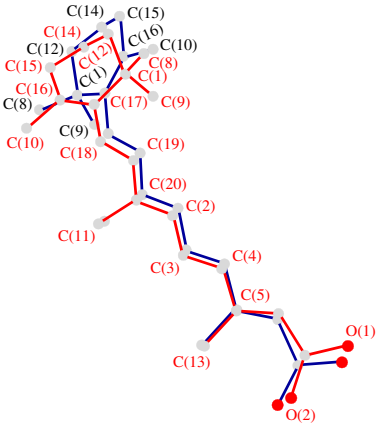
Mean deviation of the atoms/Å:

S(1)···S(1)	0.000000
S(2)···S(2)	0.220283
C(1)···C(1)	0.225489
C(2)···C(2)	0.387938
C(4)···C(4)	0.392404
C(5)···C(5)	0.493455
O(1)···O(1)	2.866398
O(2)···O(2)	4.778768
N(2)···N(2)	1.910011
O(3)···O(3)	2.621340
O(4)···O(4)	4.654791
N(1)···N(1)	1.794682
C(3)···C(3)	2.831047
C(6)···C(6)	2.699179

Figure 2 L-Cystine·HCl **1** (red, space group $C2$, REFCODE = CYSTCL02)[6] *vs.* old hexagonal L-cystine **2** (blue, space group $P6_122$, REFCODE = LCYSTI10).[2] In order to generate this figure, the absolute configuration of the HCl derivative was inverted because the C–S–S–C torsional angle of this substance is opposite in sign to that of the free aminoacid. Otherwise, match would have been impossible. As it is, the disagreement is profound, as exemplified by the distance between chemically related atoms, as listed in the table. Note that distance for the O(4) pair is close to the default limit of 5.00 Å.

(*d*) Since polymorphism can be caused by wide variety of factors, such as temperature changes[4] and/or changes of solvent medium,[5] we used data from polymorphic forms irrespective of origin (see conclusions), since we were interested in ascertaining whether or not there is a relationship between stereochemistry changes and the observed polymorphic behavior.

(*e*) We selected a uniform class of simple amino acids (exclusively non-protonated species) as opposed to studying polymorphs of all amino acid species. Here, we preferred to compare a small class of chemically uniform entities. Therefore, NH_3^+-containing species obtained from amino acid solutions, acidified with strong acids, were eliminated from consideration. The effect of protonation will be the subject of a separate study, currently under way. We know, for example, that the HCl derivative of L-cystine has an almost exactly opposite C–S–S–C torsional angle (–82.55°)[6] when compared with that of the neutral amino acid (+73.57° in the hexagonal form;[2] and +69.32° in the tetragonal form[25]). Figure 2 shows a comparison of the stereochemistry of the L-cystine[2] *vs.* the stereochemistry observed in the hydrochloride derivative.[6] For details, read the figure caption describing how that figure was generated.

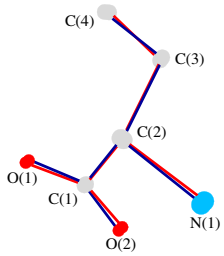


Mean deviation of the atoms/Å:

C(5)···C(5)	0.000000
C(6)···C(6)	0.135772
C(7)···C(7)	0.335928
C(20)···C(20)	0.262134
C(19)···C(19)	0.329450
C(18)···C(18)	0.356596
C(11)···C(11)	0.321168
C(17)···C17	0.548055
C(1)···C(1)	2.008620
C(2)···C(2)	0.287180
C(3)···C(3)	0.194565
C(4)···C(4)	0.182843
C(13)···C(13)	0.176694
O(1)···O(1)	0.479276
O(2)···O(2)	0.448445
C(9)···C(9)	2.632172
C(12)···C(12)	1.626324
C(14)···C(14)	1.015909
C(15)···C(15)	3.235107
C(16)···C(16)	2.856483
C(8)···C(8)	4.425555

Figure 3 Vitamine A, present in monoclinic (red, space group $P2_1/n$, REFCODE = VITAAC01) and triclinic [blue, space group $P\bar{1}$ (no. 2), REFCODE = VITAAC10] polymorphs. Both structural determinations were carried out by C. H. Stam, *Acta Crysttallogr., Sect. B, Struct. Crystallogr. Cryst. Chem.*, 1972, **28**, 2936. Note that the two conjugated, olefinic chains match fairly well, except for small torsional angular deviations that occur at the single bonds. However, the fit of the two cyclohexene rings is very poor due to the fact that their double bonds are *cis*- and *trans*- with respect to the nearest double bond of the chain. Therefore, match of the rings is impossible. That is the origin of the long C–C distances listed in the table.

