

Calculation of lattice energies of organic crystals: the PIXEL integration method in comparison with more traditional methods

Angelo Gavezzotti*

Dipartimento di Chimica Strutturale e Stereochimica Inorganica, Università di Milano, via Venezian 21, 20133 Milano, Italy

Received May 24, 2004; accepted July 30, 2004

Lattice energies / Organic crystals / PIXEL method / Computational crystallography

Abstract. The lattice energies of 47 crystal structures of organic compounds spanning a wide range of chemical functionalities are calculated using simple atom-atom potential energy functions, using coulombic terms with point-charge parameters, and using the PIXEL formulation, which is based on integral sums over the molecular electron density to obtain coulombic, polarization, dispersion and repulsion lattice energies. Comparisons among the different formulations, and the sensitivity and significance of the results against convenience, ease of application and number of parameters, are discussed. Improvements in the treatment of overlap repulsion in PIXEL are described, as well as a scheme for the minimization of the crystal lattice energy, based on the Symplex algorithm, which although computationally demanding, is shown to be feasible even with comparatively modest computing resources. The reproduction of experimental heats of sublimation is only marginally better with the PIXEL method, which however has great advantages in its being generally applicable in principle throughout the periodic table, at the expense of a minimal number of parameters, and in the fact that it sees the intermolecular interaction as the effect of the whole molecular electron density, in a physically more justifiable approach. This latter view in turn suggests a transition from a consideration of atom-atom bonds to a consideration of molecule-molecule bonding, opening a new view of packing factors in molecular crystals.

Introduction

The calculation of the lattice energy of organic crystals is one of the historical accomplishments of the joint efforts of early theoretical chemistry and crystallography. The application of simple model potentials [1] is straightforward, and even a static or lattice-dynamical [2] simulation using fixed average atomic positions, as obtained from X-ray diffraction analysis, is adequate for the derivation of sublimation enthalpies, vibrational frequencies and external entropies — hence, of sublimation free energies and saturated vapor pressures. For comparison, the calculation of the vaporization enthalpy of a liquid [3] calls at least for a million-step Monte Carlo or molecular dynamics simulation with a 10^4 -fold increase in computational requirements.

In recent times a more ambitious goal has been aimed at, the prediction of crystal structure from molecular structure using a combination of the above mentioned calculated crystal properties. If this computational approach is presumably a safer way to “crystal engineering” than the use of qualitative prescriptions on the basis of intermolecular geometries, there is still a long way to go to the finishing line [4]. The calculation of accurate lattice energies certainly requires accurate intermolecular potentials; for crystal structure prediction, the best potential is a welcome addition, but is neither a necessary nor a sufficient condition for success, there having been examples of good predictions with poor potentials, and vice versa [5]. Also, if the “strong” requirement of absolute prediction is relaxed in a “soft” approach to a survey of the crystal energy landscape, the absolute quantitative accuracy of total energy can be advantageously traded for a quantitative estimate of the relative importance of the various crystal energy terms — coulombic and polarization versus dispersion, for the attractive part, and Pauli overlap for the repulsive part. These partial terms are more easily correlated to molecular properties than total lattice energies.

This review is devoted to the description of a new potential energy scheme, called the PIXEL scheme, which takes explicitly into account the source of the intermolecular potential as a whole — the molecular electron density — as opposed to traditional atom-atom approaches. Besides, this new method has the above mentioned energy partitioning as its key feature. If still perfectible on some details of the formulation and of the parameterization, the PIXEL approach opens new views in intermolecular energy calculations and in the analysis of crystal packing factors.

The crystal structure and heat of sublimation databases

All models of intermolecular interaction depend on a number of parameters that must be adjusted against experimen-

* e-mail: angelo.gavezzotti@unimi.it

tal observations. One of the key concepts in the optimization of an intermolecular potential scheme is the calculation of the lattice energy of a selected set of crystals, whose structure is available from X-ray diffraction experiments, and the comparison of the calculated energy with the measured heat of sublimation of the material. The details of such a procedure have been illustrated and discussed in previous reviews [6, 7].

In previous work [8, 9] we have collected about 200 crystal structures with their appended heats of sublimation, for H/C, H/C/O, H/C/N, H/C/Cl, H/C/F, H/C/S, H/C/Si compounds, as well as for nitro derivatives, plus carboxylic acids, amides, alcohols and N–H...N hydrogen-bonding compounds. These data were used in the optimization of standard atom-atom potential functions. PIXEL calculations are of course much more demanding in terms of computing times, so in previous work we chose a selection of 32 crystal structures for the optimization of the four parameters on which the PIXEL method depends. To these we have now added 15 other crystal structures, which were not included in the training set of the method and are therefore particularly indicative on its performance. Experimental heats of sublimation were taken from a compilation [10].

Atom-atom potential energy approximations

The simplest scheme for the approximation of intermolecular potential energies in crystals has the following atom-atom form:

$$E_{ij} \text{ (kJ/mole)} = A \exp(-BR_{ij}) - CR_{ij}^{-6} + 1389.36q_iq_j/R_{ij} \quad (1)$$

where R_{ij} is an intermolecular distance between atomic nuclear positions, A , B and C are empirical parameters, and q_i are atomic charge parameters located at atomic nuclear positions. The total lattice energy is a sum of such terms on all atom-atom distances in a crystal. The advantages of such a scheme are all in its simple form and computational speed, as demonstrated by the fact that this is the favorite scheme in molecular dynamics simulations involving millions to billions of timesteps on 10,000-atom computational boxes. Successful and useful as this method may have been over the years, this same simplicity has encouraged its use sometimes well beyond its real capabilities; its shortcomings and disadvantages are in fact many.

First of all, one should mention the total lack of physical basis of the formulation, with atomic nuclear positions taken as the origin of the interaction, which is instead delocalized on the whole molecular electron density. For example, the electrical potential of the molecule is represented by net charges located at atomic nuclei, or the most unlikely position for a sometimes negative electrical charge in a molecular object. Besides, this charge localization prevents the estimation of penetration energies, or the part of coulombic interaction energy that comes from overlapping electron density clouds; and it has been shown [11] (if demonstration be needed) that this approx-

imation severely distorts the picture of molecular interaction at short distance.

Second, the atom-atom scheme requires a relatively large number of parameters, typically about twice the number of atoms in the molecule: for a 20-atom molecule with 4 different atomic species, the parameters are 10 A , B , C values and 20 point charges. The q_i 's are to be considered as fully empirical parameters, if they are taken to be transferable among compounds of the same chemical nature; otherwise, they must be calculated by some approximation from a molecular wavefunction (by Mulliken population analysis, or by the Electrostatic Potential fitting, or ESP scheme, for example; see beyond). Coulomb interaction energies may easily change by 100%, or even may change sign, upon a different choice of point charges.

