research papers

The lines-of-force landscape of interactions between molecules in crystals; cohesive *versus* tolerant and 'collateral damage' contact

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A quantitative analysis of relative stabilities in organic crystal structures is possible by means of reliable calculations of interaction energies between pairs of molecules. Such calculations have been performed by the *PIXEL* method for 1108 non-ionic and 98 ionic organic crystals, yielding total energies and separate Coulombic polarization and dispersive contributions. A classification of molecule–molecule interactions emerges based on pair energy and its first derivative, the interaction force, which is estimated here explicitly along an approximate stretching path. When molecular separation is not at the minimum-energy value, as frequently happens, forces may be attractive or repulsive. This information provides a fine structural fingerprint and may be relevant to the mechanical properties of materials. The calculations show that the first coordination shell includes destabilizing contacts in $\sim 9\%$ of crystal structures for compounds with highly polar chemical groups (*e.g.* CN, NO_2, SO_2). Calculations also show many pair contacts with weakly stabilizing (neutral) energies; such fine modulation is presumably what makes crystal structure prediction so difficult. Ionic organic salts or zwitterions, including small peptides, show a Madelung-mode pairing of opposite ions where the total lattice energy is stabilized from sums of strongly repulsive and strongly attractive interactions. No obvious relationships between atom–atom distances and interaction energies emerge, so analyses of crystal packing in terms of geometrical parameters alone should be conducted with due care.

1. Introduction

In the analysis of organic crystal structures, studies in terms of qualitative structural motifs such as hydrogen bonds or aromatic stacking are often helpful, but recent experience (Dunitz & Gavezzotti, 1999, 2005) reveals that a significant share of the cohesive potential energy in organic crystals is stored in structurally non-specific molecular contacts that escape a simple taxonomy. This is not surprising if considered in terms of the total molecular electron density, the only relevant feature, and therefore in terms of interaction between full molecules. Sorting out localized atom–atom interactions can only lead to incomplete results, as is recently being recognized in the literature (Dyakonenko *et al.*, 2010; Dunitz & Schweizer, 2006). Moreover, it appears that some close-neighbour contacts are only slightly attractive or even repulsive; short intermolecular separation may imply stabilizing cohesion, but also neutral or tolerant coexistence, or even compression into a forced proximity. On the one hand, while the lion's share of molecular cohesion is taken by stronger attractors, some other partners in the aggregate must accommodate it; on the other hand, for strongly polar or ionic
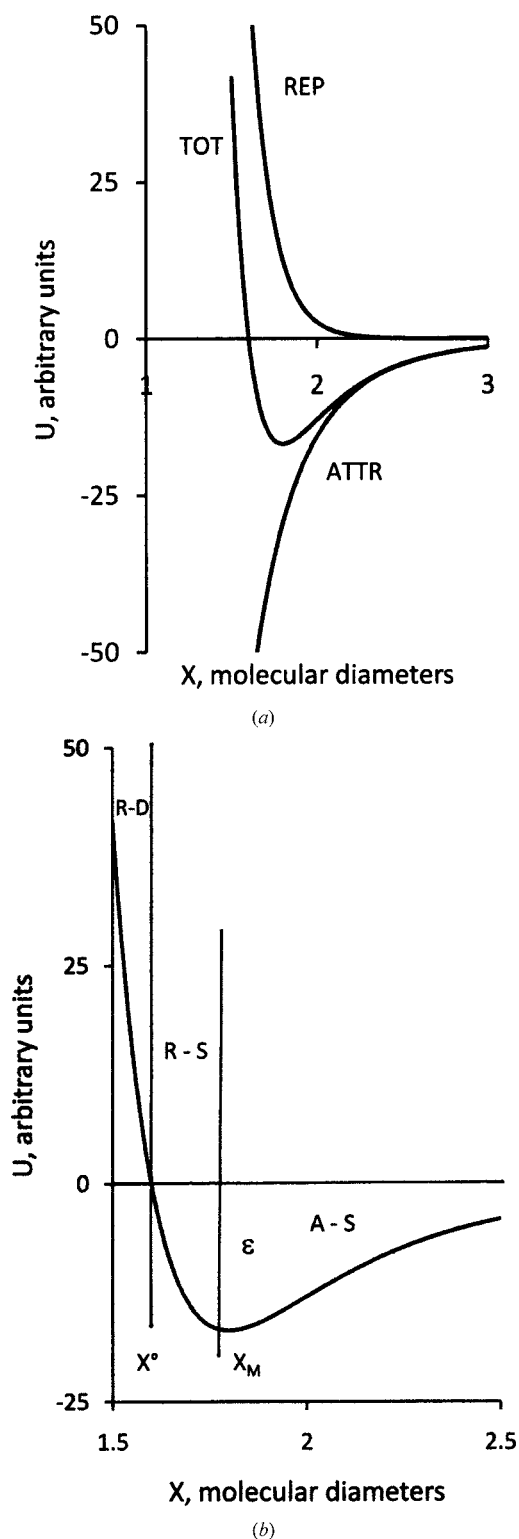
Figure 1
A typical potential energy diagram (U, kJ mol^{-1}) between two organic molecules as a function of separation, X (molecular diameters). (a) Attractive branch (*ATTR*), repulsive branch (*REP*) and total (*TOT*). (b) X° is the separation at zero energy, X_M is the separation at minimum energy, ε is the well depth at the minimum. Three zones are designated as repulsive-destabilizing (*R-D*), repulsive-stabilizing (*R-S*) and attractive-stabilizing (*A-S*).

compounds the overall stabilization in the crystal structure may be from a converging series of interactions of opposite sign. Quite often, equilibrium within a multi-molecular aggregate results from a balance of opposing molecule–molecule forces rather than from all participants being at the zero-force bottom of pairwise potential energy wells. Therefore, any complete crystal structure analysis or any predictive theory of crystallization must also consider less stabilizing or counter-effective interactions.

The present work has been prompted by the observation of an abnormal population of very short N═O···O═N contacts (Gavezzotti & Eckhardt, 2007), down to 2.66 Å, or some 0.5 Å less than twice the average atomic contact radius of oxygen. In keeping with the above concepts, there is little ground *a priori* for expecting a stabilizing interaction between terminals of the same charge. While nitro compounds provide typical examples, the study has been extended to a large database of organic crystal structures, on quantitative energetic grounds using the *PIXEL* method in its latest modification (Gavezzotti, 2008*a*). The aim is to ascertain, in statistical terms over a large sample, the frequency of energetically neutral ('tolerant') molecular contacts with non-stabilizing or mildly destabilizing interaction energies, or even of completely repulsive and destabilizing ('collateral damage') molecular pairing, relative to the number and extent of stabilizing and attractive ('cohesive') contacts. It turns out that the first coordination shell of all organic molecules frequently includes tolerant contacts, and that destabilizing contacts are rare but not impossible in crystals of strongly polar molecules. Sometimes molecule–molecule destabilizing energies up to several hundred kJ mol^{-1} appear in crystals of molecular salts and zwitterions. In such cases the lattice energies must be evaluated by converging sums of terms of opposite sign, in what may be called the 'Madelung mode' of organic crystal packing.
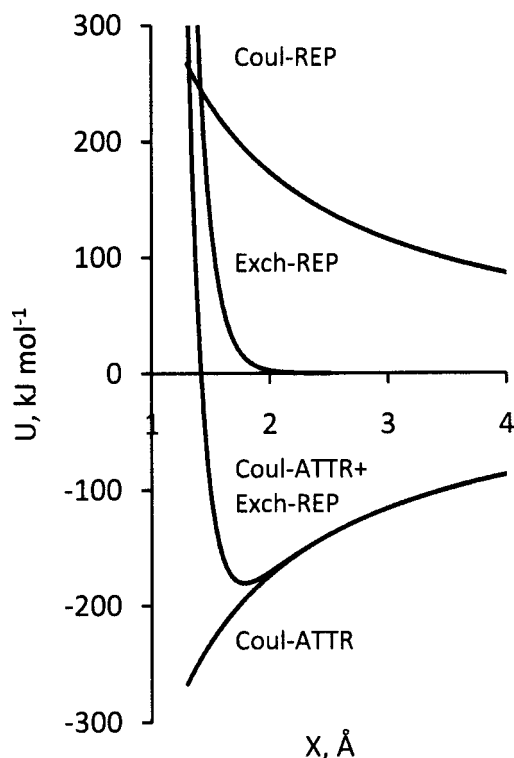
2. Methods