Recently, we became aware of polymorphic behavior in a disparate set of compounds we were examining for reasons totally divorced from considerations of polymorphic behavior of crystalline materials currently under scrutiny and for utterly different purposes.[7–9] The fact that these substances appeared to crystallize so readily in polymorphic forms piqued our curiosity. Moreover, in two cases,[7,9] there was a definite connection between the torsional angles of rigid groups, such as $–NO_2$ ligands, held by single bonds to a metal substrate, and the occurrence of polymorphic forms. Thus, the impetus for this study.



Mean deviation of the atoms/Å:

C(2)···C(2)	0.000000
C(1)···C(1)	0.023350
C(3)···C(3)	0.072150
C(4)···C(4)	0.095800
N(1)···N(1)	0.052749
O(2)···O(2)	0.087088
O(1)···O(1)	0.076412

Figure 4 DL-2-Aminobutyric acid, compounds **1** (red, space group $I2/a$, REFCODE = DLABUT03)[11] *vs.* **2** (blue, space group $P2_1/a$, REFCODE = DLABUT05).[12] Despite the change in space group, the two molecules superpose into one another nicely. Note the small interatomic distances listed above. Except for translations present in the body-centered monoclinic form, the symmetry operations of the two space groups are the same. However, comparison of the match between the monoclinic ($I2/a$) polymorph with the tetragonal form (see Figure 5) suggest this is not a valid observation. No match is shown between the $P2_1/a$ and the $P4_2/n$ forms since agreement is nearly exact, as expected from the above comparison.

The selection of α-amino acids as our target sample is readily justified: α-amino acids are not only fundamental building blocks in biology but have been the object of much attention in the experimental and theoretical literature. Quick perusal of data bases reveal an enormous number of entries. The question of how uniform are the conformations of amino acids in crystalline form has not been recently explored. Moreover, there is an important feature of such an inquiry if one explores the conformations of amino acid molecules present in polymorphs sharing a common space group; and, more importantly, the stereochemistry of those in which the asymmetric unit contains more than one molecule. In the latter case, the conditions of crystallization are identical for the constituents of the asymmetric unit, and no questions can be raised concerning potential crystallization differences as the source of the stereochemical discrepancies, if any. Unfortunately, there is little experimental data fitting those requirements. But, there are some, and we report on them.

Since the current method of comparison of the stereochemistries of molecules in polymorphic crystals of α-amino acids is not widely known, we present some useful comments concerning the data and figures presented in this report.

(*a*) First, this study would have been impossible a few months ago since the fundamental source of our structural analysis, program MATCHIT,[10] became available in user form in December 2002.

(*b*) Hydrogen atoms were omitted in this enquiry because they were not reported in many X-ray structure determinations; and, if reported, often were poorly located or calculated at idealized positions, when geometry permitted. Thus, in order to achieve a sensible level of uniformity, we limited our study to the stereochemical effects associated with the molecular skeleton defined by the non-hydrogen atoms. In future inquiries, if the stereochemistry of the hydrogens plays a vital role, they will be considered, if accurately available.

(*c*) When comparing the stereochemistry of compounds crystallizing as racemates, it is imperative that the correct enantiomeric pairs were selected, inasmuch as it is frequently the case that two separate structural reports accidentally give coordinates of opposite enantiomers. The same problem occurs when enantiomorphic space groups can, themselves, have right- or left-handed helical chirality, as in the case of $P3_1$ *vs.* $P3_2$, $P6_5$ *vs.* $P6_1$, *etc.*

(*d*) We had to be careful in displaying a MATCHIT comparison when there is a significant discrepancy in the stereochemistries of the pair selected for comparison. In such cases, the results may be significantly affected by the choice of the atoms selected as the origin of coordinates (easily recognized in the figures, since the distance between them = 0.0000 Å, see tables attached to figures in the text). When such a problem was encountered, one must try several choices till the best fit was obtained. That condition was imposed on all the figures shown in the text. For instance, a good illustration of that problem was found to be acute in the case of the two polymorphs of Vitamin A acid. After much trial and error, we were able to obtain an excellent fit for the olefinic chain, as shown in Figure 3. The two cyclohexene rings cannot be forced to match since their double bond are either *cis* or *trans* with respect to the stereochemistry of the nearest double bond of the chain. For more details, read the figure caption.

(*e*) If the asymmetric unit of a crystal under consideration contains more than one molecule ($z' > 1.0$), those species were first compared internally. If they agreed well, only one match was made with the molecule(s) of the other crystal(s). If the internal agreement between the components of the crystal with $z' > 1$ was poor, the discordant match was selected for display. For example, L-cystein (Figure 11) contains a pair of mole-cules in the asymmetric unit whose stereochemistry is obviously different. Once this was established, decisions were made as to how many comparisons were made with such a pair. Reasons of space were often the deciding factor, as will be noted below.

(*f*) If in our figures there are no entries for the distances between atoms of a molecular pair, that distance exceeds 5.00 Å – the built-in default value beyond which an entry will not be accepted in MATCHIT.

Class A Polymorphs. Those exhibiting small stereochemical variations among molecules present in different crystals.

