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Oxime–Carboxyl Hydrogen Bonds: the Preferred Interaction Determining Crystal Packing of 'Carboxyoximes'

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Abstract

The statistical analysis of hydrogen-bond interactions formed by oximes and carboxylic acids has been performed. *Ab initio* quantum-chemical calculations have been used to rationalize the observed preference for the oxime–carboxyl interaction compared with homologous binding (carboxyl–carboxyl and oxime–oxime). The crystal packing observed in the structure of pyruvic acid oxime (hydroxyiminopyruvic acid) has been explained as the consequence of a combination of the energetically optimal structure of the isolated molecule and the optimal interaction of monomers forming a dimer.

1. Introduction

The carboxyl group is one of the most common groups having both donor and acceptor functions. There are 3180 entries in the Cambridge Structural Database (CSD, release October 1996; Allen & Kennard, 1993) of organic error-free structures with *R* factors less than 0.10. The oxime group is a much less common donor–acceptor group (370 entries). What makes them similar is their dual function in hydrogen-bond formation. Moreover, both of them have one donor function (OH) and two acceptor atoms (nitrogen and hydroxyl oxygen for oximes or carbonyl oxygen and hydroxyl oxygen for carboxylic acids). This dual character very often results in dimeric structures (550 structures of acids and 79 structures of oximes), where the functional groups from neighboring molecules are linked with pairs of centrosymmetric hydrogen bonds. For several years we have been interested in those structures where both groups coexist. This situation is rather rare (only few occurrences in the CSD). If both groups are present in the same or in different molecules, one could foresee either homologous binding (carboxyl–carboxyl and oxime–oxime) or the formation of hydrogen bonds between carboxyl and oxime groups. The homologous scheme might result in centrosymmetric hydrogen bonds for achiral molecules. The alternative cannot contain centrosymmetric hydrogen bonds. This could result in polar chain formation in the structure when both groups are in a single molecule (Padmanabhan *et al.*, 1989). The formation of chain structures (Maurin *et al.*, 1992*a*,*b*, 1994) as well as the co-crystallization of oximes with carboxylic acids (Maurin *et al.*, 1993) has shown a preference for such an interaction. Homologous binding has only been observed for 3-*tert*-butyl-5-hydroxyimino-2,6,6-trimethylheptanoic acid (Fig. 1; Heathcock *et al.*, 1985; Oare *et al.*, 1990). However, the presence of the voluminous *tert*-butyl moiety together with methyl substituents in close proximity to functional groups might be responsible for this effect. For 3-ethyl-5-hydroxyimino-2,6,6-trimethylheptanoic acid (Heathcock *et al.*, 1985; Oare & Heathcock, 1990), where the *tert*-butyl group is exchanged for an ethyl group, the usual polar chains of molecules were observed (Fig. 2).

Is it always true that in structures where both oxime and carboxyl groups are present the most common intermolecular interactions are unsymmetrical hydrogen bonds between both groups? Does the predicted observation originate from the molecular level or should it be ascribed to the crystal packing? The theoretical study presented here may help answer these questions. The following model systems were studied: isolated molecules of acetic acid and acetic aldehyde oxime and different possible dimeric systems in which both molecules might be involved.

To give insight into the packing patterns some studies on the pyruvic acid oxime structure (Maurin, 1995;

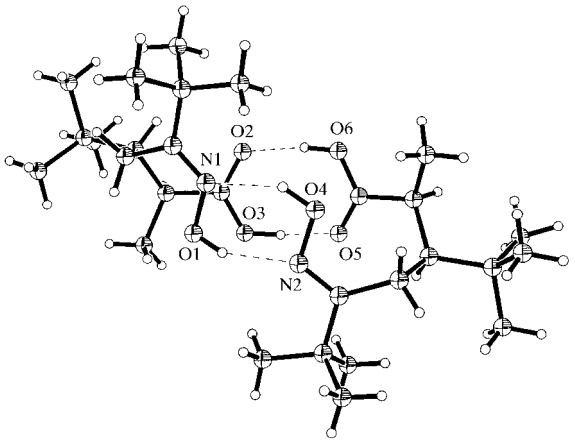


Fig. 1. View of the 3-*tert*-butyl-5-hydroxyimino-2,6,6-trimethylpentanoic acid dimer (atomic coordinates obtained from the CSD).