2.1. Crystal model and classification of interactions

Consider a reference organic molecule in its crystal, surrounded by its first coordination shell defined here as a group of molecules with the 12 highest interaction energies to the reference one, as an absolute value, *i.e.* either stabilizing or destabilizing. The tentative coordination number (12) is taken by analogy to the close packing of spheres. The interaction potential between any two molecules (neglecting internal degrees of freedom) is a function of three position and three orientation coordinates, *i.e.* $U = U(x, y, z, \theta_1, \theta_2, \theta_3)$. For the present purposes we consider molecular pairs formed by the reference molecule and any of the surrounding ones, frozen in their reciprocal orientation, allowing only one degree of freedom, that is displacement along the vector joining the centers of mass, X. Let X_C be the observed value of the modulus of this vector in the crystal, X_M the value at the energy minimum, and X° the value at $U = 0$ on the short side.

Fig. 1 is a schematic picture of the situation for a typical organic molecule consisting of 20–40 atoms, with zero net

charge and in a closed-shell ground state. Molecular contacts should be stabilizing *versus* destabilizing, as the contact potential energy is $U < 0$ or $U > 0$, respectively, while attractive *versus* repulsive refers to the contact force ($F = -dU/dX$) as $F < 0$ or $F > 0$, respectively. The stabilizing terms originate from Coulombic contributions between opposite charges, which are usually moderate for neutral molecules, and from polarization effects including dispersion. Destabilizing terms originate from the Coulombic contributions between like charges, very seldom present in crystals of neutral molecules, and from 'Pauli overlap' (or 'exchange') repulsion. A stabilizing molecule–molecule contact is classified as *neutral* if $0 < \varepsilon < 5$, *moderate* if $5 < \varepsilon < 20$, *strong* if $20 < \varepsilon < 50$, and *very strong* if $\varepsilon > 50$ kJ mol^{-1}. In approximate structural terms, moderate contacts include, for example, dispersive π-stacking between small rings or very weak hydrogen bonds, while strong contacts include $O-H\cdots O\!=\!C$ hydrogen bonds or favourable Coulombic interactions between polar groups or extensive interactions between polarizable delocalized electronic systems. At the same time a stabilizing contact is defined as *frustrated* if $X_C > X_M$, *pair equilibrium* if $X_C \simeq X_M$, and *tolerant* if $X^\circ < X_C < X_M$. A destabilizing contact has $X_C < X^\circ$. When considering the force acting between the molecules, frustrated contacts are attractive ($F < 0$), tolerant and desta­bilizing contacts are repulsive ($F > 0$), while $F = 0$ for pair equilibrium contacts. The overall force on a molecule is the vector sum of all molecule–molecule forces, attractive or repulsive, and is of course zero for a stable structure, while the total lattice energy is always stabilizing and results from a summation of nearly always stabilizing molecule–molecule terms.

A different picture applies for contacts where dispersive terms are much smaller and the energy is dominated by the Coulombic polarization term. These occur for the approach of polar moieties, up to full atomic ions (*e.g.* Na$^+$, Cl$^-$) or organic molecular ions (*e.g.* RCOO$^-$, RNH$_3^+$). In such cases (Fig. 2) the Coulombic interaction curve is attractive-stabilizing ($U, F < 0$) for ions (or strongly charged termini) of opposite charge. Equilibrium is attained at very short range by the onset of overlap repulsion. For moieties or ions of the same charge the Coulombic energy curve is uniformly repulsive-destabilizing ($U, F > 0$). Coulombic terms are very strong and decay slowly ($U_C = 1389.36\ q_i\ q_j\ /R$ for charges in atomic units, R in Å and energies in kJ mol^{-1}). The total lattice energy is largely stabilizing and comes from a Madelung-type sum, with significant convergence-truncation problems in the summation (such as are usually handled by Ewald summations). The *PIXEL* architecture does not provide convergence acceleration techniques so that lattice energies cannot be reliably estimated for such crystals, but pair-interaction energies are quite reliable.

2.2. Intermolecular energies

Energy calculations may not help in the formulation of a theory, but can reliably decide to which category a given contact should be assigned. In order to obtain at least an estimate of the forces between neighbouring pairs, the following computational experiment is carried out. A molecular pair is extracted from the crystal without deformation, and the interaction energy is calculated by artificially contracting or expanding the distance vector along the separation direction, thus generating an approximate energy profile for translational molecular libration, or stretching, of the dimer. Such potential-energy profiles may be known as 'lines-of-force' diagrams for a crystal structure. The force is estimated by comparing the observed distance X_C and the minimum energy distance X_M. As such, the lines-of-force model only represents what the molecular pair would do if allowed to librate *in vacuo*; the approximation is less and less realistic as X is more and more different from X_C, because larger molecular motions may involve deviations from the center of the mass vector as well as molecular rotations. For small displacements, however, the calculation provides a reliable picture of the energetic compromises the molecular cluster has to take when the crystal is being constructed.