DL-2-Aminobutyric acid. A pair of polymorphs were reported to crystallize in space groups *I*2/*a* (ref. 11) and $P4_2/n$ (ref. 12). The results of the match are presented in Figure 4, where it is clear the agreement is excellent. The largest deviation between chemically related atoms is found in the case of C(3) (0.135 Å). A second drawing (Figure 5) shows the match between the *I*2/*a* polymorph[11] and that reported by Voogd *et al.*[13] in space group $P2_1/a$. Here, the match is even better, finding the largest deviation between chemically common atoms to be 0.096 Å, at C(4). Therefore, this is a case where it is unnecessary to carry out a match between the polymorphs in space group *I*2/*a* and $P4_2/n$. We actually performed the match, and found that the largest distance between related atoms was 0.170 Å, at C(4). For the sake of brevity, we exclude this figure from the text, as will be the case in all subsequent polymorphic pairs in which the differences found for additional pairs add no significantly useful information.

Glycine. Power *et al.*[14] reported a polymorph of glycine in space group $P2_1/n$, while Kvick *et al.*[15] determined the structure of the $P3_2$ polymorph. The pair were matched and the results displayed in Figure 6. Here, O(2) is farthest away from its relative (0.106 Å). A comparison between the $P2_1/n$ polymorph and a third one,[16] space group P_{21}, is shown in Figure 7. In this case, the distance between N(1) atomic pairs is 0.124 Å. Note that glycine is an extensively investigated substance, having 25 entries in the Cambridge file. The reason for such intense scrutiny is the very interesting electric properties of these polymorphs, a recent examination of which has been carried out by Langan *et al.*,[17] who studied the crystalline behavior of the α-form from 288 to 427 K by neutron diffraction. In that regard, we must remark that, although the distances between common atoms in the three polymorphs are not particularly large, such small deviations can be amplified to a remarkably large extent by Avogadro's number, thus: consider a crystal of glycine (MW = = 75.07 g mol^{-1}) weighing 75.07×10^{-5} g, containing 6.023×10^{18} molecules. The tiny interatomic differences of *ca.* 0.1 to 0.2 Å, found in the three polymorphs, are telescoped across such a crystal into very large displacements, indeed. Thus, electric dipoles must be oriented in quite different fashions. If, on top of those considerations of translational displacements, one adds the differences in symmetry operations present in the three space groups, it is less surprising to realize that the paraelectric/ferro-electric properties of these polymorphs offer such contrasts. We must emphasize that this is not an explanation of the difference electrical behavior of these molecules. It is, however, a sugges-tion that, given the displacements observed for their atoms, the fact that they significantly differ in physical properties becomes less strange.

L-Histidine. This amino acid has been found to crystallize in two polymorphic forms; namely, in the monoclinic system,[18] space group $P2_1$, and in the orthorhombic space group[19] $P2_12_12_1$. The results are displayed in Figure 8, where the table of discrepancies lists O(2) as the most distant pair of atoms (0.102 Å).

DL-Norleucine. Figure 9 shows the result of matching the two polymorphic forms of DL-norleucine recorded thus far. Form *1* crystallizes in space group[20] $P2_1/a$ while the other one crystallizes in *C*2/*c*.[21] The two polymorphs superpose remarkably well, the largest distance between related atomic pairs is that of C(6), which are 0.050 Å apart. Other than the lattice centering (two translations), the two space groups share a common set of symmetry operations; therefore, it may be less surprising that the two crystalline forms agree so well in their conformations, if packing forces are assumed to play a significant role in the stereochemistry of crystalline molecules.

Class B Polymorphs. Those exhibiting medium to large stereochemical variations among molecules present in different crystals.

DL-Methionine. Taniguchi *et al.*[22] reported the existence of two forms of DL-methionine. One, space group $P2_1/a$, was obtained by crystallization, at room temperature, of an aqueous solution of the amino acid; the other form, space group $I2/a$, was obtained by heating the previous form beyond the transition temperature of 333 K. Were it not for the orientation of the terminal S-carbon [C(5)], the agreement would be almost as impressive as that observed for the DL-norleucine pair (above). However, C(5) atoms point nearly 180° away from one another, and their distance is a whopping 3.059 Å. Attempts to make C(5) atoms match fail if for no other reason than, forcing them to do so, leads to an equally dismal discrepancy in the positions of the amine nitrogens.