Maurin *et al.*, 1995) are presented. It is easy to see that a change in the carboxyl group configuration should result in a dramatic change in the crystal packing pattern. Pyruvic acid oxime is very suitable for studies on the relation between molecular conformation and crystal packing. Owing to the rotation hindrance of both functional groups due to π resonance, only two different conformations are possible. By performing theoretical calculations for pyruvic acid oxime, I hoped to find the reason why (*a*) oxime–carboxyl rather than oxime–oxime and carboxyl–carboxyl hydrogen bonds are formed and (*b*) the cyclic tetrameric and not the linear form of packing is preferred.

2. Methods

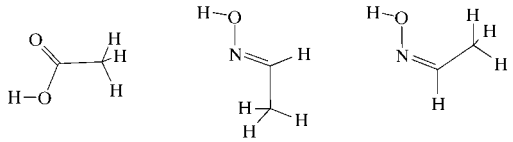
2.1. *Statistics*

A survey of the CSD has been carried out to establish the mean values of the donor–acceptor (*DA*) distances in hydrogen bonds which are characteristic for carboxylic acids and oximes when both groups serve as either a donor or an acceptor, or as both at the same time.

Theoretical *ab initio* quantum-chemical calculations have been performed for model monomers and dimeric systems. The SCF RHF method was used for this purpose. The program *Gaussian*92 (Frisch *et al.*, 1992) was used in all the theoretical calculations. The standard 6-31G** basis set was used in the final calculations.

2.2. *Theoretical studies*

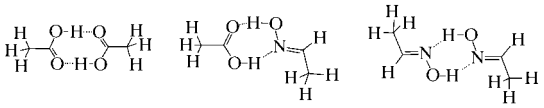
2.2.1. *Acetic acid–acetic aldehyde oxime interactions*. Calculations for acetic aldehyde oxime (*B*), both (*E*) and (*Z*) isomers, and acetic acid (*A*) were carried out to obtain the energetically optimal geometries of isolated molecules (I).



A *B* [(*E*) isomer] *B* [(*Z*) isomer]

(I)

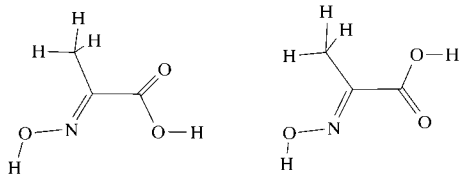
Next, three dimeric systems, (II), were studied: acetic acid–acetic acid (*AA*), acetic aldehyde oxime–acetic aldehyde oxime (*BB*) and acetic acid–acetic aldehyde oxime (*AB*).



AA *AB* *BB*

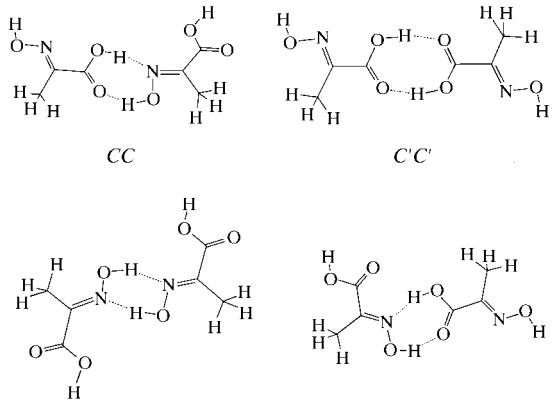
(II)

2.2.2. *Calculations for pyruvic acid oxime*. Geometry optimization was carried out for the monomer in two different conformations, (III), as well as for four different dimers, (IV).



C *D*

(III)



CC *C′C′*

C″C″ *DD*

(IV)

3. Results and discussion

3.1. *Statistics*

3.1.1. *Oximes and carboxylic acids as donors and acceptors*. Oxime structures can be divided into seven classes (Chertanova *et al.*, 1994). The first three involve different isolated functions of oximes: donors, acceptors where N is the acceptor site, and acceptors where O is the acceptor site (Bertolasi *et al.*, 1982). The remaining four are combinations of the first three. A similar clas-

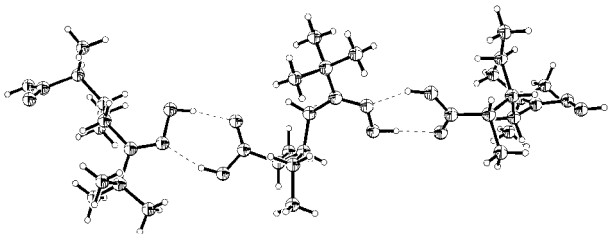


Fig. 2. View of the molecular chain of 3-ethyl-5-hydroxyimino-2,6,6-trimethylheptanoic acid (atomic coordinates obtained from the CSD).