Lattice-energy calculations with partition into pair-wise molecule–molecule contributions were carried out on a sample of 1079 crystal structures of neutral compounds, chosen to represent most if not all of the functionalities of organic chemistry. The dataset consists of structures considered in previous work (Gavezzotti, 2008*a*,*b*, and references

Figure 2
Potential energy for the Coulombic interaction between two charges of ±0.5 e as a function of distance. REP: repulsive, same charge; ATTR: attractive, opposite charge. Short-range Pauli-exchange repulsion provides the minimum of the total energy curve for particles of opposite charge.

therein) for different purposes, supplemented by new searches through the CSD (Allen, 2002). The general criteria are: reliability (R factor < 0.075), all three-dimensional coordinates determined for non-H atoms, no error flags, no powder data and a relatively small number of atoms in the molecule for practical feasibility of the calculation; in practice, the largest number of non-H atoms in a molecule is $\sim$ 30, with the majority of molecules having 15–25 non-H atoms. A set of crystal structures of zwitterions (40 structures, mostly of amino acids and oligopeptides) and of ionic organic chlorides (58 structures) with the number of atoms < 25 was also employed (a complete list of all CSD refcodes and lattice energies for the crystal structures considered here, with an approximate partitioning into chemical classes, is given in the supplementary material, Tables S1–S2[1]). Automatic retrieval and H-atom re-assignment procedures were applied to prepare standard files for the *OPiX* package (see *e.g.* Gavezzotti, 2008b): in particular, H-atom positions were recalculated according to the usual, well tested and documented geometrical procedures based upon the position of the attached non-H atoms or, for hydrogen-bonded H atoms, by extending the X-ray D—H distance to standard values. This standardization of the H-atom positions is indispensable for the reliability of the calculation. Standard modules of the *OPiX* package were applied to calculate all the crystal and molecular parameters: molecular diameter, average molecular radius (the average of the three dimensions of the molecule in its inertial reference frame), molecular volume and surface, packing coefficient, approximate atomic charge parameters, molecular and cell dipoles, atom–atom approximate lattice energies and short intermolecular interatomic contacts.

Interaction energies were calculated by the *PIXEL* method which provides separate Coulombic, polarization, dispersion and repulsion contributions to the total energy (as described recently by Gavezzotti, 2008a; MP2/6-31G** densities), with two minor modifications:

(i) for nitro compounds, the dispersion damping parameter was set at D = 2.4 against a standard of 3.0, as in previous studies (Gavezzotti & Eckhardt, 2007); Fig. S1 (deposited) shows the excellent agreement achieved in this way between calculated lattice energies and experimental sublimation enthalpies;

(ii) the polarizability of the chloride ion was set at an estimated value of 3.66 Å^3.

PIXEL is an approximate parametric method that provides a fast and usually reliable estimate of intermolecular energies (Volkov & Coppens, 2004; Dunitz & Schweizer, 2006; Aldridge *et al.*, 2009) in comparison to DFT (density functional theory) or *ab initio* MP2 calculations (Civalleri *et al.*, 2010).

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[1] Supplementary data for this paper are available from the IUCr electronic archives (Reference: GP5037). Services for accessing these data are described at the back of the journal. For reproducibility of the calculations described here, *PIXEL* computer software and input and output files are available from the author upon request. Full documentation for the computer programs used (the *OPiX* package) with worked examples is available at the author's website, http://users.unimi.it/gavezzot.

3. Results

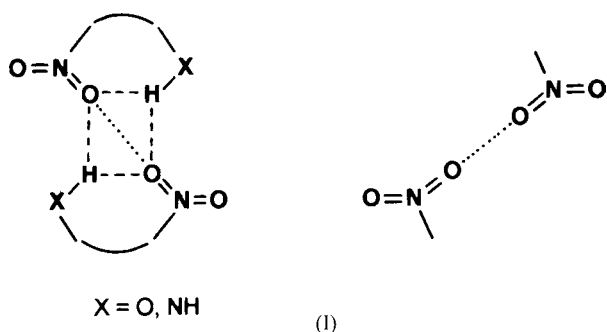### 3.1. Crystals of nitro compounds: short O$\cdots$O separations versus contact energies

Since crystals of nitro compounds were the originators of the present study, and are among the main suspects for the presence of non-cohesive molecular interactions, a detailed study was separately conducted on this class of compound. The results serve as a typical illustration of the methods and results.

The interaction in a centrosymmetric nitromethane dimer was first explored by computing the dimerization energy at $\sim$ 25 000 points on the potential-energy surface. Fig. S2 shows that the interaction energy becomes stabilizing only when the O atoms in the nitro groups are not in direct coplanar contact, and when the interaction involves an inverted-dipoles configuration – further enhanced here by interactions between the positively charged methyl group and the negatively charged nitro group. Fig. 3 shows a one-dimensional plot as a function of O$\cdots$O separation for the coplanar approach
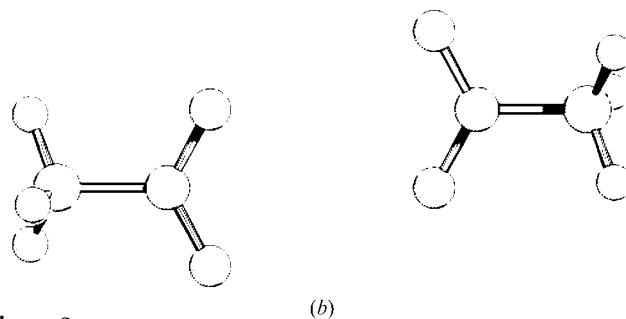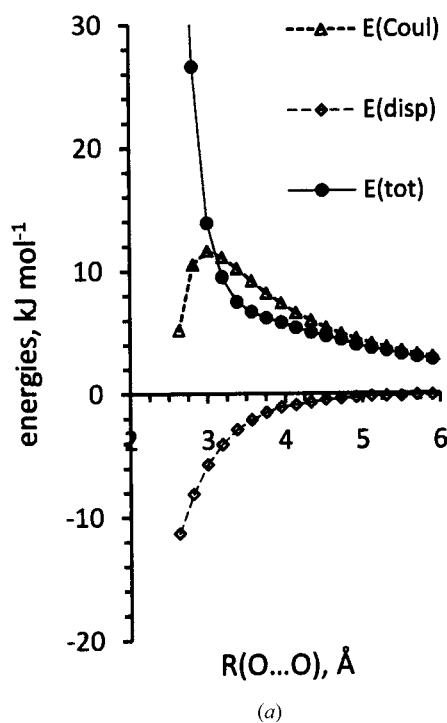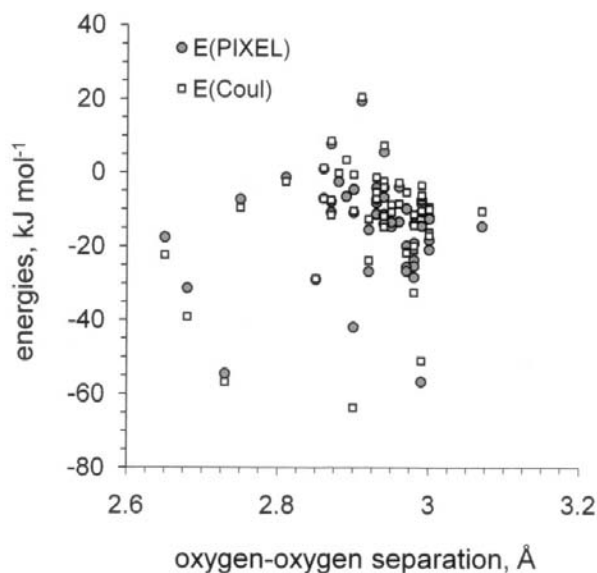

Figure 3
(*a*) Total *PIXEL* energy (shaded circles) for the interaction of a nitromethane dimer in the configuration in (*b*). The Coulombic and dispersion terms are also shown (polarization and repulsion terms not shown). See Fig. S1 (deposited) for a full energy map.

shown in the inset. The interaction energy is almost entirely composed of Coulombic repulsion, slightly mitigated by a small dispersion component. This approach is always destabilizing and repulsive, as intuitively expected, but the energy cost of a compression to short oxygen–oxygen distance is less than 10 kJ mol^{-1}.