L-Cystein: *Case 1*. In the case of this amino acid, there are two molecules in the asymmetric unit in the polymorph crystallising in space group $P2_1$.[23] Figure 11 shows the match diagram between these two molecules (**1a** and **1b**), and it is clear that the comparison is very poor. The best match was obtained by using C(2) as the origin. But, even then, the carboxylate oxygens are 0.312 Å [O(1)] and 0.627 Å [O(2)] apart. More disturbing, however, is the distance between sulfur atoms (2.573 Å). Qualitatively, one can say that the 'blue' molecule (**1b**) seems to orient the terminal –SH functional group in such a way as to make a hydrogen bond with a carboxylate oxygen. The 'red' molecule does not. Given the fact that no O–S or S–N distances are recorded in the numerical table, those distances must exceed 5.00 Å; thus, they are meaningless. Also, since there are two molecules in the asymmetric, in the ratio 1:1, the implication is that they were in equilibrium in the mother liquor, at the time of crystallization and that (*a*) their solubilities were approximately the same, (*b*) their kinetics of crystallization were very similar and that (*c*) despite being in equilibrium, the lifetimes of each, in that solution, were long enough to permit the crystallization process to proceed with both contributing equally to contents of the asymmetric unit.

L-Cystein: Case 2. When molecule **1a** of LCYSTN04 is compared with the molecule in the asymmetric unit of LCYSTN12, crystallizing in space group $P2_12_12_1$ (ref. 24) the result is displayed in Figure 12. This comparison is somewhat better than in Case 1. Nonetheless, the agreement is short of spectacular. The positions of the oxygen atoms in the two carboxylates still differ by 0.158 Å [O(1)] and 0.244 Å [O(2)]. The sulfurs diverge less than in Case 1; however, their distance is still considerable (1.808 Å).

L-Cystein: Case 3. Figure 13 depicts the comparison of molecule **1b** (in LCYSTN04) with the one present in the asymmetric unit of (LCYSTN12). The results are summarized in the table of interatomic distances, where it obvious that the results are just as bad as in Case 1. In fact, the S–S distance is even longer than in the previous case. Altogether, the qualitative aspects of the stereochemistries depicted in Figure 13 are basically the same as in Case 1, suggesting that they are energetically preferred conformations of cystein.

L-Cystine. There are two polymorphs in the literature. One form, crystallizing in $P6_122$ (refs. 2 and 3) and another one crystallizing in $P4_1$ (ref. 25). In Figure 14, we compare the stereochemistry of the tetragonal form with the newer report on the hexagonal crystals.[3] Although the disparities are not extreme, the shortest distances between symmetry related atoms is *ca*. 0.25 Å. The largest distances being in the range of 0.75 Å. No doubt these discrepancies are to be traced, at least in part, to the difference in the C–S–S–C torsional angles observed in the two forms. We do not show a plot of the older (hexagonal) L-cystine *vs*. the tetragonal form since Figure 1 shows that the two hexagonal structural determinations agreed nicely.

Tetragonal L-Cystine vs. *L-Cystine Hydrochloride*. We showed (see Figure 2) that hexagonal ($P6_122$) L-cystine and tetragonal L-cystine ($P4_1$) have widely different stereochemistries from that reported[6] for L-cystine·HCl, if for no other reason that the C–S–S–C torsional angles are opposite in sign, and of approximately the same magnitude: +73.57° in the hexagonal form,[2] +69.32° in the tetragonal form[25] and –82.55° in the hydrochloride.[6] In order to obtain even a tenuous match in the current case (Figure 15), the absolute configuration of the hydrochloride was inverted, as was done in Figure 2. Thus, the C–S–S–C portion of the molecules come together reasonably well. But, as expected, the match of the remaining fragments is as poor as observed earlier in Figure 2. In the current case, the agreement is never better than *ca*. 0.5 Å and there are some extreme disagreements; among them, C(3) (2.525 Å), O(1) (2.606 Å), O(3) (3.869 Å) and O(2) (4.293 Å).

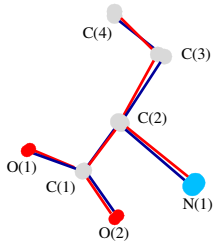
L-Glutamic acid. Case 1. An interesting case of polymorphism occurs in the case of L-glutamic acid, whose structure has been determined in two crystalline forms sharing the same space group, $P2_12_12_1$, but having widely different cell constants. The shapes of the molecules present in refs. 26 and 27 are shown, superimposed, in Figure 16. The lower part of the superimposed shapes shows a reasonable agreement from C(3) down to O(1) and O(2). Atoms C(3) are separated by 0.224 Å. Above C(3), the remaining fragments are oriented in very different fashion, leading to such large distances as O(4) (2.765 Å) and O(3) (3.143 Å). If such pair of conformations were to persist in peptides containing L-glutamic acid, the conformation at those sites could acquire widely different shapes. Even smaller discrepancies would still differ by, heretofore, unsuspected large conformational features.

L-Glutamic acid. Case 2. DL-Glutamic acid was also characterized structurally.[28] Inasmuch as such a centrosymmetric crystal contains both the D- and the L-isomers, we decided to match that polymorph with L-glutamic acid[26] to ascertain the extent to which the L-form present in ref. 28 agrees or disagrees in stereochemistry with that reported in ref. 26. The results are shown in Figure 17. There, it is obvious that the disagreement is major. For example, C(3) differ by 1.482 Å, a distance comparable to an olefinic bond. The oxygens of both carboxylates are widely apart, O(1) by 1.518 Å, O(2) by 1.227 Å, O(3) by 1.430 Å and O(4) by 1.544 Å. Thus, remarks made in the previous section are equally appropriate here. For brevity, we do not match the molecules reported in refs. 27 and 28. We simply say that the results are equally disturbing. Moreover, the idea of relative skeletal rigidity of amino acids is seriously in question, given these results.

