research papers

Geometry of the 2-aminoheterocyclic–carboxylic acid $R_2^2(8)$ graph set: implications for crystal engineering

Daniel E. Lynch* and Glyn D. Jones

School of Science and the Environment, Coventry University, Coventry CV1 5FB, England

Correspondence e-mail:
d.lynch@coventry.ac.uk

The geometry of the $R_2^2(8)$ graph set formed between a 2-aminoheterocyclic ring containing an Nsp^2 atom (in the 1-position of the ring) and a carboxylic acid has been studied. Collating data from known co-crystal structures containing five- and six-membered heterocyclic rings from the Cambridge Structural Database revealed unexpected differences between two kinds of non-hydrogen contact distances, and between specific bond distances and angles of the heterocycle. Not only were the interatomic non-hydrogen distances between the N atoms (heterocycle) and O atoms (carboxylate) asymmetric, but also the 2-amino N atom (N21) to the heterocyclic C atom (C2) bond was shorter than the C2 to N1sp^2 bond. However, this shortening of the C2—N21 bond was not observed in the examples where N21 was substituted with a non-H atom. For the six-membered rings the data also showed that as the C2—N21 bond shortened the N1—C2—N21 bond angle increased.

1. Introduction

According to Allen *et al.* (1998), when a 2-aminoheterocyclic ring containing an Nsp^2 atom in the 1-position of the ring crystallizes in the presence of a carboxylic acid there is a 76% probability that the two groups will form a hydrogen-bonded $R_2^2(8)$ graph set (Bernstein *et al.*, 1995) dimer (as shown in Fig. 1*a*). This probability is increased to 82% if proton transfer to the heterocyclic nitrogen occurs, thus forming an organic salt complex (as for Fig. 1*b*). These levels of predictability make the two configurations of this specific $R_2^2(8)$ motif respectively the fifth and fourth most probable associated recognition sites in the solid state. As a practical application of such high levels of predictable interaction, the base binding site (N=C—NH), appropriately arranged in a host molecule, has been used to great effect in selectively binding guest molecules containing multiple carboxylic acids in attempts to mimic biological functions and to better understand the processes of molecular recognition (Ballester *et al.*, 1997; Metzger *et al.*, 1997).

The geometry of the $R_2^2(8)$ pattern formed between carboxylic acids and the side chains of the amino acids arginine, asparagine and glutamine has been previously studied (Shimoni *et al.*, 1996), but in each of these cases the Nsp^2 atom is not contained in a heterocyclic ring. Over the past 13 years the principal author has been studying the individual structures of adducts of carboxylic acids with 2-aminoheterocyclic ring systems, such as 2-aminopyridine (2APy), 2-aminopyrimidine (2AP) and the 2-aminothiazole derivatives, and more recently has uncovered several unexpected geometrical anomalies, such as the differences between the N1···O11 and N21···O10 interatomic distances (Lynch *et al.*, 1997; Lynch, Nicholls *et al.*, 1999; naming indicated in Fig. 1*c*) and the N1—C2 and C2—N21 bond lengths (Lynch *et al.*, 2000). Analysis of
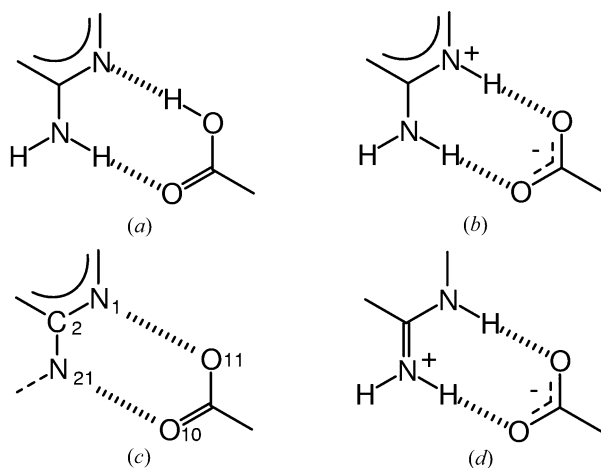
Table 1
Average distances (Å) and angles (°) for the geometrical features described in the six-membered ring heterocyclic series, with s.u.s in parentheses, as well as the number of structures (N_s) used to calculate each value.