X = O, NH

(I)

Is the oxygen–oxygen distance a reliable signal of the strength of the interaction? Paradigms found for very short O$\cdots$O contacts in crystals of nitro compounds are shown in (I). Such contacts appear when strong N—H$\cdots$O or O—H$\cdots$O hydrogen-bond features act as chaperones (CSD refcodes: ACEMUR, ELUBIW, GERPOJ, FAQRAQ, MOPQAJ, OMOLAD, PUWGET, TACWOJ, VETLIQ, WUXHAY, XENCAV, LIXNEM, WEHJUP, FEMPUI, PUTCOW, KOBXOO, OLOBIA, ONITPH, DADQIJ, XIXQOL, RIHCER, YEFFAR, TADVAW, NOGUNA01, YALTUA), but also in the less obvious 'standalone' O$\cdots$O contact mode (*e.g.* QOYJOD, ENPROP) shown on the right side of (I). Fig. 4 is a plot of molecule–molecule interaction energies for pairs involving a short N=O$\cdots$O=N separation

(a table of pair interactions which appear in Fig. 4 has been deposited, Table S3).

The field at very short R(O$\cdots$O) and stabilizing molecule–molecule energies corresponds to arrangements [(I), left side]

(a)

(b)

(c)
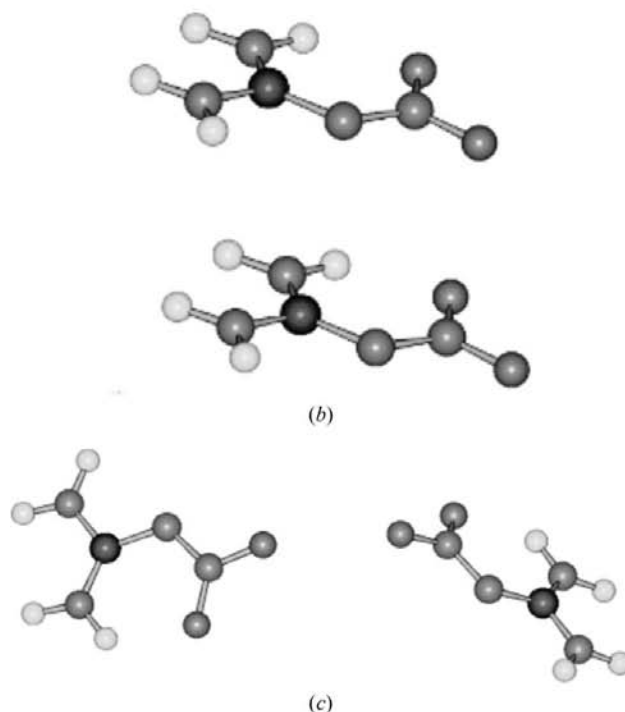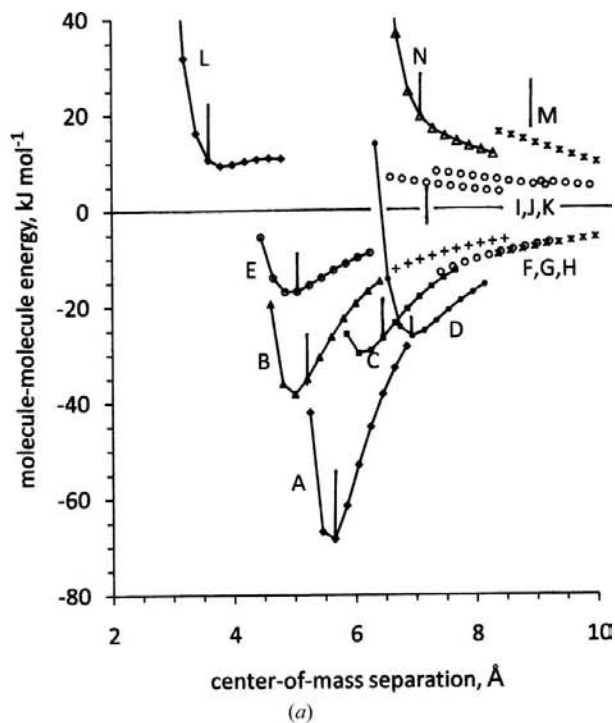
Figure 5
(a) The lines-of-force diagram for the crystal structure of NTRGUA03 (Murmann *et al.*, 2005). Pairs are denoted by letters. Vertical bars denote the actual position of the pair on the potential curve, X_C. The O$\cdots$O distance in N is 2.91 Å. The L and N pairs are shown in (b) and (c), respectively, all other pairs are in Fig. S3 (deposited). See energy and symmetry details in Table S4 (deposited).

Figure 4
Total *PIXEL* and Coulombic energies between molecular pairs with very short oxygen$\cdots$oxygen separation in crystals of nitro compounds. Twice the standard oxygen radius is 3.16 Å.
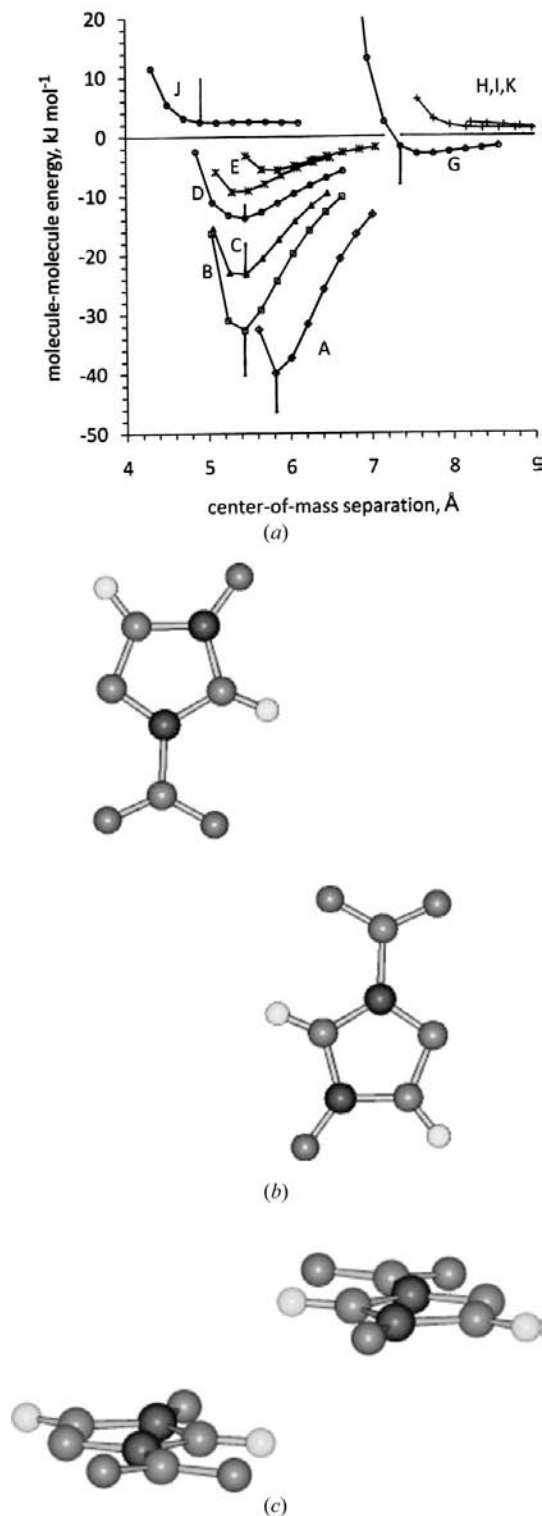
where the hydrogen-bond stabilization largely compensates for whatever mild destabilization may occur from oxygen