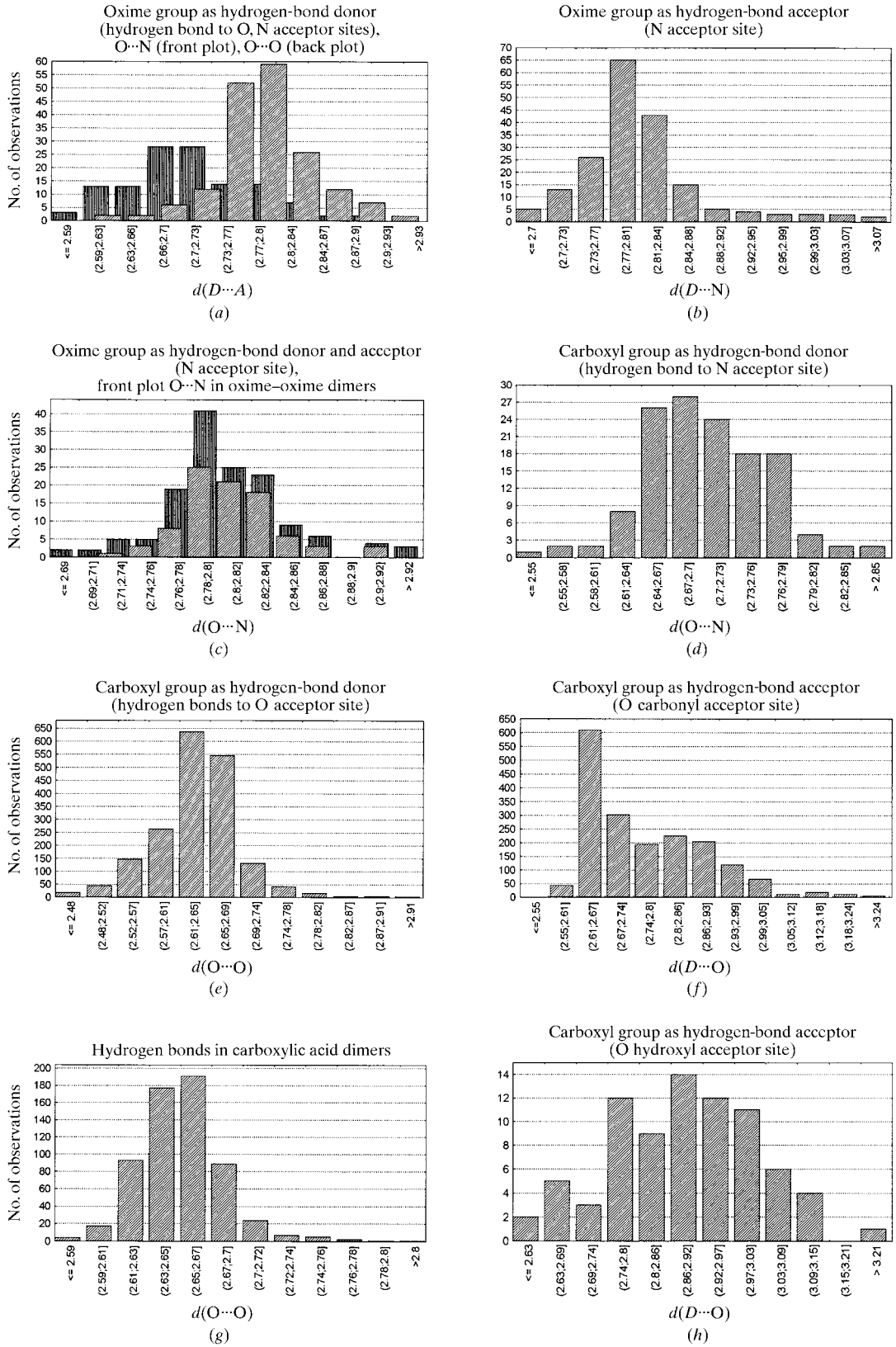


Fig. 3. Histograms of the hydrogen-bond $D\cdots A$ distances for oximes (*a*, *b* and *c*) and carboxylic acids (*d*, *e*, *f*, *g* and *h*).

sification can be used for carboxylic acids, with the exception that N is replaced by a carbonyl O atom.