Co-crystals	N1···O11		N21···O10	N1—C2		C2—N21	N1—C2—N21	N_s
NH$_2$	2.69 (8)	<	2.85 (10)	1.352 (9)	>	1.321 (16)	118 (1)	98
Adduct	2.68	<	2.90	1.35	>	1.33	118	31
Salt	2.69	<	2.83	1.35	>	1.32	118	67
NHC	2.66 (6)	<	2.93 (10)	1.346 (14)	<	1.39 (2)	114 (2)	37
Adduct	2.67	<	2.95	1.35	<	1.39	114	30
Salt	2.58	<	2.85	1.35	=	1.35	116	7
NHS	2.67 (7)	<	2.80 (4)	1.340 (9)	<	1.385 (7)	114.3 (8)	8

Co-crystals	N1—C2		C2—N21	N1—C2—N21	CSD reference
2AP	1.349	>	1.342	117.5	AMPYRM01
2APy	1.345	<	1.351	116.5	AMPYRD
2A4P	1.333	>	1.322	119.4	ICYTIN
	1.331	>	1.323	120.3	
4APO	1.337	<	1.342	117.1	CYTOSIN01
SMZ	1.343	<	1.412	112.1	SLFNMD10

on the carboxylic acid. If simple resonance were the only explanation then all such unions between a 2-aminoheterocyclic and a carboxylic acid would result in the formation of a salt complex, or in at least a delocalized H atom (equidistant between O11 and N1) to aid in the stabilization of the heterocyclic N atom. Furthermore, the N1—C2 and C2—N21 bond lengths would be similar, as observed in the hydrohalide salts. The occurrence of proton transfer in pyridine–carboxylic acid complexes was thought to require a pK_a difference of 3.75 between the two constituent molecules (Johnson & Rumon, 1965). In this paper the authors studied a range of pyridine–benzoic acid co-crystals using IR spectroscopy to identify which combinations formed adducts and which formed salts. However, this 'rule of thumb' with pK_a differences, which has yet to be disproved for pyridine–carboxylic acid complexes, does not apply to 2-aminoheterocyclic complexes, as observed by Etter & Adsmond (1990) and the principal author (Lynch *et al.*, 1997), where the possible occurrence of proton transfer further complicates an explanation of the dynamics of the $R_2^2(8)$ association under

the parent structures of 2AP and 2APy reveals that the N1—C2 and C2—N21 bond lengths are approximately equal (Table 1), with the coplanar NH$_2$ group contributing to the molecular resonance, but the principal author has found that these distances (studied in individual structures) have been found to alter (N1—C2 > C2—N21) upon co-crystallization with a carboxylic acid.
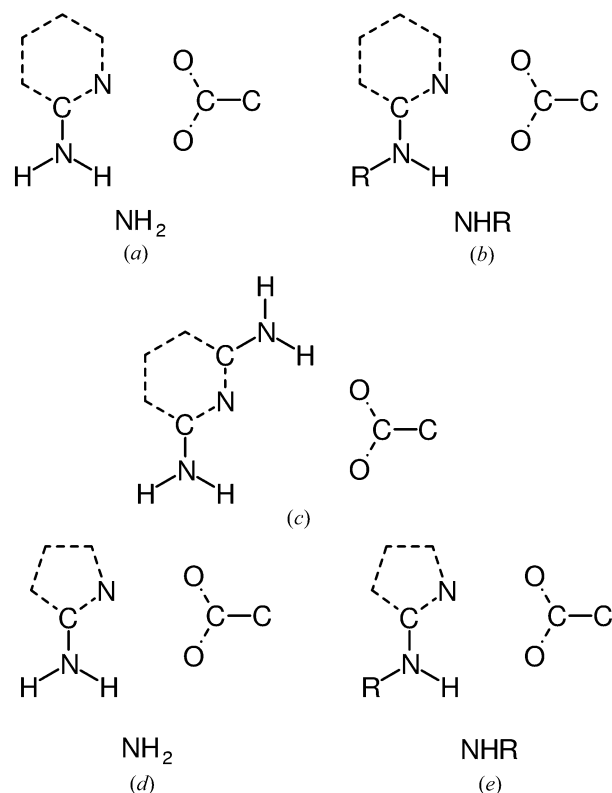
The initial interpretation of this phenomenon was suggested following analysis of the 2APy salt complex with propynoate (Wheeler & Foxman, 1994), where the authors discussed the possibility of a resonance contribution to the C2—N21 bond (as shown in Fig. 1d). Although this explanation may be suitable for salt complexes, including the hydrohalide salts of such molecules, it does not fully explain the bond length discrepancy in adduct structures where the H atom is retained

Figure 1
Chemical diagrams showing the 2-aminoheterocyclic–carboxylic acid $R_2^2(8)$ dimer for (a) an adduct or (b) a salt complex; (c) the naming scheme adopted for this study and (d) the resonance form suggested by Wheeler & Foxman (1994) to explain the shortened C2—N21 bond length