To avoid these difficulties and uncertainties in the derivation of atomic charges, some years ago we undertook a project of optimization of atom-atom parameters without recourse to point-charge parameters [8, 9], the coulombic part of the interaction being parametrically embedded in the 6-exp part of the potential. This formulation was called the UNI scheme. Table 1 has the full list of crystals with their UNI lattice energies; the coulombic energies calculated by the point-charge method using ESP-derived atomic charge parameters are also shown, although they are not part of the UNI calculation. While the overall agreement between observed heats of sublimation and calculated lattice energies is remarkable for such an approximate formulation, several discrepancies appear, notably the underestimation of ΔH_{subl} for very small molecules, or for some anhydrides, where particularly strong coulombic interactions are present.

All calculations involving lattice sums may suffer from convergence problems. While these are irrelevant for the first two terms in equation (1), they may be important for the slowly decaying R^{-1} terms. In old-fashioned calculations involving a fixed cutoff distance in the sums, due to computational restrictions, convergence acceleration techniques had to be used. Nowadays, in non-polar space groups, the inclusion of a large number (up to 1000) complete neutral molecular units without any cutoff greatly reduces or altogether eliminates the problem. In polar space groups the problem may still be acute when the molecular dipole aligns along the polar direction and the overall cell dipole is large. The issue of accurate calculation of coulombic energies in such cases has not yet been fully settled; we use the Kroon-van Eijck method [12]. The results are satisfactory; see for example the two polymorphs of tetrazole in Table 1, where the cell dipole energy in the polar polymorph is nearly equal to the total coulombic energy of the centrosymmetric polymorph.

Finally, one may mention that the widespread use of atom-atom potentials has somehow generated a sort of "atom-atom prejudice", a view of intermolecular phenomena which assigns great importance to localized atom-atom interaction geometries, like C–H...O, or Cl...Cl short contacts. Some of these interpretations of crystal packing, especially those involving short atom-atom distances without proper consideration of penetration effects,

Table 1. Calculated lattice energies of organic compounds using the UNI atom-atom potentials, coulombic energies by the atomic point-charge scheme, heats of sublimation and cell dipole energies (kJ mol⁻¹).

E(UNI)	E_{qq}	ΔH_s	$E_{c.d.}$	Name and short label	
-59.1	-44.2	67	-0.2	acetic acid ACAC	old set
-71.5	-47.7	70	-7.3	acetamide ACAM	
-44.4	-6.0	44		benzene BENZ	
-92.0	-47.5	89		benzoic acid BZAC	
-103.7	-43.8	102		benzamide BZAM	
-61.4	-23.0	69		benzoquinone BZQU	
-17.1	0.0	32		solid Cl ₂ CLOR	
-80.3	-24.1	97		2,3-diazanaphthalene DAZN	
-66.8	-4.0	65		1,4-dichlorobenzene DICL	
-83.1	-32.0	89		1,4-dicyanobenzene DCNB	
-104.8	-24.9	96		1,4-dinitrobenzene DNIT	
-48.4	-44.2	61	-0.7	formic acid FMAC	
-63.0	-50.6	72		formamide FMAM	
-52.7	-32.9	69		fumaronitrile FUMN	
-48.6	0.1	51		<i>n</i> -hexane HEXN	
-76.9	-42.0	83		imidazole IMAZ	
-55.1	-31.1	70		maleic anhydride MALA	
-96.6	-18.9	91		naphthoquinone NAPQ	
-72.8	-6.4	72		naphthalene NAPT	
-85.5	-13.2	79		4-nitrotoluene NTOL	
-71.9	-74.9	98		oxalic acid OXAC	
-80.2	-48.1	87		pyridone PRDO	
-56.2	-14.9	49	-0.8	pyrimidine PRMD	
-88.1	-23.4	88	-2.2	phthalic anhydride PTLA	
-56.8	-6.1	57		pyrazine PYRZ	
-125.3	-77.0	121		succinic acid SCAC	
-61.3	-38.3	82		succinic anhydride SUCA	
-76.7	-22.6	80		tetroxocane TOXO	
-88.5	-45.5	84		triazole TRAZ	
-63.4	-15.9	58		triazine TRIZ	new set
-119.3	0.6	94		tetrathiafulvalene TTFU	
-84.9	-74.5	88		urea UREA	
-12.1	-11.1	24		acetylene ACEY	
-100.5	-8.8	105		anthracene ANTC	
-25.4	-1.7	29		cyclopropane CYPR	
-86.7	-28.3	84		2,3-dimethylphenol DMPH	
-54.7	0.0	58		<i>n</i> -heptane HEPT	
-129.0	-88.9	121		melamine MELM	
-63.9	0.1	68		<i>n</i> -octane OCTA	
-86.2	1.0	87	-0.5	pentachlorobenzene PNCL	
-25.3	-0.1	29		propane PROP	
-64.0	-28.3	79		pyridine N-Oxide PYRO	
-74.0	-42.3	83		Succinimide SCIM	
-94.8	-46.6	88		tetrazole, <i>P</i> ₂₁ / <i>m</i> TETZ	
-100.5	-4.6	88	-48.8	tetrazole, <i>P</i> ₁ TETZ1 ^a	
-79.8	-9.4	92	-4.3	trithiane TRIT	
-59.6	-12.0	58	-6.9	trioxane TROX	
-113.9	-56.1	109		thiourea TURE	

a: Not used in the final optimization rounds

are often unwarranted. This point has recently been reviewed [13]. The atom-atom method is a powerful and versatile computational tool but it should not be carried beyond its limits, which are those of a skillful empirical

machinery for the reproduction of total energies in solids or liquids, without any presumption of portraying the actual physics of the interaction.

The semi-classical density sums (PIXEL) method

We have recently proposed a new method for the calculation of intermolecular potentials from molecular properties only [14, 15]. In this new approach, the simultaneous action of the entire molecular electron density comes to the fore, and a molecule is described by some 10,000 interaction sites instead of just the few dozen atomic sites. This view changes dramatically our perspective with respect to atom-atom approximations. The basic procedures in the Pixel approach will now be reviewed.

The valence-only molecular electron density is calculated at the MP2/6-31G** level, on a grid with a standard step of 0.08 Å, using for example GAUSSIAN98 [16]. This calculation also yields the potential derived charges by the “population = ESP” keyword. The original density typically consists of a few million pixels. A pixel has density ρ_i and volume V_i and hence a charge $q_i = \rho_i V_i$. The number of pixels must be high for an accurate reproduction of the total electron number, but must be largely reduced for the actual integration. Therefore, the density for the final calculation is modified by a) condensation: cubic super-pixels of $n \times n \times n$ original pixels are formed, with volume equal to $n^3 V_i$ and charge equal to the sum of all charges in the original pixels. n is called the condensation level. This is a key step in the procedure, more appropriate than taking larger steps in the generation of the density, which would cause inaccuracies in the integral electron count; and b) screenout: super-pixels with charge $q < q_{\min}$ (in modulus) are screened out; this gets rid of the many and many zero-density pixels, and of a few near-zero ones. A typical q_{\min} value is 10^{-6} electrons.