3.1.2. *Oximes as hydrogen-bond donors*. When one functional group acts as an intermolecular hydrogen-bond donor, the most common acceptors in organic structures are O or N atoms of the other molecules. Fig. 3(*a*) shows a histogram of $D\cdots A$ distances from the oxime hydroxyl oxygen to either O (rear plot) or N atoms (front plot), with mean values 2.71 Å for O$\cdots$O and 2.80 Å for O$\cdots$N distances, respectively.

3.1.3. *Oximes as acceptors*. Fig. 3(*b*) shows the histogram of $D\cdots A$ distances when the oxime N atom acts as an acceptor (148 structures in the CSD). The sample mean of $d(D\cdots A)$ is 2.82 Å and the median is 2.80 Å.

3.1.4. *Oximes as donors and acceptors*. In 113 structures the oxime group acts as both donor and acceptor (where N is the acceptor site). In 79 of these, centrosymmetric oxime–oxime dimers were formed. Fig. 3(*c*) shows the histogram for $D\cdots A$ distances (front plot corresponds to the oxime–oxime dimers). In both cases the mean value of $D\cdots A$ distances is ~2.80 Å.

3.1.5. *Oxime as acceptor with O as acceptor site*. The oxime O atom acts as an acceptor in only 27 structures. The $D\cdots A$ distances here are much longer: the sample mean value is 2.92 Å and the median is 2.86 Å. In nine cases these hydrogen bonds are $OH_{oxime}\cdots O_{oxime}$ hydrogen bonds, where the maximal number of contacts are ~2.71 Å in length. Owing to the paucity of the structural data corresponding to this class of compound, it is hard to draw any statistically valuable conclusions.

3.1.6. *Carboxyl group as hydrogen-bond donor*. Among the large number of structures where the carboxyl group acts as a hydrogen-bond donor there are only 97 where the $OH_{carboxyl}\cdots N$ linkage is formed. The mean value of the $D\cdots A$ distance for this subgroup is 2.71 Å (Fig. 3*d*). Most carboxyl groups (1457 entries in the CSD), however, are hydrogen bonded to O atoms, where the mean value of the $D\cdots A$ distance is 2.64 Å (Fig. 3*e*).

3.1.7. *Carboxyl group as hydrogen-bond acceptor*. Fig. 3(*f*) shows the values of $D\cdots A$ distances when the carbonyl O atom of the carboxyl group acts as the acceptor. The mean value in this group is 2.77 Å, whereas the median is 2.72 Å. One can see the large number of distances in the range 2.61–2.67 Å, which corresponds to the maximum in Fig. 3*(e)*. This might be ascribed to the carboxyl–carboxyl contacts and more particularly to the carboxylic acid centrosymmetric dimers (Fig. 3*g*) where the mean value of $D\cdots A$ distances is 2.66 Å and the median 2.65 Å. The highly asymmetrical distribution of $D\cdots A$ distances in Fig. 3(*f*) suggests the existence of well defined subclasses of interactions. Fig. 3(*h*) shows the unusual group of contacts where the hydroxyl O atom of the carboxyl group serves as an acceptor for the hydrogen bond. Only 81 entries of this type are recorded in the CSD. The hydrogen-bond lengths are much longer here – the mean value of $D\cdots A$ distances is 2.84 Å and the median of 2.87 Å is almost the same as the median value for oximes when the oxime hydroxyl oxygen serves as the acceptor. If the ten shortest $D\cdots A$ distances were omitted (shorter than 2.55 Å) the distribution would be an almost perfect normal distribution with mean and median values of 2.89 Å. Do these short contacts form another class or are they only coincidental discrepancies? On close inspection it is found that these contacts belong to seven ionic structures. The anomalously short distances are accompanied by short H$\cdots$H intermolecular distances (0.78–1.03 Å), which should be interpreted as the disordered positions of H atoms between COOH and COO^- groups rather than localized atoms of COOH groups and, therefore, the interaction should be described as the interaction between the carboxyl (in other cases the amide or hydroxyl) group acting as the donor and COO^- as the acceptor. Consequently these data have been omitted from Fig. 3(*g*).