Figure 6
(*a*) The force-lines diagram for the crystal structure of QOYJOD (Zhurova & Pinkerton, 2001). Vertical bars denote the actual position of the pair on the potential curve, X_C. Pairs *G* and *J* are shown in (*b*) and (*c*), respectively, all other pairs are in Fig. S4 (deposited). See energy and symmetry details in Table S4 (deposited).

proximity. The field at center–right shows a continuum of moderately stabilizing to moderately destabilizing interactions; a few points in the upper-right field correspond to rather strongly destabilizing molecular pairs. There is no relationship between intermolecular O···O contact distances and molecule–molecule interaction energies, either stabilizing or destabilizing, in Fig. 4.

Two examples of lines-of-force diagrams demonstrate what can be learned about crystal constitution by such a method. Fig. 5 shows the diagram for the crystal structure of nitro-guanidine, $O_2N-N{=}C(NH_2)_2$ (CSD refcode NTRGUA03; Murmann *et al.*, 2005; pictures of the structure of molecular pairs, Fig. S3, and Table S4, with detail of the symmetry operations and pair energies have been deposited). The molecule is in fact a concealed zwitterion with a computationally estimated dipole moment of 8.54 Debye (from the 'ESP' charges, see below). A tightly woven network of hydrogen bonds (pairs *A*–*D*) provides the main stabilization, two of them (*B* and *C*) however being slightly frustrated. The *E* pair is an unspecific stack/Coulombic pair; the *F*, *G* and *H* pairs can be described as long-range, largely frustrated hydrogen bonds or Coulombic interactions. The *I*, *J*, *K* and *M* pairs are 'collateral damage' Coulombic repulsive destabilizing. The *L* pair is a parallel overlapping dipole pair generated by short-distance translation; finally, the *N* pair is strongly destabilizing/repulsive, stand-alone collateral damage resulting from direct confrontation of nitro-oxygen regions. This is one of the strongest destabilizing contacts in our dataset. Significantly, in spite of extensive crystallographic studies including neutron diffraction (Bryden *et al.*, 1956; Choi, 1981; Bracuti, 1999; Murmann *et al.*, 2005) the existence of repulsive contacts has never been noticed or even suspected – nor could it have been at the time, when reliable methods of energetic analysis were not available – in what was considered a 'satisfactory system of hydrogen bonds' (Bryden *et al.*, 1956).

Fig. 6 shows the lines-of-force diagram for the crystal structure of 5-nitro-2,4-dihydro-3*H*-1,2,4-triazol-3-one (CSD refcode QOYJOD; Zhurova & Pinkerton, 2001; pictures of the structure of molecular pairs, Fig. S4, and Table S4 with detail of the symmetry operations and pair energies have been deposited). The molecular pair *A* has an N—H···O=C hydrogen bond, pair *B* has a weaker N—H···N hydrogen bond, pair *C* has a short O···C separation (2.85 Å) over a C=O···C(NO$_2$) contact, with large Coulombic component, and could be classified as an incipient nucleophilic attack by the carbonyl oxygen on the positive carbon site; interestingly, there is also a C=O···O=N contact as short as 2.98 Å. These are all strongly stabilizing, equilibrium pairs. Pairs *D* and *E* are non-specific, escaping any simple chemical identification; they are moderately stabilizing, equilibrium pairs. Pair *G* has a very short N=O···O=N distance of 2.81 Å; it is a neutral contact, being stretched or compressed at almost no energy cost. The faintly favourable Coulombic aspect of the collateral N—H···O interaction, even at the faraway H···O distance of 4.05 Å, is enough to compensate for whatever repulsion comes from the O···O approach. Pairs *H*, *I* and *K* are Coulombic collateral damage at long range, which is quite usual. More

Table 1
Charges fitted to the calculated electrostatic potential for a selection of typical organic groups, which do not sum up to zero owing to the presence of neighbouring atoms.

| Group	$q(C)$	$q(O)$	$q(N)$	$q(S)$	$q(H)$
CONH	+0.5	−0.5	−0.5	–	+0.4
CONH$_2$	+0.7	−0.6	+1.1	–	+0.5
O(C=O)O	+0.9	−0.5	–	–	–
C≡N	+0.5	–	−0.5	–	–
CN=NC	+0.15	–	−0.35	–	–
SO$_2$	–	−0.5	–	+1.0	–

interesting is the presence of a destabilizing stack interaction at short range (pair J), with a relatively strong Coulombic repulsion ($+10.8$ kJ mol^{-1}) counterbalanced by a moderate dispersive contribution (-8.9 kJ mol^{-1}). Note how the availability of pair energies allows a rational and systematic classification and ranking of the determining factors in crystal packing, which are more reliable than an analysis in terms of short atom–atom distances.

3.2. Intermolecular contact landscape in general organic crystals

Fig. 7 shows a plot of the *PIXEL* interaction energy between molecular pairs in the first coordination shell for the crystal structures of uncharged compounds (no salts and no formal zwitterions). There are only 20 crystal structures with destabilizing molecular pair energies $E > +10$ kJ mol^{-1} for a total of 36 contacts, and 97 crystal structures with $E > +5$ kJ mol^{-1} for a total of 338 contacts (detail is deposited as Table S5). We consider the latter as the threshold of consistency and reliability for classifying a contact as destabilizing, as checked by comparison with other methods of calculation (Civalleri *et al.*, 2010); thus, we estimate that only about 9% of all crystal structures of non-charged compounds contain destabilizing molecule–molecule contacts. The first coordination shell, however, contains quite a number of 'tolerant' or indifferent contacts in the $+5$ to -5 kJ mol^{-1} range. It is presumably the presence of such weakly bound, barely decisive partners, in large numbers, that makes the total energy differences so difficult to evaluate, and therefore a completely *ab initio* crystal structure prediction so difficult. Fig. 7 also shows that, as expected, destabilizing contacts appear at higher molecular separation. There is then an obvious continuum of stabilizing interaction energies in the -5 to -50 kJ mol^{-1} range, corresponding to the energy scale of normal 'van der Waals' interactions – a mixture of weak Coulombic polarization and weak dispersive interactions, up to the strong hydrogen bonding of a cyclic carboxylic acid dimer. Outliers appearing in the range -60 to -130 kJ mol^{-1} may reflect unusual molecular constitution, but, as previous experience has shown, a detailed analysis is seldom productive, and often leads to the detection of small imperfections in the crystallographic data (in such large basis sets the possibility of including slightly wrong structures that pass even the
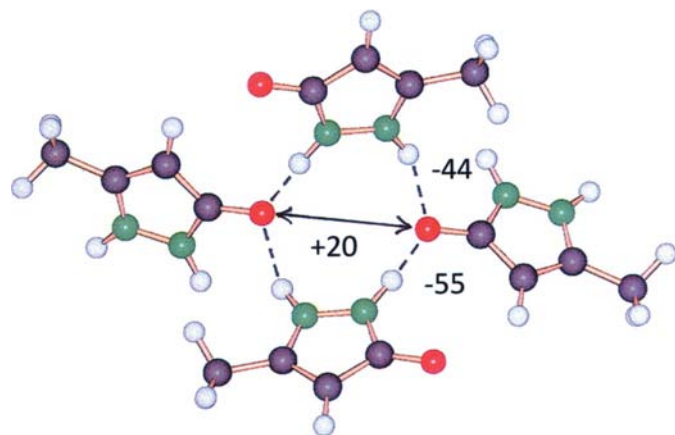
most sophisticated checks can never be dismissed – statistical noise). For example, a slightly shorter cell dimension due to a transcription error may well go undetected and produce an unusually large interaction energy. This is why single cases in databases, especially outliers, apparently showing unusual effects should always be considered *cum grano salis*.