Figure 2
Chemical diagrams showing the templates used to perform the CSD searches: (a) and (b) were used for the six-membered ring series, while (d) and (e) were used to search for five-membered ring examples. Structures fitting the template shown in (c) were not considered in this study. Atoms not indicated are 'any atom', while dashed bond lines indicate 'any bond'. R = any non-H atom.

investigation in this study. Currently, no detailed survey of the geometry of the $R_2^2(8)$ motif for 2-aminoheterocyclic derivative systems, with either six- or five-membered rings, has been undertaken. Here we report the results of such a survey and highlight consistent changes that occur in the N=C—NH base site and suggest possible explanations for these anomalies.

2. Methodology

In order to ensure that any differences arising due to the formation of the $R_2^2(8)$ pattern were real, *i.e.* were not artefacts due to low-quality data and high s.u. ranges, only structures with $R < 0.08$ were considered. Practically, this meant that all distances and angles used quoted s.u.s in the fourth significant figure. Candidates with $R < 0.08$, fitting the molecular parameters outlined in Fig. 2, and exhibiting an $R_2^2(8)$ graph-set association, were identified using the Cambridge Structural Database (Allen, 2002), while individual geometrical parameters were determined using *PLATON*97 (Spek, 2003) and *Mercury* (Version 1.2.1, Bruno *et al.*, 2002). Following the

naming scheme in Fig. 1(*c*), the geometrical features recorded were the interatomic distances N1---O11 and N21---O10, the 2-aminoheterocyclic bond distances N1—C2 and C2—N21, and the angle N1—C2—N21. However, structures matching Fig. 2(*c*) were not included in this study because such structures exhibit their own unique bond geometry through the H$_2$N—C—N—C—NH$_2$ moiety (unpublished observation of the principal author).

All carboxylic H-atom positions were noted as indicated in either their original publications or the Cambridge Structural Database. No structures were re-investigated by the authors of this paper to reaffirm the locations of these H atoms. The classification of each structure as either an adduct or a salt was solely reliant upon the original analysis of the author/s of each individual publication/structural entry. Wherever possible the original publications were checked to confirm that the carboxylic H atoms were located from Fourier syntheses and no cases were found where the position of the H atom was considered ambiguous. Thus, the exclusion of structures with $R > 0.08$ was advantageous.
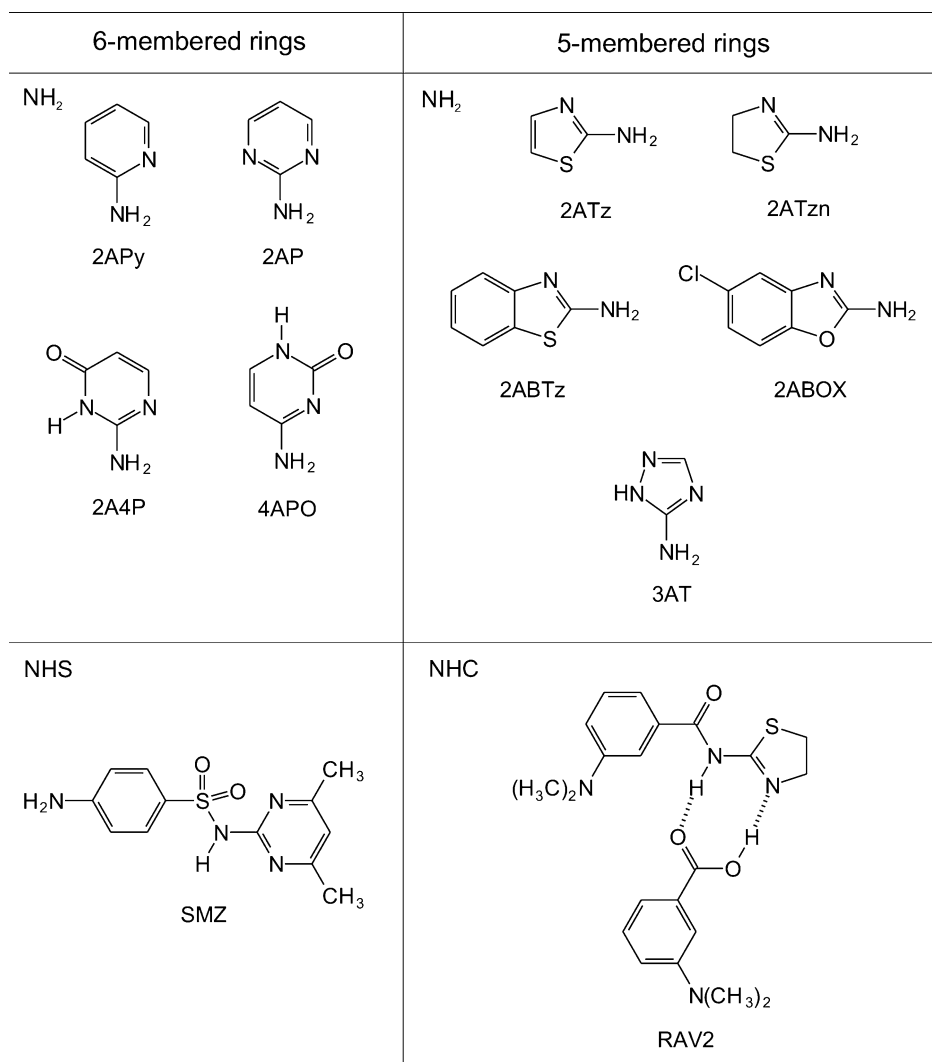