Table 1. *Comparison of hydrogen-bond interactions in system (1) AA (acetic acid–acetic acid) + BB [(E)-acetic aldehyde oxime–(E)-acetic aldehyde oxime] and (2) 2 × AB [acetic acid–(E)-acetic aldehyde oxime]*

Total energies E (Hartree†), stabilization energies corrected for basis set superposition error and geometrical deformations ΔE_{BSSE} (kJ mol^{-1}) (Turi & Dannenberg, 1993*a*; Pudzianowski, 1995).

System	E (Hartree†)	ΔE_{BSSE} (kJ mol^{-1})
CH_3COOH (*A*)	−227.821186	
CH_3HCNOH (*B*), (*E*) isomer	−207.897240	
CH_3HCNOH (*B*), (*Z*) isomer	−207.896027	
$CH_3COOH\cdots CH_3COOH$ (*AA*)	−455.669040	−60.5847
$CH_3HCNOH\cdots CH_3HCNOH$ (*BB*)	−415.809038	−32.6516
$CH_3COOH\cdots CH_3HCNOH$ (*AB*)	−435.739123	−46.7465
Difference (2 × *AB*) − (*AA* + *BB*)	−0.000168‡	−0.2575

† 1 Hartree = 2.625 × 10^3 kJ mol^{-1}. ‡ −0.4411 kJ mol^{-1}.

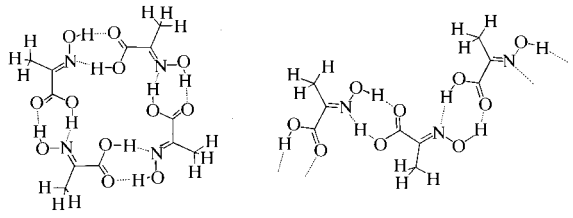
3.2. *Theoretical calculations*

To answer the question on the preferential 'oxime–carboxyl' interaction we studied several model systems. Table 1 shows that the (*E*) isomer of acetic aldehyde oxime [*B*, (I)] is favored over the (*Z*) isomer. The difference in total energy is −3.1849 kJ mol^{-1}. This is in agreement with the well known observation that in the simple reaction of hydroxylamine hydrochloride with aldehydes, only the (*E*) isomers of the oximes are formed. A further study was performed for the (*E*) isomer only. We reviewed two possible situations and compared the total energies of the systems: one containing oxime–oxime and acid–acid dimers and the second consisting of two molecules of oxime–acid dimers. Such systems involve the same number of atoms, bonds and intermolecular contacts, but differ in the nature of the latter. The data listed in Table 1 show that

the total energy for the *AB* system (II) is lower than for the system consisting of *AA* and *BB* dimers. The energy gain, however, is rather small (only -0.4411 kJ mol^{-1}) compared with the hydrogen-bond energy (-32.6516 to -60.5847 kJ mol^{-1}; last column of Table 1).† Small differences between the two systems (last row of Table 1) might be responsible for the difficulties we sometimes encountered during the co-crystallization of oximes with acids. Other factors, such as the solubility of components and crystal packing, may disable co-crystal formation. The situation discussed here is different from those described by Etter & Adsmond (1990), where carboxylic acids were co-crystallized with amino pyridines and the pK_a difference between the components were high. The large discrepancies in pK_a might even result in proton transfer to the more basic component, as we observed for genistein complexes with amines (Mazurek *et al.*, 1998).

3.3. *Why does pyruvic acid oxime form tetramers?*

The two different conformers *C* and *D*, system (III), of pyruvic acid oxime lead to different packing schemes. Since both molecules are planar, we examined only two systems: (*a*) infinite chains, when the *D* conformer is involved, and (*b*) tetramers, when the *C* conformer is the main building block (V). In the calculations the model dimers were used as the representative parts of both larger structures. This procedure enabled a comparison of both the total energies and the stabilization energies for closed and infinite structures. The results of the *ab initio* calculations listed in Table 2 show the following.