L-Glutamic acid. Case 3. An extreme case of disagreement in molecular conformations is depicted in Figure 18, where the molecule found in polymorph[27] is compared with that in ref. 28. Inasmuch as the latter is a racemic species, the reported structure and its inverse were compared with the chirally pure amino acid molecule. No doubt, this is the worst match we have observed, thus far. Recall that the matching program has a cut-off of 5.00 Å, beyond which no interatomic distances are listed. Thus, since there are no entries for O(3) and O(4), the implication is clear. C(5) barely made the list. It is truly remarkable that the entire C(4)–C(5)–O(3)–O(4) fragments deviate from one another in such drastic fashion. However, that is what the published data produces.

We have analyzed the facts on molecular conformations of α-amino acids from published sources. At this stage we simply state them and refrain from excessive speculation since the information available on the origin of the observed phase transistion(s) were as useful as 'the crystals were a gift from XXXX'. It is hoped that, in the future, journals are a little more strict in insisting on a scientifically useful detailing on the mode of generating crystalline substances for X-ray analysis.

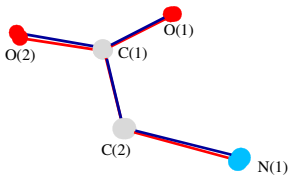
We thank the Robert A. Welch Foundation for support of these studies (Grant 592 to IB) and for postdoctoral support to Uday Mukhopadhyay. Ivan Bernal thanks Professor Raymond E. Davis (University of Texas, Austin) for his help and encouragement in developing MATCHIT, whose roots are firmly based on his pioneering program BMFIT.



Mean deviation of the atoms/Å:

C(2)···C(2)	0.000000
C(1)···C(1)	0.044380
C(3)···C(3)	0.135373
C(4)···C(4)	0.071866
O(1)···O(1)	0.047493
O(2)···O(2)	0.074738
N(1)···N(1)	0.114502

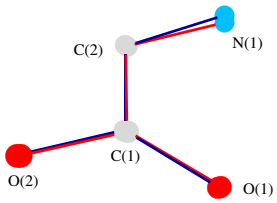
Figure 5 DL-2-Aminobutyric acid, compounds **1** (red, space group *I*2/*a*, REFCODE = DLABUT03)[11] *vs.* **2** (blue, space group $P4_2/n$, REFCODE = DLABUT11).[13] Once more, an even more drastic space group change failed to cause serious discrepancies in conformations of the two molecules under comparison. Because of that, no comparison was made between the molecules reported in refs. 12 and 13.



Mean deviation of the atoms/Å:

C(2)···C(2)	0.000000
C(1)···C(1)	0.027900
N(1)···N(1)	0.028803
O(1)···O(1)	0.025706
O(2)···O(2)	0.105993

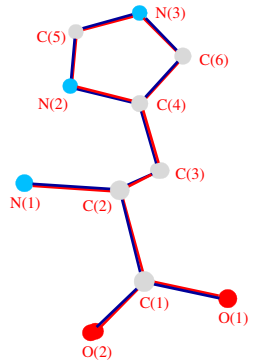
Figure 6 Glycine, compounds **1** (red, space group $P2_1/n$, REFCODE = GLYCIN05)[14] *vs.* **2** (blue, space group $P3_2$, REFCODE = GLYCIN16).[15] The difference in stereochemistry of glycine in these two polymorphs is incredibly close given the drastic differences in space groups. Note that **2** crystallizes in an enantiomorphic space group (γ-form), whereas **1** crystallizes in a centrosymmetric space group (α-form). Since the molecular skeleton is virtually identical, the physical properties of these two crystalline forms must be due to packing differences and not to molecular stereochemical variations.



Mean deviation of the atoms/Å:

C(1)···C(1)	0.000000
C(2)···C(2)	0.019063
O(1)···O(1)	0.015086
O(2)···O(2)	0.012297
N(1)···N(1)	0.124053

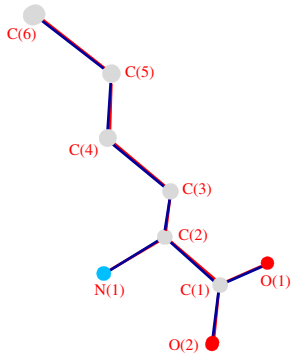
Figure 7 Glycine, compounds **1** (red, space group $P2_1/n$, REFCODE = GLYCIN05)[14] *vs.* **2** (blue, space group $P2_1$, REFCODE = GLYCIN25).[16] The distances between chemically equivalent atoms is still excellent, even if N(1) deviates considerably more than other atoms in this pair and in the preceding one. Again, we are matching a molecule in an enantiomorphic lattice (**2**; β-form) *vs.* one in a centrosymmetric space group (**1**, α-form). The geometry at C(2) shows the configuration at C(2) has been properly preserved, as was the case in Figure 6. Matching of the β- and γ-forms is unnecessary, for obvious reasons.