The recognition of chemical composition in the 97 crystal structures with destabilizing contacts with $E > +5$ kJ mol^{-1} reveals a consistent pattern. A few chemical groups among them may be identified: primary and secondary amides (molecules with $-C=ONH_2$ and $-C=O-NH-$ groups), 31 cases; molecules with NO$_2$ groups, 21 cases; nitriles (C≡N group), nine cases; sufones, sulfoxides, thioamides (SO$_2$, S=O,
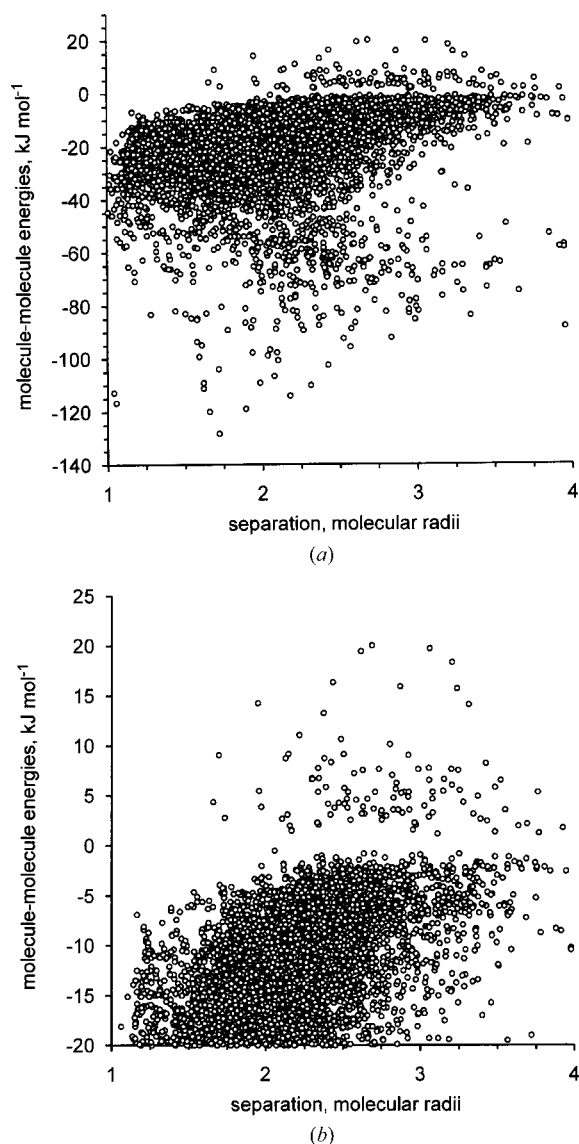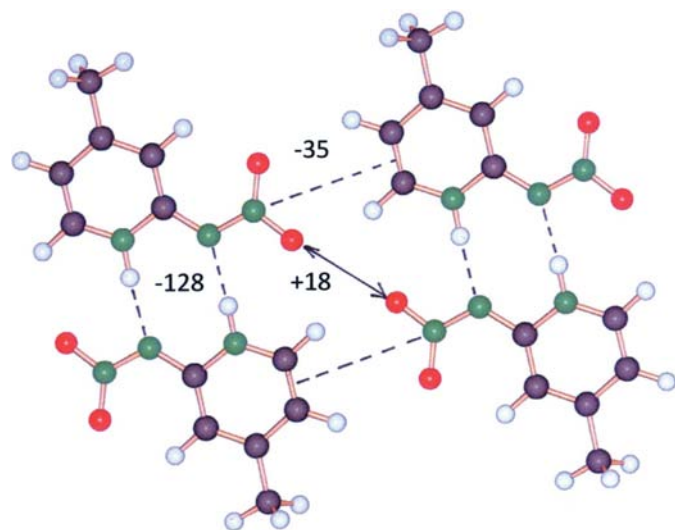

Figure 7
Total *PIXEL* molecule–molecule energy for molecular pairs in crystal structures of non-charged compounds: (*a*) all contacts within the first coordination shell; (*b*) enlargement of the zone close to zero. The horizontal axis is the molecule–molecule distance in units of the average molecular radius. The zone between -2 and $+2$ kJ mol^{-1} is excluded as not really reliable. Data points above $+10$ appear as less dense than mentioned in the text due to overlap.

—S=O—N—H—, —C=S—NH— groups), 18 cases; molecules with —C=O groups, mainly lactones, nine cases; the rest being less clearly classifiable compounds with a mixture of functionalities. The chemical feature common to all these compounds is the presence of a strongly polar group; the charge evaluation according to the electrostatic potential fit (Besler *et al.*, 1990) gives the charge separations shown in Table 1. The presence of one of the above-mentioned chemical groups imparts to the molecule a strongly polar character,

which is almost a zwitterionic character although no formal valence-imposed charge is present. A close analysis of the implied molecule–molecule contacts reveals the unavoidable, unfavourable Coulombic pairing of such polar groups. Clearly in a multi-molecular aggregate it is almost impossible to satisfy all requirements without incurring some collateral damage of this kind. The destabilizing energy owes its presence to the slow decay of Coulombic interactions, still relevant even at the comparatively longer range of 5–6 Å. In fact, the total repulsive energies are almost identical to the sum of Coulombic and polarization energies (Table S5, deposited). For some typical cases, the strong pull from the hydrogen bonding (Figs. 8–9) or from hydrogen bonding and stacking (Fig. S5, deposited) creates a tetramer in which the diagonal interaction is desta-
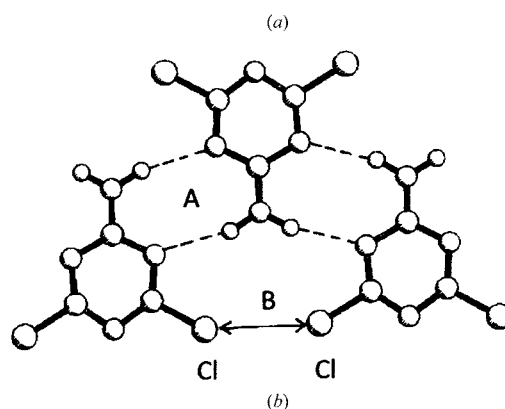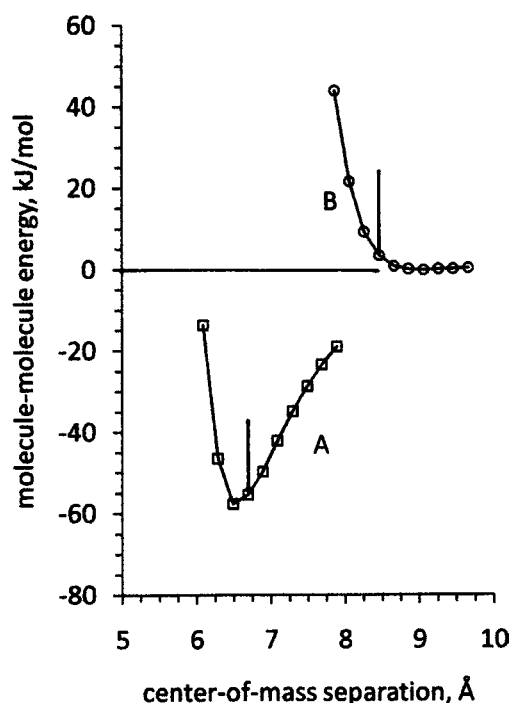