Any number of molecules can appear in a Pixel calculation, electron densities being rotated and translated in space according to some matrix operations. In a crystal, these are the space group symmetry operations. The proce-

dures thus uses rigid, undeformed electron densities. The fortuitous overlap of pixels, with zero or near-zero pixel-pixel distance, may cause singularities; hence, all pixel-pixel distances below half the step size are reset at half the step size: we call this number the ‘collision avoidance’ threshold. Intermolecular energies and fields only are calculated; all intramolecular electrostatic and polarization effects are assumed to be constant and hence are not evaluated. This is equivalent to a rigid-molecule approximation.

Let ρ_k be the electron density in a volume V_k in a molecule A; each of the P_A e-pixels is then assigned a charge $q_k = \rho_k V_k$. In addition, molecule A has N_A nuclei. A second molecule B has P_B e-pixels and N_B nuclei. So, each molecule in the computational box is represented by a set of P e-pixel charges and a set of N nuclear charges. The electrostatic potential generated by molecule A at each point of the charge density of molecule B and at each nucleus of molecule B is then calculated, and the total coulombic potential energy between the two molecules is a sum of coulombic terms over all pixel-pixel, pixel-nucleus and nucleus-nucleus pairs. The first term only is computer-intensive, including $P_A P_B \approx 10^8$ terms.

The electrostatic field, ϵ , due to molecule A at point (i) in molecule B is also a sum of a term due to the e-pixels and a term due to the nuclei. Each e-pixel in molecule B is then polarized by this field. After defining a distributed linear polarizability at point (i), α_i , the corresponding induced dipole and polarization energy (assuming isotropic, parallel-field polarization) is given by $\mu_i = \alpha_i \epsilon_i$ and $E_{\text{POL}, i} = -1/2 \mu_i \epsilon_i$, respectively. The total polarization energy due to the perturbation of molecule B by molecule A is then taken as a summation on all (i) points. This model for the polarization energy is automatically a many-body one, since the fields at any molecule are calculated over contributions from all molecules around it. The polarization is static, i.e. densities are not dynamically deformed by polarization.

Atom	$\alpha_{\text{atom}}/\text{\AA}^3$ previous work [18]	present work ^a	atomic radius/ \AA
C (aliphatic)	1.05	1.05	1.77
C (unsaturated)	1.25	1.35	1.77
C (aromatic bridgehead) ^b	1.80	1.90	1.77
O	0.80	0.70	1.58
N	0.88	1.00	1.64
H	0.39	0.39	1.10
Cl	2.30	2.30	1.76
C–S–C sulfur	3.00	3.00	1.81
Parameters			
ϵ_{max} , V m^{-1}	170	170	
D , \AA	3.25	3.50	
K^c	3300	3300 ^d	
γ^c	0.97	0.97 ^e	

a: From ref. [17]

b: Like C(9) in naphthalene

c: For E_{REP} in kJ mol^{-1} when the electron density is in e \AA^{-3}

d: Or variable, see text

e: Fixed at 1.00 when K is variable

Table 2. Atomic polarizabilities, atomic radii and parameters in the PIXEL method.

In order to assign pixel polarizabilities, each pixel is assigned to the atom to which the distance is the smallest fraction of the atomic radius (see Table 2). Calling α_{atom} the atomic polarizability, and Z_{atom} the number of valence electrons in that atom, we then write

$$\alpha_i = (q_i/Z_{\text{atom}}) \alpha_{\text{atom}}. \quad (2)$$

The atomic polarizabilities are taken from reference sources [17] and are thus, in principle, non-adjustable parameters in the formulation.

Polarization contributions at very short separations pose a complex problem. These high-field contributions are physically unrealistic, resulting from fortuitous short distances in the overlapping density meshes. To avoid this difficulty, the polarization energy at pixel i is damped as $E_{\text{POL},i} = -1/2 \alpha_i [\varepsilon_i d_i]^2$, where $d_i = \exp -(\varepsilon_i/(\varepsilon_{\text{max}} - \varepsilon_i))$; the polarization energy is zero for $\varepsilon > \varepsilon_{\text{max}}$. The threshold value ε_{max} must be considered an adjustable empirical parameter in the formulation.

Intermolecular dispersion energies are calculated as a sum of pixel-pixel terms in different molecules, by London-type expression, involving the above defined distributed polarizabilities and an overall ionization energy, E_{ION} . To avoid singularities due to very short pixel-pixel distances in an inverse sixth-power formula, each term in the sum is damped according to a function, $f(R)$:

$$E_{\text{DISP}} = E_{\text{ION}}(-3/4) \times \sum \sum f(R) \alpha_i \alpha_j / [(4\pi\varepsilon^0)^2 (R_{ij})^6], \quad (3)$$

$$f(R) = \exp [-(D/R_{ij} - 1)^2] \quad \text{for } R_{ij} < D \quad (4)$$

while $f(R) = 1$ for $R_{ij} > D$. D , the damping threshold distance, is an adjustable empirical parameter. We use for E_{ION} the energy of the highest occupied molecular orbital, which is another non-adjustable parameter in the formulation, being directly obtained from the molecular orbital calculation.

The repulsion energy between molecules A and B is approximated through the overlap between their electron densities, S_{AB} :

$$E_{\text{REP,AB}} = K(S_{\text{AB}})^\gamma, \quad (5)$$

$$S_{\text{AB}} = \sum \sum [\varrho_i(\text{A}) \varrho_j(\text{B})] V \quad (6)$$

where K and γ are adjustable parameters. The overlap integral is calculated by numerical integration, and the computing times are reasonable because the integral has to be evaluated only in the relatively small space common to the two electron densities – that is, where both ϱ 's are not zero.

The total intermolecular interaction energy is then:

$$E_{\text{TOT}} = E_{\text{COUL}} + E_{\text{POL}} + E_{\text{DISP}} + E_{\text{REP}}. \quad (7)$$

Optimization of the computational conditions and of the parameters

The whole PIXEL procedure has only four fully adjustable parameters, that is, ε_{max} , D , K and γ , which must be optimized to reproduce the heat of sublimation of organic

crystals and to provide reasonable interaction energy curves in selected molecular dimers. The atomic polarizabilities may also be to some extent adjustable, within very restricted ranges. The values adopted in previous work [18, 19], together with some more accurate values used in this work, are collected in Table 2.