Figure 3
Chemical diagrams of the base molecules named in this study.

3. Discussion

3.1. Six-membered ring heterocyclics

In total, 98 suitable examples fitting the structural models shown in Fig. 2(*a*) (designated as NH$_2$) and 45 fitting Fig. 2(*b*) (designated as NHR) were found. The calculated mean result for each geometrical feature is listed in Table 1 along with the number of structures (N_s) used to compile that specific data set. For most results (as indicated in Table 1) it was necessary to separate the data into either adduct (Fig. 1*a*) or salt (Fig. 1*b*) complexes because significant differences arose that needed to be individually highlighted. Furthermore, with the last three parameters referring to the heterocyclic base site, the comparable distances in the parent molecules are also included. Four heterocyclic base molecules appear in the vast majority of examples: these are 2-aminopyridine (2APy), 2-aminopyrimidine (2AP), 2-aminopyrimidin-4(1*H*)-one (2A4P or isocytosine) and 4-aminopyrimidin-2(1*H*)-one (4APO or cytosine; Fig. 3). The NHR analogues were subdivided into NHC and NHS, fitting the two types of heterocyclic bases found. All NHS structures contained sulfamethazine (SMZ), except for one that contained 5-methoxysulfadiazine,

thus the separation from the NHC structures was carried out to observe any differences owing to the presence of the sulfonyl group. All SMZ examples, including the 5-methoxysulfadiazine example, were adducts with the carboxylic acid groups retaining their H atoms.

The average results for N1---O11 in Table 1 show that the primary hydrogen-bonding attachment between the acid group and the heterocyclic N atom remains consistent, irrespective of whether the base is of the type NH_2 or NHR. The limiting values over all examples were 2.996 Å (upper) and 2.526 Å (lower). The results for the secondary hydrogen-bonding interaction, N21---O10, show slight differences, with distances for the NH_2 examples being on average shorter than for NHC, although in both cases the separated adduct and salt results show minimal differences, with the salt examples being slightly shorter. This may be due to the increased electrostatic attraction between the charged constituents and/or the increased hydrogen-bond donor strength (or hardness in terms of hard–soft acid–base theory) of N^+-H as opposed to $O-H$. However, the average N21—O10 distance for the NHS examples is shorter than those for the NH_2 and NHC examples, which may be a direct result of the attachment of the electron-accepting sulfonyl group. Sulfonamides are electron accepting and may attract the lone pairs of electrons on O10 (a carbonyl oxygen), which is closer to N—H, although more likely is the fact that the sulfonamide N—H is quite acidic with $pK_a = 2.65$ (Merck & Co. Inc., 2001), thus promoting reduced hydrogen-bond donor–acceptor distances. In contrast, the sulfonamide NH_2 group has a pK_a value of 7.4. The overall limiting values for N21—O10 are 3.213 Å (upper) and 2.567 Å (lower). A comparison of the two interatomic distances N1—O11 and N21—O10 for all data reveals that in all but 12 examples, N1—O11 is always shorter by $\simeq 0.2$ Å. Of these 12 exceptions, nine involve 4APO and three involve 2A4P, or derivatives thereof. A comparison of N21—O10 *versus* N1—O11 is shown in Fig. 4: although this indicates that there is no specific correlation between the two, it does aid in the visualization of the distribution of all of the data.