Figure 8
Pattern of close neighbours in the crystal structure of 3-methyl-3-pyrazolin-5-one, CSD refcode MPYAZO11 (Zhang *et al.*, 2004). Red: oxygen; green: nitrogen. Dotted lines denote stabilizing interactions, the arrow denotes a destabilizing interaction. The numbers are the molecule–molecule energies involved (kJ mol^{-1}). Two N—H$\cdots$O hydrogen bonds are stabilizing, the C=O$\cdots$O=C interaction is destabilizing with an O$\cdots$O distance of 3.77 Å. The other diagonal interaction (top–bottom), with a confrontation of N—H groups, is also destabilizing (+8 kJ mol^{-1}).

Figure 9
As in Fig. 8, but for the crystal structure of 4-methyl-2-nitraminopyridine, CSD refcode BENZOK (Laihia *et al.*, 2003). The double hydrogen-bonded pairs are strongly stabilizing, the favourable NO$_2\cdots$(HC)$_2$ pairing is moderately stabilizing. The ensuing NO$_2\cdots$NO$_2$ encounter is unfavourable, with an O$\cdots$O distance of 3.17 Å.
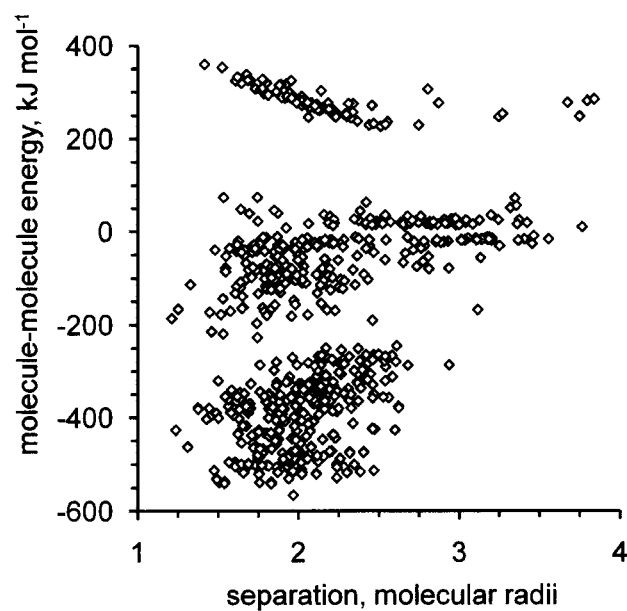

(a)

(b)

Figure 10
(a) The lines-of-force diagram for two pairs shown in (b) in the crystal structure of QIZHIQ (2-amino-4,6-dichlorotriazine; Archer *et al.*, 2000). Vertical bars denote the actual separation in the crystal. The force over contact A is slightly attractive (separation at the right of the minimum), while the force over contact B is slightly repulsive (see Fig. 1b, zones A–S and R–D, respectively). The arrow joins the two chlorine atoms. See details in Table S4 (deposited).
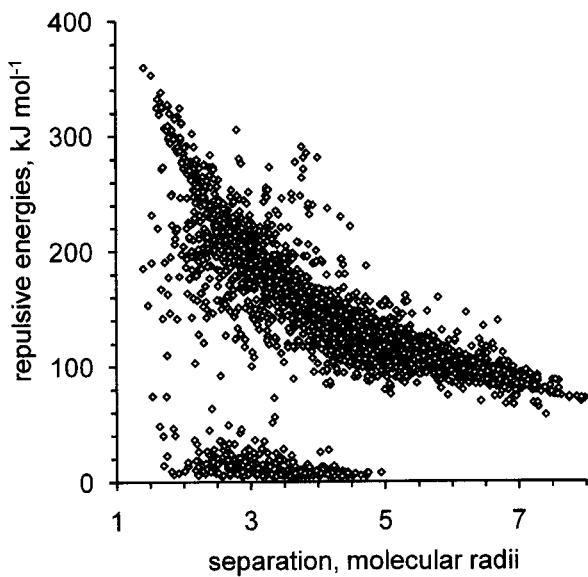
bilizing. A strong unfavourable arrangement found in the crystal structure of a sulfone compound, with the nearly zwitterionic SO_2 groups in direct confrontation without any collateral chaperon, is shown in Fig. S6 (deposited). We propose that along with the usual and widespread habit of denoting possibly stabilizing intermolecular interactions by dotted lines, structural scientists should also be prepared to point out destabilizing interactions by double-pointed arrows, as seen in Figs. 8–9.

Fig. 10 shows a typical lines-of-force illustration of a compromise in the crystal structure of 2-amino-4,6-dichloro-triazine (CSD refcode QIZHIQ). The strong N—H···N
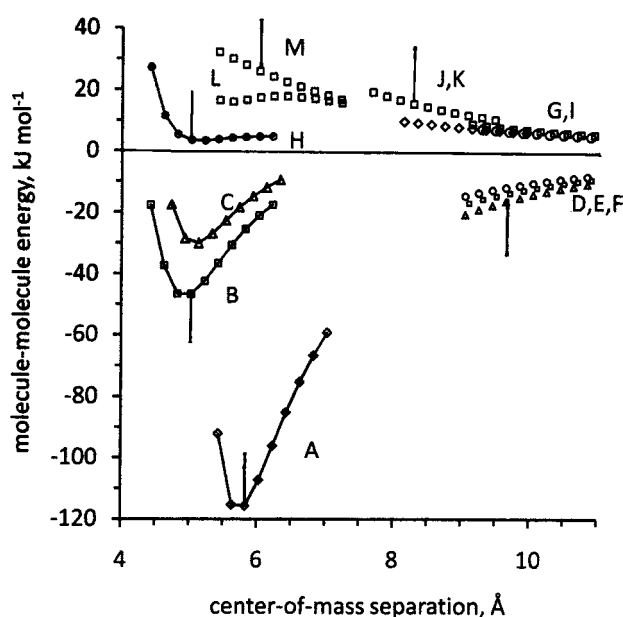
double hydrogen bonds pull molecules together, as anticipated (Archer *et al.*, 2000), but apparently it was not realised that this entails a compression of the flanking Cl···Cl contact. Energy calculations reveal that the hydrogen-bonded pair is slightly stretched away from its energy minimum while the Cl···Cl pair is moderately compressed to a tolerant approach.