For better comparisons and for a finer tuning of the values of the parameters, the lattice energies for the 47 crystal structures were calculated at condensation $n = 4$ with several values of the D and ε_{max} parameters, and a least-squares fit of the polarization and dispersion terms was obtained. The repulsion energy can be calculated for any value of the K and γ parameters, given the corresponding overlap integrals. Eventually, these three contributions could be estimated in a continuous way for any value of the four parameters within a reasonable range, and since the coulombic contribution is parameter-free, total lattice energies were also available as a continuous function of the four parameters. The root-mean square difference between total energies and enthalpies of sublimation was then minimized with respect to the values of these parameters by a Symplex procedure. The optimized parameters were then used for the calculation of the binding curves of two test dimers, the stacked parallel benzene dimer and the cyclic acetic acid dimer.

The Symplex optimization is very effective, but the target surface is in this case extremely multiform and many minima and valleys are present – in other words, many different sets of parameters yield the same root mean square deviation between lattice energies and heats of sublimation. Besides, some parameter sets corresponding to promising minima in the rms deviation were then found to yield unrealistic binding curves for the two test dimers, or to produce unrealistic, very small values of the polarization or dispersion energies. After these attempts, it was concluded that only a small increase of the screening parameter for dispersion, D , from 3.25 to 3.50 Å, was appro-

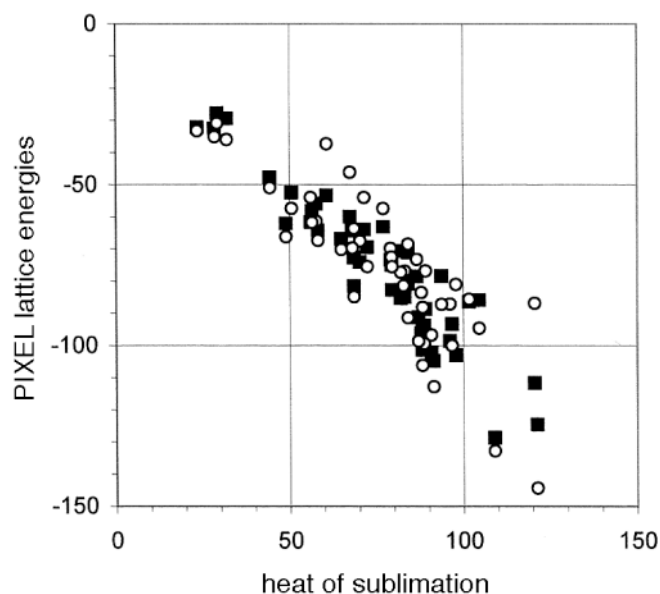


Fig. 1. PIXEL calculated lattice energies (kJ mol^{-1}) for 47 crystal structures. Full squares: variable K , open circles: fixed $K = 3300$, $g = 0.97$ calculations. Least-squares fitting lines have $R^2 = 0.864$ and 0.722 , respectively. The non-zero cell dipole energies (triangles) are also shown.

appropriate, as a consequence of the increase in the atomic polarizability of aromatic carbon and of nitrogen; otherwise, the root-mean-square deviation could not be significantly reduced, without loss of adherence to physically plausible conditions. Thus, the set of parameters used in previous work [18], with only minor modifications, comes out of these tests as still the best overall compromise, for the 32 crystal structures in the training set as well as for the 15 new ones. This result, if positive on one side, leaves open the problem of improving the general performance of the method; in fact, Figure 1 shows that there is still a rather substantial and systematic underestimation of the lattice energies of hydrogen-bonded crystals.

With these parameters, the parallel benzene dimer has a minimum at an interplanar distance of 3.5 Å with a binding energy of 17 kJ mol⁻¹, an acceptable result; the cyclic hydrogen-bonded formic acid dimer has a minimum at an O...H distance of 1.95 Å, somewhat too long, with a binding energy of 42 kJ mol⁻¹, somewhat underestimated.

Influence of the basis set; tests with a cc-pVDZ wavefunction

At this stage, an attempt at improving the performance of the method by improving the quality of the basis set in the calculation of the electron densities seemed advisable. All electron densities were recalculated using the more diffuse and complete cc-pVDZ basis set, and steps of 0.075 Å. The increase in computing effort is significant; this stage becomes rather heavy for the larger molecules in our set of structures. The different basis set has of course no effect on the computing times for the actual PIXEL calculations, which are affected only by the number of e-pixels.

The most significant difference between the cc-pVDZ and the 6-31G** basis sets is in the spatial extent of the electron density, which in the cc-pVDZ description is more diffuse for the π -clouds of the aromatic systems, and

is slightly more contracted for molecular regions corresponding to more electronegative atoms or chlorine. Correspondingly, the overlap, and hence the repulsion energy, is larger in contacts involving the former systems. In many cases however, the stabilizing coulombic, polarization, and to some extent also dispersion energies are larger, so that total energies are much less affected than the separate contributions. Figure 2 shows plots of the differences in repulsion energies and of the differences in coulombic energies: further analysis revealed a linear relationship of nearly unit slope between the two sets of differences, so that the good performance of the 6-31G** basis set seems to result from a cancellation of errors in the repulsive and attractive contributions. One notable exception is the crystal structure of naphthoquinone, which shows a much larger overlap repulsion energy in the cc-pVDZ description (a difference of 25 kJ mol⁻¹); this fact could be due to some special charge-transfer effect in this crystal structure, which the Pixel method of course cannot describe.

When the new basis set is used, a re-calibration of the four PIXEL parameters is necessary. The rms deviation over the cc-pVDZ results, using the standard parameter set, was somewhat larger than with the 6-31G** results. Symplex optimization, using the same procedure described above, gave rather erratic results; there were no clear and unequivocal signs of significant improvement of the rms deviation without loss of physical significance. The more accurate wavefunction obtained with the better basis set gives obviously more accurate numerical results, but does not in itself provide a solution to the problem of improving the agreement between calculated lattice energies and heats of sublimation.