C *D*

(V)

(*a*) The first conformer (*C*) is more favored. The difference in total energy ($C - D$) is -7.8712 kJ mol^{-1} and consequently the difference in total energy between two dimers ($CC - DD$) is -11.8384 kJ mol^{-1}.

(*b*) Interesting conclusions could be drawn from the difference in hydrogen-bond interactions (last column in Table 2). While for the first dimer (*CC*) the stabilization energy is 3.2707 kJ mol^{-1} higher (less negative) than for the *DD* dimer and the total energy favors the *CC* dimer, this suggests that the structure of the monomer determines the chosen structure of the dimer and consequently the choice of tetrameric structure.

Table 2. *Comparison of hydrogen-bond interactions in system (1) CC (pyruvic acid oxime dimer-1 conformer: oxime–carboxyl hydrogen bond), (2) DD (pyruvic acid oxime dimer-2 conformer: oxime–carboxyl hydrogen bond), (3) C′C′ (pyruvic acid oxime dimer-1 conformer: carboxyl–carboxyl hydrogen bond) and (4) C″C″ (pyruvic acid oxime dimer-1 conformer: oxime–oxime hydrogen bond)*

Total energies *E* (Hartree†), stabilization energies corrected for basis set superposition error and geometrical deformations ΔE_{BSSE} (kJ mol^{-1}) (Turi & Dannenberg, 1993*a*,*b*; Pudzianowski, 1995).

System	*E* (Hartree†)	ΔE_{BSSE} (kJ mol^{-1})
C	−395.516311	
D	−395.513313	
CC	−791.054974	−51.4838
DD	−791.050465	−54.7545
C′C′	−791.056111	−53.2310
C″C″	−791.051897	−45.1178
Difference $C - D$	−0.002998 (−7.8712 kJ mol^{-1})	
Difference $CC - DD$	−0.004509 (−11.8384 kJ mol^{-1})	3.2707
Difference [2 × *CC* −(*C′C′* + *C″C″*)]	−0.001940 (−5.0935 kJ mol^{-1})	−4.6188

† 1 Hartree = 2.625×10^3 kJ mol^{-1}.

Why are oxime–carboxyl rather than oxime–oxime and carboxyl–carboxyl hydrogen bonds formed? To study this problem we compared two model systems: one consisting of two oxime–carboxyl dimers of *C* (*CC*) and another consisting of a carboxyl–carboxyl dimer of *C* (*C′C′*) and an oxime–oxime dimer (*C″C″*). The total energy difference between these two systems is not very large (-5.0935 kJ mol^{-1}). This time, however, both the total energy of the systems and stabilization energies (last row of Table 2) favor the system with 'hetero' oxime–carboxyl bonding. The energies of the hydrogen bonds presented in Tables 1 and 2 might be compared with the results obtained for analogous cyclic hydrogen bonds systems in the *N*-methyl acetamide dimer (Dixon *et al.*, 1994), where the stabilization energy was found to be -59.034 kJ mol^{-1} (*ab initio* MP2 calculations), or with DFT results for different *N*-substituted formamide dimers (McGrady *et al.*, 1995). Surprisingly, there are no high-level *ab initio* data for oximes and their dimers. Only one paper concerning carboxylic acid dimers exists (Turi & Dannenberg, 1993*b*). The value of the stabilization energy for the cyclic dimer of acetic acid, 49.404 kJ mol^{-1} [MP2/631 G(d) calculations], agrees well with those listed in Tables 1 and 2.

The main conclusion from the present theoretical study is that changing the acid conformer, which would result in different packing, is not possible owing to the large difference in total energy both for the single molecule itself and the dimer. The crucial factor here is not the interaction energy, but the stability of the monomer. Furthermore, one should note the difference

† Supplementary data for this paper are available from the IUCr electronic archives (Reference: AB0387). Services for accessing these data are described at the back of the journal.

in the total energies of the two possible dimeric systems carboxyl–carboxyl and oxime–oxime compared with oxime–carboxyl, favoring the latter. The results confirm the experimental results for 'carboxyoximes'. This conclusion agrees with described interactions of acids with oximes.

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