Mean deviation of the atoms/Å:

C(2)···C(2)	0.000000
C(1)···C(1)	0.043847
C(3)···C(3)	0.044641
C(4)···C(4)	0.032726
C(5)···C(5)	0.022772
C(6)···C(6)	0.036994
N(1)···N(1)	0.025369
N(2)···N(2)	0.041842
N(3)···N(3)	0.045990
O(1)···O(1)	0.020846
O(2)···O(2)	0.101581

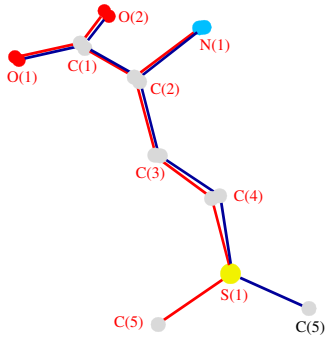
Figure 8 L-Histidine, compounds **1** (red, space group $P2_1$, REFCODE = LHISTD04)[18] *vs.* **2** (blue, space group $P2_12_12_1$, REFCODE = LHISTD10).[19] With the minor exception of O(2), the deviations from nearly perfect match did not exceed 0.046 Å. Therefore, for this pair of polymorphs, at least, the implication is that the skeleton of this amino acid is not very susceptible to conformational changes, possibly as a result of a hydrogen-bonding 'lock' between N(1) and N(2). Further work in this area would be desirable, including NMR studies.



Mean deviation of the atoms/Å:

C(2)···C(2)	0.000000
C(1)···C(1)	0.019248
C(3)···C(3)	0.009352
O(1)···O(1)	0.027386
O(2)···O(2)	0.025366
N(1)···N(1)	0.007923
C(4)···C(4)	0.028976
C(5)···C(5)	0.026601
C(6)···C(6)	0.049829

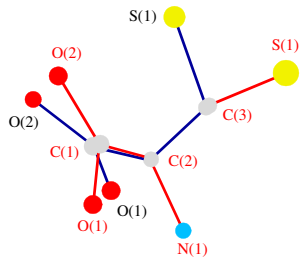
Figure 9 DL-Norleucine, compounds **1** (red, space group $P2_1/a$, REFCODE = DLNLUA01)[20] *vs.* **2** (blue, space group *C*2/*c*, REFCODE = DLNLUA02).[21] We could not expect a better fit than this pair in the two polymorphs of DL-norleucin, whose distance are only a few standard deviations from those of the bonds determined for the original studies. In a way, this result is interesting from the point of view of the fact that the long, aliphatic, C(3)–C(6) chain should be quite flexible.



Mean deviation of the atoms/Å:

S(1)···S(1)	0.000000
O(1)···O(1)	0.081688
O(2)···O(2)	0.080621
N(1)···N(1)	0.072986
C(1)···C(1)	0.069602
C(2)···C(2)	0.081782
C(3)···C(3)	0.111498
C(4)···C(4)	0.168089
C(5)···C(5)	3.059364

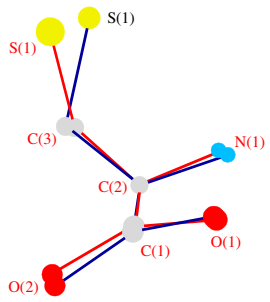
Figure 10 DL-Methionine, polymorphs **1** (red, space group $P2_1/a$, REFCODE = DLMETA02)[22] *vs.* **2** (blue, space group *I*2/*a*, REFCODE = DLMETA03).[22] The structures of both polymorphs were reported in a single paper. The skeletal match, except at C(5), is very good. Interestingly, C(5) atoms point in totally opposite directions, which is remindful of the stereochemical differences described in the case of L-cystein (Figure 11) where the sulfur atoms display a similar opposition. Another interesting feature of these polymorphic pair, which may account for the differing conformations of C(5), is the fact that **1** (β-form) was obtained at room temperature from an aqueous solution, while **2** (α-form) was obtained by heating the β-form beyond the phase transition, which occurs at 333 K.