For a systematic test of the effect of the condensation level, lattice energies were calculated for the 32 crystal structures in the reduced set at condensation $n = 4, 5$ and 6. The total computing times were 44, 14 and 6 hours respectively. Figure 3 shows the essential results: the total energies at $n = 5$ are only 5% larger than those at $n = 4$,

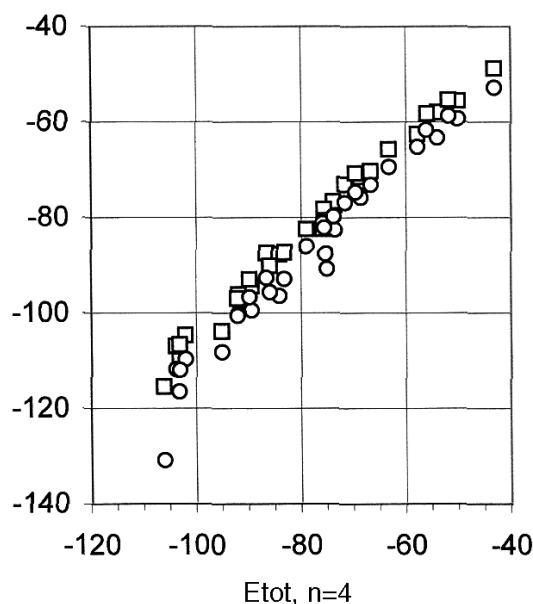
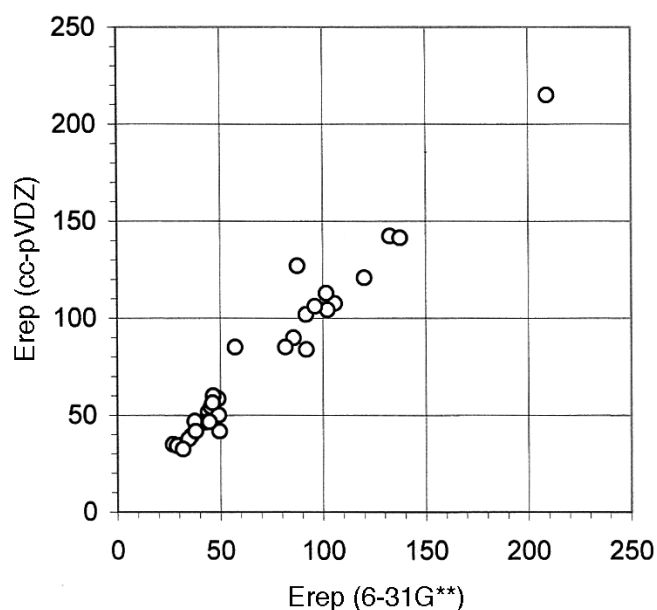


Fig. 2. (a) A comparison of cc-pVDZ and 6-31G** coulombic energies. (b) The same for repulsion energies. kJ mol⁻¹ units.

Fig. 3. PIXEL lattice energies calculated at $n=5$ (squares) or $n=6$ (circles) for 32 crystal structures, relative to the values calculated at $n = 4$, cc-pVDZ wavefunction. kJ mol⁻¹ units.

with a steady linear relationship between the energies calculated in the two different condensation schemes. In particular, the dependence of the coulombic energy from the value of n reveals that the true coulombic energy (an extrapolation at $n = 1$) is $E(\text{coul, true}) = 0.9E(\text{coul, } n = 6)$ or $E(\text{coul, true}) = 0.95E(\text{coul, } n = 4)$. A similar trend holds for the polarization contribution, while the dispersion energy is practically insensitive to n between 4 and 6. In conclusion, even a calculation with $n = 6$ is good enough for a reasonably accurate estimate of the lattice energy. The threefold (for $n = 5$) or seven-fold (for $n = 6$) decrease in computing times with respect to $n = 4$ is particularly appealing in view of the application of the method to the optimization of crystal structures, when the minimization scheme calls for a large number of calculations of the lattice energy.

A critical view of the repulsion model

The approximation adopted here, where the repulsion energy is given by $E_{\text{REP, AB}} = K(S_{\text{AB}})^\gamma$, is in many ways questionable. In particular our results here demonstrate that a model in which the repulsion energy is proportional to the magnitude of the overlap integral cannot use the same constants over different classes of compounds. This view is also confirmed by comparisons with partitioned energy values obtained from the intermolecular energy perturbation theory (IMPT) calculations [18]. A wrong evaluation of the repulsion energy has an adverse effect on the forces, or first derivatives of the potential, which come to the fore when the optimization of the lattice energy of a crystal is attempted. In fact tests conducted using the general parameter set obtained above showed that some crystal structures are heavily distorted by the potential, i.e. hydrocarbons contract and hydrogen-bonded crystal structures tend to expand.

One of the simplest ways to improvement is adopting a different value of the constant K in different chemical environments; this same conclusion had been reached in previous work using the distributed multipole approach [20]. An estimate of the degree of variance of the PIXEL repulsion energy parameters was obtained as follows. The exponential dependence was suppressed, i.e. γ was set equal to unity throughout, so that the flexibility of the parameterization is completely transferred to the value of K . Table 3 shows the modified values of the proportionality constant, K' , which are necessary to rescale the repulsion energy so as to reproduce the sublimation enthalpies, keeping of course all other parameters constant. Hydrogen-bonded compounds, acids, amides and phenols, plus N=O compounds, need an average constant value $K' = 3200$. Hydrocarbons and aromatic azahydrocarbons show a spread of K' values, apparently depending on the number of carbon + nitrogen atoms ($K' = 5400 - 130 N_{\text{atoms}}$), as a first approximation independently of whether the compound is aliphatic or aromatic. Crystals of compounds with triple bonds, acetylene or nitriles, show a steep dependency on molecular size, or $K' = 6950 - 133 N_{\text{atoms}}$. Aliphatic C/H/O compounds like ethers, quinones and anhydrides use an average $K' = 3600$, while aromatic ones require $K' = 4200$. A

similar value is adequate for chloro compounds, as well as for compounds forming N—H...N hydrogen bonds.

The physical interpretation of this variation in K' is not easy. First of all, the variation may incorporate an unknown amount of error in the calculation of other energy contributions. For example, the fact that the required value is much smaller in hydrogen-bonding systems could reflect an underestimation of stabilization, in particular the energy stabilization that comes from even partial covalency, and which is intrinsically missing from the PIXEL picture of bonding. Then, the variation in required K could depend on intrinsic quantum chemical reasons, or on an intrinsic limitation of the proportionality model, or on errors or limitations in the evaluation of the wavefunction, or in approximations in the numerical evaluation of the overlap integral. In many cases, apparently, a higher repulsion constant is necessary for compounds with many unsaturated carbon atoms; therefore, tests were conducted using a correction in which the overlap between more polarizable atoms was artificially increased. This led to no success, and in fact some high values of K' are also needed for saturated hydrocarbons. Particularly puzzling is the dependence on molecular size, e.g. in the benzene-naphthalene-anthracene series.