The parameters N1—C2, C2—N21 and N1—C2—N21 are all from the base component and are therefore inter-related. Comparisons between the three parameters can be observed in Figs. 5 and 6, as well as Table 1. Comparison of the average N1—C2 distances from Table 1 indicates that this bond length is consistent across NH_2- and NHC-type examples, with the NHS bond length being slightly reduced. However, inspection of the full data set (Fig. 5) reveals not only that the bond lengths for the parent bases are essentially in the middle of the distribution, but also that, in terms of the N1—C2 bond length, there is very little distinction between all examples, except for one 2APy equivalent base unit in the Ballester *et al.* (1997) paper. This N1—C2 bond length (seen in the top left-hand corner of Fig. 5) is 1.413 Å, which becomes the upper value for the N1—C2 bond lengths, while the lower value is 1.297 Å. Investigation of the C2—N21 bond lengths in Fig. 6 shows a different scenario with a distinct difference between NH_2- and NHR-type examples. There is also a distinct difference in the C2—N21 bond lengths of the parent bases with all bar two NH_2-type examples displaying shorter distances, only 2A4P has a C2—N21 bond length approximately in the middle of the C2—N21 bond-length range. The average values reflect this with the NH_2 average being $\simeq 0.07$ Å shorter than the NHR values. Comparison should also be made between both bond lengths with C2—N21 being $\simeq 0.03$ Å shorter than N1—C2 for the NH_2 examples, whereas for the NHR examples N1—C2 is $\simeq 0.04$ Å shorter than C2—N21. Overall, only subtle differences occur when comparing adducts and salts, although note that the average salt bond distances for the NHC examples are the same.

Investigation of the N1—C2—N21 bond angle shown in Figs. 5 and 6 reveals that there is a distinct difference between the NH_2- and NHR-type examples, with the average values
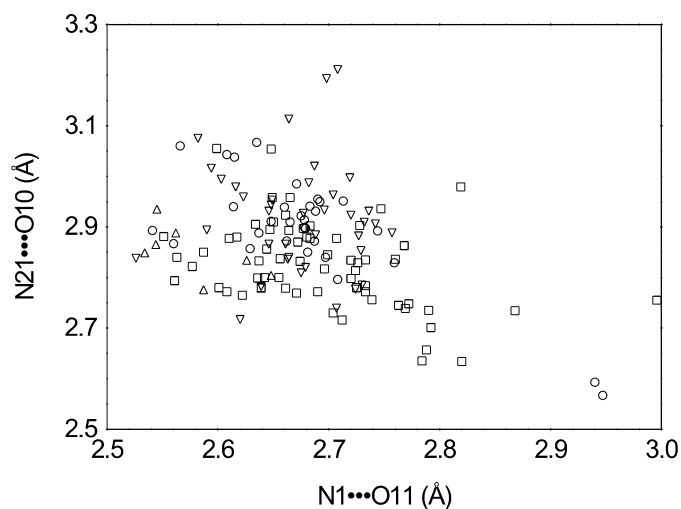

Figure 4
Plot of N21---O10 interatomic distance (Å) *versus* N1---O11 interatomic distance (Å). Key: ○ NH_2 adducts, □ NH_2 salts, ▽ NHR adducts and △ NHR salts.
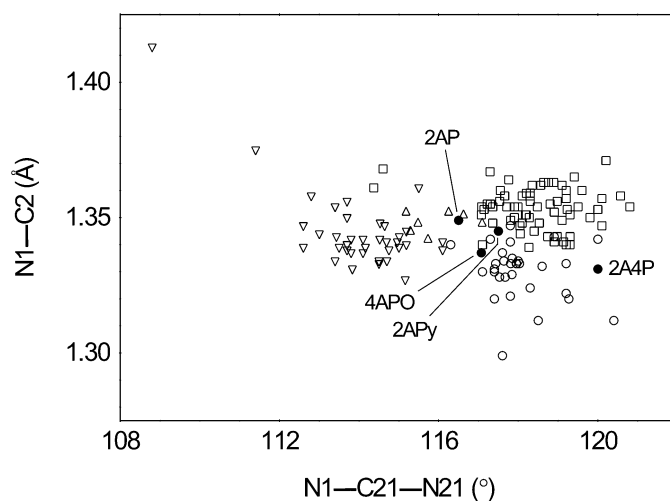

Figure 5
Plot of N1—C2 bond length (Å) *versus* N1—C2—N21 bond angle (°). Key: ○ NH_2 adducts, □ NH_2 salts, ▽ NHR adducts and △ NHR salts.

Table 2
Average distances (Å) and angles (°) for the geometrical features stated in the five-membered ring heterocyclic series, with s.u.s in parentheses, as well as the number of structures (N_s) used to compile each value.