Mean deviation of the atoms/Å:

C(2)···C(2)	0.000000
C(1)···C(1)	0.143027
C(3)···C(3)	0.310319
N(1)···N(1)	0.115896
O(1)···O(1)	0.311910
O(2)···O(2)	0.626699
S(1)···S(1)	2.572561

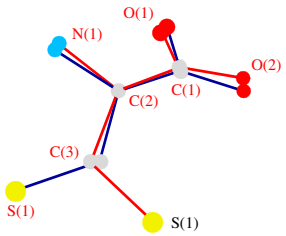
Figure 11 L-Cystein, compounds **1a** (red, space group $P2_1$, REFCODE = LCYSTN04)[23] *vs.* **1b** (blue, space group $P2_1$, REFCODE = LCYSTN04).[23] There are two independent molecules (**1a** and **1b**) in the asymmetric unit of this polymorph. Interestingly, the match is poor, in general. At the S(1) atoms, it is very disturbing since the two molecules came from the solution under identical conditions, at the same time. Thus, no environmental origin can be used as an excuse for the disparity observed.



Mean deviation of the atoms/Å:

C(2)···C(2)	0.000000
N(1)···N(1)	0.148776
C(1)···C(1)	0.066771
C(3)···C(3)	0.200806
O(1)···O(1)	0.157810
O(2)···O(2)	0.243774
S(1)···S(1)	1.808490

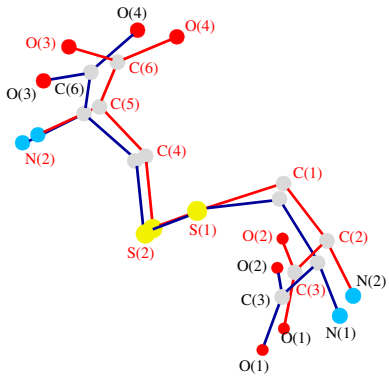
Figure 12 L-Cystein, compound **1a** (red, space group $P2_1$, REFCODE = LCYSTN04)[23] *vs.* **2** (blue, space group $P2_12_12_1$, REFCODE = LCYSTN12).[24] It is interesting to note that **1a**[23] differs in stereochemistry to a lesser extent with respect to **2**, than it does with its twin **1b** (see Figure 11). This is surprising if one takes into account that the space groups differ, whereas **1a** and **1b** are both in the asymmetric unit of same polymorphic crystal. Moreover, it is unlikely that the crystallization conditions, solvents (if any), *etc.*, were the same, whereas in the case of **1a** and **1b**, they were identical. In this case, it is impossible to ascertain those facts since Kerr *et al.*[24] give no details as to the origin of their crystal. In this match, the sulfur atoms are closer together; however, the match is still very poor.



Mean deviation of the atoms/Å:

C(2)···C(2)	0.000000
C(3)···C(3)	0.259799
N(1)···N(1)	0.163304
O(1)···O(1)	0.216910
O(2)···O(2)	0.258554
C(1)···C(1)	0.061395
S(1)···S(1)	2.786133

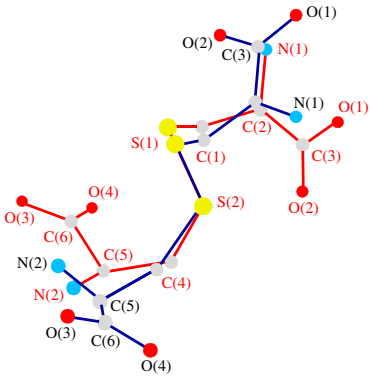
Figure 13 L-Cystein, compound **1b** (red, space group $P2_1$, REFCODE = LCYSTN04)[23] *vs.* **2** (blue, space group $P2_12_12_1$, REFCODE = LCYSTN12).[24] The match between **1b** and **2** is just as bad as that observed for **1a** and **1b**. In fact, if anything, the S–S distance is somewhat worse. Note that the problem is not to be associated with chirality mismatch at C(2) (the α-carbon) since they are polymorphic crystals of L-cystein, and their space groups are similar.



Mean deviation of the atoms/Å:

S(1)···S(1)	0.000000
S(2)···S(2)	0.246194
O(2)···O(2)	0.670575
O(3)···O(3)	0.745174
O(4)···O(4)	0.764312
N(1)···N(1)	0.443874
N(2)···N(2)	0.437793
C(1)···C(1)	0.361580
C(2)···C(2)	0.471209
C(3)···C(3)	0.577426
C(4)···C(4)	0.265560
C(5)···C(5)	0.361927
O(1)···O(1)	0.661318
C(6)···C(6)	0.563610

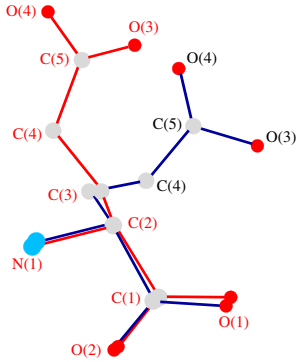
Figure 14 Match of tetragonal L-cystine **1** (red, space group $P4_1$, REFCODE = LCYSTI11)[25] *vs.* newer hexagonal L-cystine **2** (blue, space group $P6_122$, REFCODE = LCYSTI14).[3] Since the amino acid is L-cystine in both cases, the chirality of the two compounds is the same; but, the C–S–S–C torsional angle changes enough (+69.32° in **1** *vs.* +73.57° in **2**) to cause the mismatch of the other fragments, as given in the table.