As a first attempt of modulation of the overlap repulsion constant, the K' values in Table 3 were fitted in a linear expansion in the number of atoms of each species in the molecule. Even though the numerical fit was successful, this approach leads to little increase in physical significance; if the repulsion constant depends on atom types, then it must also be orientation-dependent, i.e. the value of the constant must be different when e.g. two benzoic acid molecules interact in a stacked dimer (purely hydrocarbon interaction) or when they interact over a hydrogen bond. To take care of this dependency, overlap score factors were calculated as follows. For a pair of molecules in a given reciprocal position, the ratio between each atom-atom distance and the corresponding sum of atomic radii, F_{ij} , was calculated. Each of these distances was assigned to a class (C/H, oxygen, nitrogen, chlorine, sulfur), yielding a score of $S = 100$ if F_{ij} is up to 0.75, or a score decreasing as $s_{ij} = 100 \exp(-10(F_{ij} - 0.75))$ for $F_{ij} > 0.75$. After summing over all distances, the integral value of the score for each pair of classes, S_{km} , is obtained, and after renormalization, the actual value for the repulsion constant for that particular molecular pair is obtained as $K' = S_{km}K'_{km}$. k and m run over atom classes, and matrix K'_{km} (Table 4) contains typical values of K' for the k - m class pair; they are meta-parameters, as they are numbers which are used in defining a final parameter in the PIXEL formulation. In this preliminary investigation the K' values were optimized by a few cycles of trial and error by inspection of the K' data in Table 3, but we are presently attempting to find a more physical basis, possibly in terms of diffuseness of the wavefunction, or of ionization potential and electron affinity, or of atomic 'hardness' parameters.

We call this approach the 'variable K' ' approach, because the overlap repulsion constant is not unique for a given compound, but changes for every molecular pair in a crystal structure. The results for crystals are quite satis-

Table 3. Results of the PIXEL calculations. 6-31G** wavefunction, PIXEL parameters in Table 2, kJ mol⁻¹ units.

Name ^a	E_{coul}	E_{pol}	E_{disp}	E_{rep}	E_{tot}	ΔH_{subl}	$E'_{\text{rep}}{}^b$	K'
ACAC	-78.2	-35.8	-37.7	92.9	-58.8	67.0	84.7	2980
BZAC	-94.3	-46.2	-69.0	120.9	-88.8	89.0	120.5	3354
FMAC	-84.1	-39.9	-32.8	104.2	-52.7	60.0	96.8	2992
OXAC	-115.5	-47.7	-55.6	115.8	-103.1	98.0	120.7	3325
SCAC	-147.6	-66.4	-82.0	184.6	-111.6	121.0	175.0	3088
ACAM	-80.8	-27.7	-43.7	96.3	-56.0	63.0	89.3	3316
BZAM	-73.8	-25.9	-77.8	91.0	-86.5	102.0	75.5	3148
FMAM	-79.3	-25.5	-34.9	75.7	-64.0	72.0	67.7	2999
PRDO	-79.7	-31.9	-63.5	96.5	-78.5	87.0	88.0	3298
UREA	-97.6	-32.3	-41.5	75.0	-96.4	88.0	83.4	3649
DMPH	-55.2	-26.5	-70.3	80.7	-71.3	84.0	68.0	3125
DNTB	-39.3	-10.7	-86.4	37.6	-98.7	96.0	40.3	3270
NTOL	-23.3	-7.2	-77.0	33.9	-73.5	79.0	28.5	3016
PYRO	-45.4	-15.1	-66.7	52.2	-74.9	79.0	48.2	3486
PROP	-7.0	-2.5	-49.9	26.8	-32.5	29.0	30.3	5080
CYPR	-10.0	-3.1	-43.2	28.4	-28.0	29.0	27.4	4340
HEXN	-10.7	-3.8	-81.2	43.2	-52.5	51.0	44.6	4651
HEPT	-11.4	-4.0	-87.1	46.6	-55.8	58.0	44.4	4288
OCTA	-11.1	-3.7	-95.5	45.9	-64.3	68.0	42.2	4136
BENZ	-13.3	-5.1	-59.5	30.1	-47.8	44.0	33.9	5068
NAPT	-19.6	-9.3	-93.2	52.7	-67.6	72.0	50.0	4268
ANTC	-26.1	-12.3	-115.9	68.4	-82.8	105.0	49.3	3242
DAZN	-39.6	-14.4	-95.0	55.6	-91.6	97.0	52.0	4205
PRMD	-28.5	-8.8	-64.1	40.2	-61.2	49.0 ^c	52.4	5830
PYRZ	-27.6	-7.7	-61.3	38.4	-58.1	57.0	39.5	4575
TRIZ	-24.4	-6.7	-68.1	34.9	-64.3	58.0	41.2	5179
CLOR	-19.7	-10.2	-55.7	56.3	-29.3	32.0	53.6	4280
DCLB	-18.9	-7.5	-86.2	45.6	-67.0	65.0	47.7	4473
PNCL	-24.4	-12.6	-129.0	75.1	-90.9	87.0	79.0	4544
ACEY	-16.3	-5.6	-28.4	18.3	-32.1	24.0	26.2	6445
FUMN	-41.1	-10.5	-64.0	34.0	-81.7	69.0	46.7	6058
DCNB	-42.3	-10.1	-92.6	51.2	-93.8	89.0	56.0	4874
MALA	-36.6	-8.4	-51.6	22.3	-74.2	70.0	26.6	3689
SUCA	-47.0	-12.3	-56.0	30.0	-85.3	82.0	33.3	3490
BZQU	-36.0	-8.6	-63.2	35.0	-72.8	69.0	38.8	3488
TROX	-32.3	-7.4	-58.4	43.3	-54.9	51.0	47.1	3639
TOXO	-35.8	-13.9	-70.6	37.5	-82.8	80.0	40.3	3574
PTLA	-37.7	-10.3	-84.3	39.4	-93.0	86.0	46.3	3979
NAPQ	-36.7	-11.4	-105.9	51.8	-100.5	91.0	63.0	4353
SCIM	-71.8	-25.3	-62.9	75.1	-85.0	83.0	77.0	3545
MELM	-151.4	-61.6	-95.5	184.1	-124.7	121.0	187.6	4301
TETZ	-99.4	-44.9	-51.9	95.0	-101.3	88.0	108.2	4574
IMAZ	-78.0	-38.7	-46.5	92.5	-70.8	83.0	80.3	3729
TRAZ	-87.1	-42.8	-57.7	106.7	-80.9	84.0	103.6	4097
TRIT	-62.1	-31.8	-113.0	107.2	-99.8	88.0	118.9	4652
TTFU	-43.6	-24.1	-111.6	100.9	-78.4	94.0	85.3	3591
TURE	-111.7	-76.4	-66.3	102.9	-128.8	109.0	145.4	5614

a: See Table 1 for the labels

b: Repulsion energy rescaled by K' so as to match exactly the heat of sublimation with $\gamma = 1$

c: Experimental value is probably a heat of vaporization from the liquid

Table 4. The K' -matrix described in the text. Values refer to the overlap repulsion constants between classes of atomic species.^a

	C, H	N	O	Cl, S
C, H	4500	4500	2500	4000
N	4500	3300	3000	3500
O	2500	3000	3500	3500
Cl, S	4000	3500	3500	4500

a: For energies in kJ mol^{-1} when the electron density is in e \AA^{-3} .

factory, as shown in Table 3 and Fig. 1. With this approach, the parallel benzene dimer has a minimum at an interplanar distance of 3.6 \AA with a binding energy of 13 kJ mol^{-1} , more in line with rigorous *ab initio* results, while the cyclic hydrogen-bonded formic acid dimer has a minimum at an $\text{O} \cdots \text{H}$ distance of 1.80 \AA with a binding energy of $60\text{--}65 \text{ kJ mol}^{-1}$, in better agreement with experiment and theoretical calculations.