RAV2 is currently unpublished

Co-crystals	N1---O11		N21---O10	N1—C2		C2—N21	N1—C2—N21	N_s
2ATz	2.71 (9)	<	2.79 (12)	1.321 (14)	>	1.308 (12)	124.2 (8)	22
2ABOX	2.59 (5)	<	2.844 (7)	1.317 (10)	>	1.306 (15)	127.5 (8)	5
3AT	2.71 (6)	<	2.90 (7)	1.342 (4)	>	1.316 (8)	127 (1)	7
RAV2	2.539 (2)	<	2.830 (2)	1.287 (2)	<	1.370 (2)	120.2 (1)	1

Parent	N1—C2		C2—N21	N1—C2—N21	CSD reference
2ATz	1.298	<	1.329	125.2	BAWKEP10
2ATzn	1.268	<	1.348	124.8	Lynch (2004a)
	1.275	<	1.350	125.8	
2ABTz	1.278	<	1.334	126.5	CAJWUG
2ABOX	1.305	<	1.334	129.4	Lynch (2004b)
3AT	1.340	=	1.341	125.5	AMTRAZ

being $\simeq 4°$ more acute for the NHR data, although for SMZ itself the N1—C2—N21 angle is $\simeq 2°$ lower than that of the NHS average. The plot of C2—N21 *versus* N1—C2—N21 indicates a general correlation between the two, indicating that as the C2—N21 bond length shortens, N1—C2—N21 opens up so as to maintain a consistent interatomic distance between N1 and N21. Another general correlation, although not as distinct as C2—N21 *versus* N1—C2—N21, can be seen in the plot of C2—N21 *versus* N21—O10 (Fig. 7) where, depending on whether the structure is either an NH₂ or NHR type, a slight increase in the C2—N21 bond length leads to an increase in the N21—O10 interatomic distance. In this there are no distinctions between either adduct or salt structures.

3.2. Five-membered ring heterocyclics

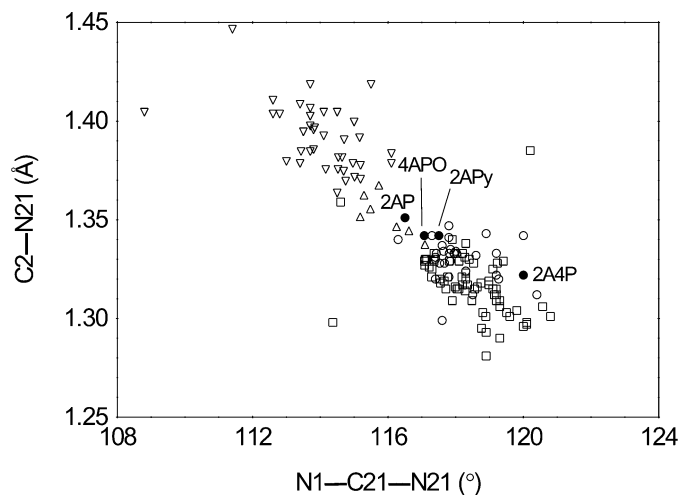Treatment of the data for the five-membered rings in terms of presentation and tabulation requires a different approach to the six-membered ring data because of several significant factors. Overall there are 35 suitable crystal structures (fitting both Figs. 2d and e), of which only one (RAV2, which is based upon 2-aminothiazoline) is an NHR type. All five-membered ring type examples were based on either 2-aminothiazole (2ATz) derivatives [primarily 2-aminothiazoline (2ATzn) and 2-aminobenzothiazole (2ABTz)], 2-amino-5-chlorobenzoxazole (2ABOX) or 3-amino-1,2,4-triazole (3AT) (Fig. 3). Of the 22 2-aminothiazoles only three are adducts, as are all five of the 2ABOX structures, whereas all seven of the 3AT structures are salts. Furthermore, direct comparison of the N1—C2—N21 angles between five-membered rings containing an S atom (in the 1 postion) and those with either O or N atoms is not possible because the increased C—S bond distances decrease the N1—C2—N21 angle. However, data can be presented with respect to each of the three base groupings, as indicated in Table 2.