Mean deviation of the atoms/Å:

S(2)···S(2)	0.000000
S(1)···S(1)	0.465069
C(1)···C(1)	0.681435
C(2)···C(2)	0.487609
C(4)···C(4)	0.665334
C(5)···C(5)	1.223336
N(1)···N(1)	1.841410
O(1)···O(1)	2.606247
O(2)···O(2)	4.293095
O(3)···O(3)	3.869162
C(3)···C(3)	2.524932
C(6)···C(6)	3.576761
N(2)···N(2)	0.609668

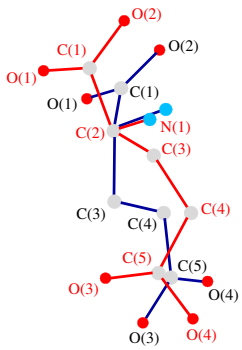
Figure 15 L-Cystine·HCl **1** (red, space group *C*2, REFCODE = CYSTCL02)[6] *vs.* tetragonal L-cystine **2** (blue, space group $P4_1$, REFCODE = LCYSTI11).[25] As was the case for the pair depicted in Figure 2, the absolute configuration of the HCl derivative was inverted to allow a more reasonable fit of the C–S–S–S fragment, which is not very close, given the 0.465 Å distance between the S(1) pair. This is in spite of the fact that S(2) was used as the origin atom. Note also that the distance between the O(4) pair of atoms is not listed, having exceeded the default value of 5.00 Å, maximum.



Mean deviation of the atoms/Å:

C(2)···C(2)	0.000000
C(1)···C(1)	0.100887
C(3)···C(3)	0.224446
O(1)···O(1)	0.188542
O(2)···O(2)	0.092278
N(1)···N(1)	0.176287
O(3)···O(3)	3.142765
O(4)···O(4)	2.764956
C(4)···C(4)	2.260690
C(5)···C(5)	2.624132

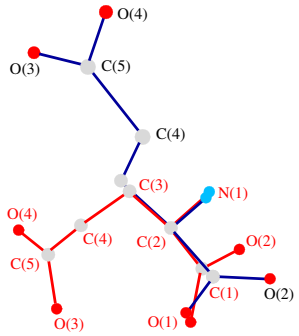
Figure 16 L-Glutamic acid, compounds **1** (red, space group $P2_12_12_1$, REFCODE = LGLUAC01)[26] *vs.* **2** (blue, space group $P2_12_12_1$, REFCODE = LGLUAC02).[27] The space group is the same for both crystalline forms, but the cell constants are quite different. The match in the lower part of the figure is not poor; however, the upper part is markedly mismatched. Distances between the carboxylic oxygens range as high as 3.143 Å. If such conformational difference can occur in polypeptides, conformations would be widely different at different sites of the same amino acid.



Mean deviation of the atoms/Å:

C(2)···C(2)	0.000000
C(1)···C(1)	1.029455
N(1)···N(1)	0.474872
O(1)···O(1)	1.518047
O(2)···O(2)	1.227013
C(3)···C(3)	1.481559
C(4)···C(4)	0.792288
O(3)···O(3)	1.430283
O(4)···O(4)	1.544560
C(5)···C(5)	0.852832

Figure 17 L- and DL-glutamic acid, compounds **1** (red, space group $P2_12_12_1$, REFCODE = LGLUAC01)[26] *vs.* **2** (blue, space group *Pbca*, REFCODE = CADVUY01).[28] The chirality at C(2) is clearly the same for both molecules depicted in this figure; otherwise, the $-NH_3(+)$ moieties would not point in the same direction. Yet, the conformational differences are very large, comparable to interatomic bonds. Consequently, it appears that glutamic acid is quite flexible in its conformational preferences. In fact, in that respect it resembles L-cystein (see Figures 11–13).



Mean deviation of the atoms/Å:

C(2)···C(2)	0.000000
C(1)···C(1)	0.309267
C(3)···C(3)	0.337180
N(1)···N(1)	0.179575
O(1)···O(1)	0.615169
O(2)···O(2)	1.261621
C(4)···C(4)	2.450576
C(5)···C(5)	4.606433

Figure 18 L- and DL-glutamic acid, compounds **1** (red, space group $P2_12_12_1$, REFCODE = LGLUAC02)[27] *vs.* **2** (blue, space group *Pbca*, REFCODE = CADVUY01).[28] Easily the worst match of the set. The conformation of the C(3)–C(4)–C(5) fragment is so disparate that the two molecules could, easily, be mistaken for different compounds. Note that O(3) and O(4) are so far from one another, their interatomic distance is not even listed in the table. Therefore, these atoms are more than 5.00 Å apart.

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1 CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk). The material can be obtained, free of charge, *via* the Internet at http://pubs.acs.org/ by citing the correct CIF or registration number.

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