Coulombic energies: a comparison of localized vs. delocalized models

A correct evaluation of coulombic energies is crucial in the interpretation of organic crystal structures. We show in Fig. 4 the results of the comparison between coulombic energies calculated by the localized point-charge model, using the best possible atomic charges (the ESP-fit charges on the MP2/6-31G** wavefunction), and those calculated by the delocalized PIXEL method. The latter have been demonstrated in several occasions (see e.g. ref. [21]) to approximate very closely those obtained by far more so-

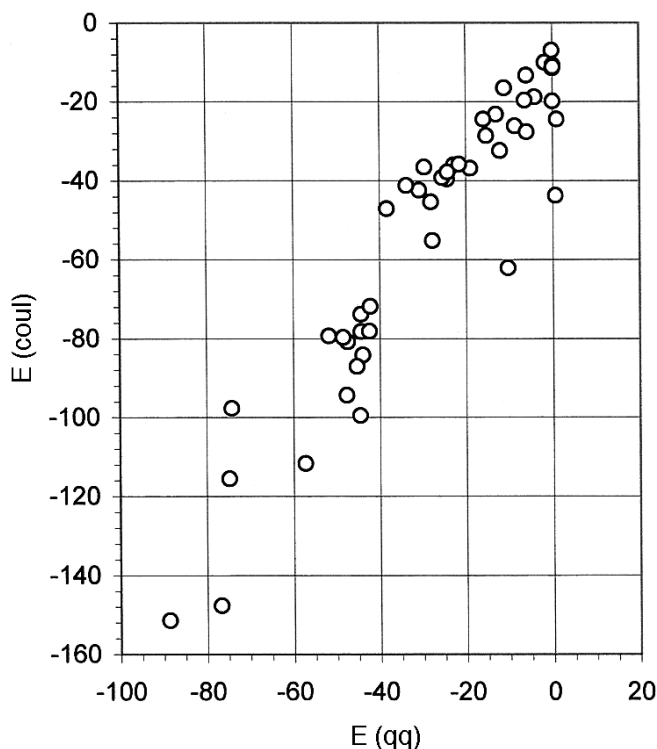


Fig. 4. PIXEL coulombic energy (E_{coul}) as a function of atom-atom point-charge coulombic energy (E_{qq}) for 47 crystal structures. kJ mol^{-1} units. Least-squares line: $E_{\text{coul}} = 1.46 E_{\text{qq}} - 11.5$.

phisticated and time-consuming quantum chemical methods. A rough linear correlation appears, but there are many deviations; when using point-charge methods, one should be aware that coulombic energies will be largely underestimated. Besides, due to the non-zero value of the intercept in the linear plot, the coulombic energy may even become positive in localized models. These effects become more and more dramatic at closer and closer intermolecular distances, affecting in particular the comparison among different molecular recognition modes.

Crystal structure optimization; lattice energy minimization

The minimization of the lattice energy of molecular crystals is here carried out as a device for the evaluation of the quality of the crystal potential, rather than for the actual prediction of crystal structures. In fact, the computational experiment aims at demonstrating that the deviation of the optimized structure from the experimental one is as small as possible when the potential is as accurate as possible.

In a given space group, the lattice energy of a crystal composed of conformationally rigid molecules is written as

$$E = E(x, y, z, \tau, \varphi, \chi, a, b, c, \alpha, \beta, \gamma) \quad (8)$$

where x, y and z are the coordinates of the center of mass, τ, φ and χ are three Euler angles for the rigid-body rotations around inertial axes, and the other six parameters are the cell dimensions. Given the form of the Pixel potential, there is no easy way of calculating the derivatives of this function analytically. Tests carried out with derivatives calculated numerically by finite increments and using a steepest-descent algorithm were unsatisfactory, due to problems with the scaling of the relative size of the derivatives and to the intrinsically low efficiency (slow convergence) of the steepest-descent procedure. The Symplex method, which does not require derivatives, is therefore the method of choice in this case. Its less desirable counterpart is that it requires a large number of calculations of the target function. For benzene at condensation $n = 5$, the calculation of one lattice energy takes about 20 minutes on a 3 GHz processor PC, so that the complete optimization of the crystal structure, requiring perhaps 100 evaluations of the energy, takes about 30 hours. Such computing times are large but not prohibitive, and could easily become routine on more powerful machines like parallel computers or clusters.

Lattice energy optimizations by PIXEL-Symplex were performed for some selected crystals (Table 5). With condensation level $n = 5$ and including all molecules whose center of mass is within 13 \AA from the reference molecule, each run was allowed 50 optimization cycles. All optimizations ran rather smoothly, and convergence at or around a stationary final energy value was attained; in some cases, oscillations as large as 0.1 \AA in cell parameters were compatible with the same lattice energy, so that the intrinsic accuracy of the optimization cannot be below such a value. The overall structural changes were small

Table 5. Results of lattice energy optimizations. For each entry, first row: starting cell parameters (Å and degrees) and energy (kJ mol⁻¹), second row: final cell parameters, rotational and translational displacements, final energy (kJ mol⁻¹).^a

	<i>a</i>	<i>b</i>	<i>c</i>	α	β	γ	rotn. (°)	transl. (Å)	Energy
acetic acid	13.31	4.09	5.77	—	—	—			-61.0
	13.30	4.09	5.79	—	—	—	1, 1, 3	0.09	-65.8
benzene	7.44	9.55	6.92	—	—	—			-50.2
	7.01	9.21	6.75				1, 1, 7	—	-53.5
<i>K'</i> = 5500	7.26	9.43	6.88				1, 0, 3	—	—
benzoquinone	7.06	6.80	5.77	—	102	—		—	-75.3
	6.69	6.56	5.70	—	98	—	3, 3, 1	—	-83.9
1,4-dichlorobenzene	7.36	5.96	3.96	92	113	91			-69.3
	7.25	5.91	3.93	91	118	94	1, 0, 0	—	-74.3
<i>n</i> -hexane	4.13	4.70	8.54	83	87	75			-55.7
	4.12	4.68	8.54	87	87	74	0, 0, 1	—	-56.3

a: Calculations were carried out with the 6-31G** wavefunction, PIXEL parameters in Table 2, and the variable-*K* repulsion model (for benzene, equivalent to *K'* = 4500). Condensation level *n* = 5, so lattice energies are slightly overestimated.

and in the expected direction, i.e. a contraction of the cell volume as appropriate to a “zero-Kelvin” calculation. For hydrogen-bonded compounds, shifts as large as 0.1 to 0.2 Å in the equilibrium value of the hydrogen bond distance were observed. For benzene, the deformations from the experimental structure are smaller when *K'* is larger, as expected.