The case for crystals of charged species (zwitterions and organic chlorides) is quite different (Fig. 11). In the first coordination shell (Fig. 11*a*) for the moderately destabilizing to the stabilizing part the usual organic dispersive or hydrogen-bonding interaction zone between +10 and −100 kJ mol^{-1} can be seen, as in Fig. 7. After a gap that separates the two types of interaction, the strongly stabilizing, ionic Coulombic contact zone in the −300 to −500 kJ mol^{-1}

Figure 11
Crystals of zwitterions and ionic organic chloride salts. (*a*) Total energy for molecular pairs in the first coordination shell. (*b*) All repulsive pair energies in the data set. The horizontal axis is the molecular separation in units of average molecular radii.

Figure 12
The lines of force diagram for DLALNI01 (Subha Nandhini *et al.*, 2001). The horizontal axis is the distance between centers of mass. Vertical bars denote the actual distance in the crystal, X_C. See details in Fig. S6 and Table S4 (deposited).
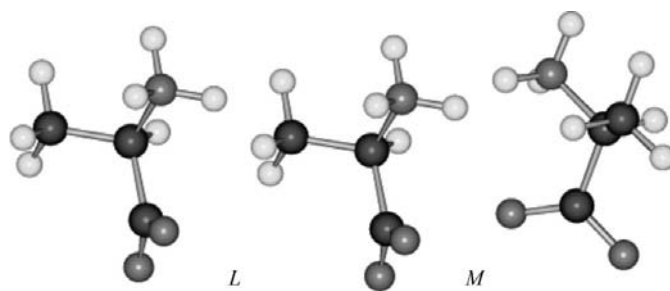
Figure 13
The short-range, repulsive-destabilizing pairs *L* and *M* (Fig. 12) in the crystal of DL-alanine. The arrangement with parallel dipoles (C—NH$_3^+$ up, C—CO$_2$ down) is evident; the interaction is repulsive even at an O···O distance of some 6–7 Å. In pair *L*, related by translation, some dispersive component mitigates the repulsion.

range can be seen, mostly ascribed to organic R^+ to Cl^- contacts. The strongly destabilizing, first-shell, ionic Coulombic zone in the +200 to +400 kJ mol^{-1} range is less populated than the stabilizing zone, because the total lattice energy overall is stabilizing. The plot of all destabilizing/repulsive contacts within the same crystal structure sample (Fig. 11b) is roughly in the shape of a Coulombic repulsive curve as a function of intermolecular separation. In fact, the same plot reporting the Coulombic energy is almost identical to that of the total energy. For a typical example of the composition of the coordination shell of an ionic crystal, Fig. 12 shows the lines-of-force diagram for the crystal of a zwitterionic compound, DL-alanine (CSD refcode DLALNI01; Subha Nandhini et al., 2001; pictures of the structure of molecular pairs, Fig. S7, and Table S4 detailing the symmetry operations and pair energies have been deposited). The pattern consists of a very strong determinant (A) that couples hydrogen bonding and attractive Coulombic interactions between ammonium and carboxylate ions. There are two more strong cohesive pairs (B,C) at short range, with N—H···O hydrogen bonds. At long range, for second-neighbour pairs, a Coulombic manifold appears consisting of almost equally important stabilizing (D, E, F) and destabilizing (G, I, J, K) pairs. Quite peculiar for this kind of crystal is the appearance, at very short distance, of one energetically neutral pair (H) and two strongly destabilizing pairs (L, M). The destabilizing energy of these pairs is entirely Coulombic, as is evident from the dipole alignment in Fig. 13. In the absence of energy calculations, the M pair might well have been judged as a pair with a stabilizing contribution due to stacking.

4. Conclusions

(i) On the basis of energy calculations on a large sample of 1177 organic crystals, a classification of pair-wise molecule–molecule interactions is proposed. The forces acting between molecules in crystals are estimated for the first time using an approximate calculation including displacements from the experimental crystal configuration. Interaction potential energies may be destabilizing ('collateral damage'), or, if stabilizing, may be neutral, moderate, strong or very strong, in the −5 to −50 kJ mol^{-1} range. Interaction forces can be zero if the dimer is at an equilibrium; when this is not the case, as often happens, forces can be attractive/frustrated or repulsive if the distance between the partners is larger or smaller, respectively, than the equilibrium distance.

(ii) Over a database of real crystals of nitro compounds, the occurrence of short oxygen–oxygen contacts is explained as secondary to stronger interactions, like hydrogen bonds, or, in other cases, as minor collateral damage in the general energetic economy of the crystal structure. In general, no relationship between short intermolecular atom–atom contacts and interaction energies is found in our study. This may well be due to incomplete sampling. The results, however, issue a considerable warning over generalizations drawn on the basis of geometrical data alone.

(iii) The overall landscape of pair-wise molecule–molecule energies and forces provides a detailed energetic structural fingerprint that may be useful in the distinction between real polymorphs and concealed identical crystal structures (a vexata quaestio, see Bernstein et al., 2008); the information may also be relevant to the assessment of the mechanical properties of materials.

(iv) Significantly destabilizing contacts occur in ∼ 9% of the crystal structures for neutral molecules. While the appearance of these counteracting contacts is not surprising a priori, the above result shows that it occurs in a minority of cases. In addition, the first coordination shell of such crystals has a very large number of neutral or just barely cohesive pairs in the first coordination shell. The nature and number of these weakly connective pairings are suspected to be a prominent factor in making exact crystal structure prediction so difficult.

(v) Repulsive destabilizing contacts appear regularly in crystals of very strongly polar compounds, and of course in ionic crystals, in what may be called the 'Madelung-mode' pairing of opposite ions with strongly repulsive and strongly attractive interactions.

The classification of molecule–molecule contacts with energy calculations provides a consistent and objective way of classifying intermolecular interactions. The PIXEL method is fast and convenient; however, it is but one of many available for the purpose. Others, even more accurate, include ab initio electron-correlated calculations (for which a benchmark database of computed intermolecular energies has been established, see Jurecka et al., 2006), density functional theory or distributed dipoles. Even simple atom–atom calculations, running in seconds, are sometimes better than nothing when force fields are carefully parameterized. Given the fact that quite affordable and well disseminated software exists (e.g. CASTEP, http://www.castep.org; CRYSTAL, http://www.crystal.unito.it; WIEN2k, http://www.wien2k.at; GAUSSIAN; atom–atom force fields in any molecular simulation package) that in many cases requires limited computer resources, energy calculations by any means are the ideal way of analyzing intermolecular structures. Interpretations based on intermolecular distances alone should be conducted critically and adequately justified before they find their way into the major structural literature. In particular, such an exercise is hardly justifiable in crystals of zwitterions or of organic salts where approximately half of the molecule–molecule contacts are strongly repulsive and destabilizing.

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