A comparison of the average N1---O11 and N21---O10 interatomic distances for the 2ABOX, 3AT and RAV2 structures in Table 2 reveals a similar asymmetric trend, as observed for the six-membered ring series, with distance differences of ≥ 0.2 Å. In contrast, the comparative 2ATz distances are much closer in their average values. This may be due in part to the fact that four 2ATz structures have N1---O11 > N21---O10, which is also observed in one 3AT example. A comparison of the average N1—C2 and C2—N21 bond lengths mirrors the trends seen between the NH₂- and NHR-type species in the six-membered ring series with C2—N21 < N1—C2 for 2ATz, 2ABOX and 3AT, but not in RAV2. Notice also the comparable similarities between the respective N1—C2 and C2—N21 distances for 2ATz, being mostly salts, and

Figure 6
Plot of C2—N21 bond length (Å) *versus* N1—C2—N21 bond angle (°). Key: ○ NH₂ adducts, □ NH₂ salts, ▽ NHR adducts and △ NHR salts.
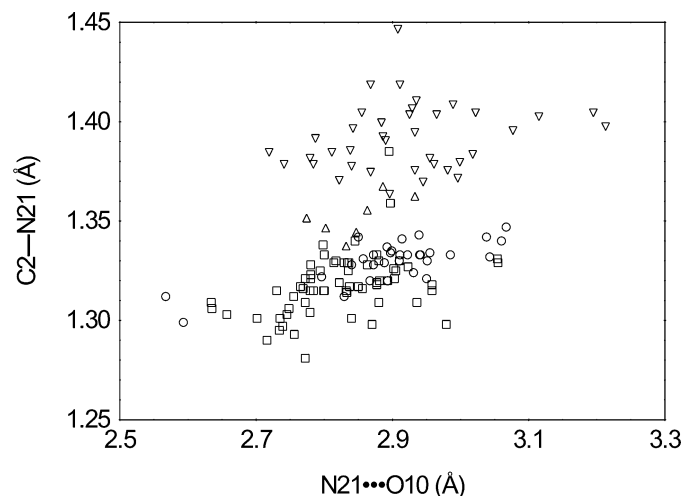

Figure 7
Plot of C2—N21 bond length (Å) *versus* N21---O10 interatomic distance (Å). Key: ○ NH₂ adducts, □ NH₂ salts, ▽ NHR adducts and △ NHR salts.

2ABOX, being all adducts. Unlike the six-membered ring parent molecules, in all of the five-membered ring parent molecules except for 3AT, there is more of a distinction between the N1—C2 and C2—N21 bond distances, which serves to highlight the effect that association of a carboxylic acid group has on these two bond lengths. As previously stated, comparison of the N1—C2—N21 angle is not possible with differing values across the three main NH$_2$-type series, but it is interesting that in RAV2 the N1—C2—N21 angle is lowered, similar to the six-membered ring NHR-type structures.

4. Conclusions

The differences between the interatomic distances N1---O11 and N21---O10 may be explained in that the attraction of the carboxylic acid O—H to the heterocyclic base is stronger (or harder in terms of hard–soft acid–base theory) than the attraction of the amine N—H to the carboxylic C=O and this hardness difference is generally reflected in the observed N1—O11 and N21—O10 distances. In the cases where N1—O11 > N21—O10 it is possible that local environmental factors such as steric hindrance or competing strong hydrogen bonds affect the alignment of the constituent molecules. In each of these exceptions there are additional strong hydrogen-bonding associations involved in the structure, primarily to the carboxylate O atoms. The implication for crystal engineers is that when using this binding association they should not assume that the connection will be symmetrical, as are the dimers of the two individual constituents. Examination of the average values, and s.u. ranges, listed in Table 1 indicates that although the N1—O11 and N21—O10 distances can be similar, to within 0.1 Å, they can be different by > 0.2 Å. For the majority of designed structures these differences are insignificant, although the intended lattice still requires some flexibility so as to incorporate the larger fluctuations that can possibly be imposed by this association, otherwise the lattice will rearrange in an auto-correcting mechanism, resulting in an unexpected packing array.

Examination of all the data with respect to the occurrence of proton transfer in the six-membered ring series reveals that if the carboxylic acid has a pK_a value lower than that of the heterocyclic base then a salt complex is formed. This departs from the suggested pK_a difference of 3.75, as suggested by Johnson & Rumon (1965), that is required in pyridine–carboxylic acid mixtures to ensure salt formation. Etter & Adsmond (1990), in their study of the hydrogen-bonding preferences of 2-aminopyrimidines, were the first to note that the Johnson and Rumon theory for pyridines also did not hold for 2-aminopyridines, but they did not suggest any alternative solution. Our theory can best be demonstrated by the fact that the 2AP, which has a pK_a value of 3.45, and fumaric acid (pK_a = 3.03) co-crystals are salts (Goswami, Mahapatra, Nigam et al., 1999), while the terephthalic acid (pK_a = 3.51) co-crystal is an adduct (Goswami, Mahapatra, Ghosh et al., 1999). Our theory also explains why all 2APy (pK_a = 6.82) and 4APO (pK_a = 8.24) co-crystals are salts; because all the acids used

had lower pK_a values. This theory also holds true for the individual examples in the five-membered ring series for which pK_a data were available. It should be noted that although pK_a values, either determined or calculated, are based upon solution data, they have proven to be valuable predictors of solid-state interactions between organic acids and bases. For example, Etter (1991) also reported a study where two substituted pyridines, when mixed separately with binary solutions of benzoic acids of differing pK_a values, were shown to selectively associate with the benzoic acid of lower pK_a, even with differences as little as 0.04.

We can currently offer no definitive explanation as to why there is a difference between the proton-transfer behaviour of pyridine and 2-aminopyridine, although we suspect that it may be related to the stabilizing effect that the N21---O10 interaction has on the entire association. For instance, Johnson and Rumon showed that an acidity difference between the acid and the base was required to overcome deprotonation and force the formation of the resonant carboxylate anion, whereas for 2-aminopyridine the acid only needs to have a pK_a value less than, even if only slightly less than, the base to form a salt. The additional N21---O10 interaction could possibly aid in the stabilization of the resonant carboxylate group, evening out the electronic disruption imposed by the associated H atom in the N1---O11 interaction, whereas in pyridine the majority (not currently quantified but an observation of the principal author) of the acid–pyridine associations are non-planar, with the carboxylate group having at best the availability of a 2-position C—H—O interaction (if the acid–pyridine association is planar; see Lynch, Chatwin & Parsons, 1999) to aid in the formation of similar hydrogen-bonding environments for the two carboxylate O atoms. It is the intention of the principal author to study the geometry, and surrounding hydrogen-bonding environment, of the carboxylic acid–pyridine interaction, including a statistical investigation of the angular differences between the planes of the carboxylate group and the pyridine ring. It should also be noted that the stability discussed above relates to the carboxylate group and does not refer to the stability of the whole motif in terms of suggesting that the $R_2^2(8)$ graph-set dimer motif in 2-aminoheterocyclic–carboxylic acid co-crystals is more stable than the pyridine–carboxylic acid association. If this were so then when we mixed 2-amino-4-(4-pyridyl)pyrimidine with 4-aminobenzoic acid (Lynch & McClenaghan, 2001a) the carboxylic acid should have preferentially associated to the 2-aminopyrimidine; instead the strongest acid (the carboxylic acid group) associated to the strongest base (the pyridyl).

To explain the shortening of the C2—N21 bond length in the NH$_2$-type structures, we suggest that as the carboxylic acid O—H group approaches the heterocyclic N1 atom, the electron density from N1 is drawn out into the hydrogen bond towards the carboxylic H atom. If proton transfer occurs then electron density from N1 is required for the N$^+$—H bond. The partial loss of electron density from the heterocyclic ring, or the N1=C2 double bond, renders the ring more electron accepting, thus attracting the electron-donating N21 towards

C2. This explanation is based upon the data presented in this paper where the acid group is a carboxylic O—H. However, consider the 2-aminopyrimidine–carbamoyl $R_2^2(8)$ association observed in the structure of 2-amino-4-chloro-6-(4-carba-moylpyperidinyl)pyrimidine hemihydrate (Lynch & McClenaghan, 2001b), where the carbamoyl N—H hydrogen bonds to the pyrimidine N atom and the 2-amino group reciprocates to the carbamoyl oxygen. In this structure the N1—C2 bond length is 1.348 (2) Å and the C2—N21 bond length is 1.354 (2) Å, a difference of 0.006 Å [the N1—C2—N21 bond angle is 116.2 (2)°]. This is the only example of its kind, so it cannot be collated with similar data, but it does suggest that less effect is imposed upon the heterocyclic ring from a weaker (or softer) acid group that in turn reduces the N21 attraction, resulting in a C2—N21 bond length that is longer than N1—C2. Alternatively, for the salt complexes it is possible that there is a resonance contribution, as indicated in Fig. 1(d), but this contribution does not significantly affect the C2—N21 bond length in addition to the attraction of the electron-accepting ring that is responsible for the shortened C2—N21 distance, as noted in these distances. However, for the NHR molecules the effect of the attachment of a non-H atom to N21 outweighs any N21—C2 attraction, most probably because of the bulk steric effects of a substituent that is large compared with an H atom. Irrespective of the exact explanation of the changes in the C2—N21 bond length, these types of structure are a good example of some of the effects that the presence of one molecule can have on another in the solid state through intermolecular association, in the absence of formal covalent bonding.

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