The PIXEL method *vis à vis* atom-atom methods

While fully *ab initio* quantum mechanical treatments are not quite adequate for the description of dispersion effects in organic crystals [22], a number of approximate quantum chemical formulations have appeared [23, 24], as well as quantum mechanical treatments coupled with partly empirical force fields [25]. The partly delocalized, distributed multipole approach [26] has been positively tested in many occasions for crystal structure reproduction and prediction. Atom-atom force fields have also been carried to the limit of sophistication by calibrating some parameters against extremely accurate quantum chemical calculations [27].

The PIXEL coulombic energy is a parameter-less quantity, it is about as accurate as the wavefunction is, and it includes penetration effects; as such it is largely superior to point-charge coulomb energies, and also superior to those obtained by the distributed multipole method. The PIXEL polarization energy is, correctly, a many-body contribution, but does not include the dynamical effects of polarization. Besides, its adherence to first principles is reduced by the fact that it depends on one empirical screening parameter. No other formulation includes a polarization term, assuming a proportionality between polarization and coulomb energies. But PIXEL calculations [18] show that this is often, but not always the case, so that the explicit inclusion of polarization is a prominent positive feature of the new method. The PIXEL dispersion term

depends on one fully empirical parameter and incorporates a number of assumptions, the weakest of which is the use of the HOMO energy for the ionization potential, while a better approximation would take into account the electronic density of states near the ionization level. Nevertheless, the distributed nature of all PIXEL interactions allows a much more flexible description of these interactions over molecular regions than is possible in atom-atom methods, which must incorporate in just one term all polarization and dispersion attractions. The PIXEL repulsion term is also parametric, and the variable constant approach for the proportionality between overlap integral and overlap energy, which we describe in this paper, requires a number of assumptions which are halfway between a purely *ab initio* method and a sort of atom-type dependent repulsion energy formulation. But at least the parameters are applicable to exact quantum mechanical quantities, the overlap integrals between molecular densities. A clear connection to quantum mechanical observables or to well defined numerical quantities is a valuable aid in the parameterization, which can be at least in part guided by chemical or electronic reasoning or by rigorous computations, much better than the blind optimization of parameters which is a characteristic of fully empirical methods.

The PIXEL construction, as already mentioned, uses rigid electron densities and therefore misses any effect that may result from substantial rearrangement of the electronic wavefunction as a consequence of molecular interaction. As such, it is ideally suited for hydrocarbons and moderately polar systems, and more and more unsuited as one moves to medium-weak hydrogen bonding (as in neutral carboxylic acids or amides) or to strong hydrogen bonding (charge-assisted or resonance-assisted hydrogen bonding [28]). As a partial remedy, one could choose to enhance the polarization term, or to reduce the repulsion term; as described, we have opted for the second choice. The influence of the parameterized part of the theory, therefore, increases accordingly in these systems. We must

also mention that our comparisons between calculated lattice energies and enthalpies of sublimation implicitly assumes no change in molecular conformation on going from the crystal to the gas phase, an assumption which introduces a further element of uncertainty in the calibration of the parameters.

The PIXEL approach is worthwhile if one considers the quality to computational price ratio. On a modern workstation, the calculation of the lattice energy of one crystal including a large number of neighbors and high resolution (low condensation number) takes some 30 minutes, while the calculation of the full interaction energy curve for a molecular dimer takes a few minutes or less. PIXEL calculations, if incomparably slower than atom-atom ones, are orders of magnitude faster than quantum mechanical ones; even the Symplex minimization of lattice energies is much faster than the equivalent job performed by a periodic orbital calculation with an evaluation of the analytical derivatives of the energy.

We believe that the PIXEL method represents a good compromise between accuracy, ease and convenience of application, and number of parameters, and that on going from atom-atom to PIXEL methods, a substantial improvement in the quality of the tools for analysis obtains. Although its description of partly covalent bonding, like the hydrogen bond, is less and less conforming to physical reality, careful parameterization has the method working in a satisfactory manner also for these systems. Even with all these caveats, we would like to underscore the great improvement in adherence to the physics of the interaction with respect to fully empirical methods, with partitioning into terms that can be more easily understood and hence adapted to the chemical characteristics of the constituting molecule of the crystal. Table 3 clearly shows, for example, the relative importance of coulombic versus dispersion terms as a function of polarity or polarities within the molecule. For the discussion of packing factors, including the relative importance of various types of interaction in determining the crystal structure, the natural partitioning into molecule-molecule energies afforded by the PIXEL approach has the added merit of shifting the focus of the analysis from atomic nuclear positions, irrelevant, to the whole molecular electron density [29, 30], revealing many of the flaws of some widespread views of crystal structure and of its defining forces in terms of pairwise interactions. These features and factors, together with its general applicability on optimization of only a few disposable parameters, demonstrate that PIXEL has a high potential for future application in theoretical organic crystal chemistry. Whether this potential will become actual, time will tell.

Appendix

The OPiX computer program package [31]

OPiX is a program package for the calculation of molecular and intermolecular properties. It is written in featureless Fortran and it has been seen to compile and operate on all types of computers.

OPiX uses file-to file input options, and there are no windows or menus.

A preliminary module provides interfacing between modules and communication with other program packages as well as coordinates for hydrogen atoms on the basis of standard geometries. Given the importance of H-atom positions in crystal energy calculations, this renormalization is mandatory when X-ray crystal atomic coordinates are used. The other modules are described in the following.

Zipopec module: gives geometric information, molecular volumes and surfaces, moments of inertia, etc.; using known cell dimensions, space group and atomic coordinates for a crystal, calculates lattice energies, packing coefficients, short atom-atom and significant molecule-molecule distances and energies, using empirical atom-atom force fields (default: UNI potentials). The molecular and cell dipoles are calculated, and the correction to the lattice energy due to the net cell dipole is estimated.

The UNI force field is a particularly convenient set which does not require charge parameters. Rather unusually, some cross i - j potentials are not obtained as averages of the corresponding i - i and j - j potentials.

Prom module: given a rigid molecular model, generates many possible crystal structures in the most common space groups. The Prom module consists of three submodules: Prom: generates raw crystal structures; Sorter: detects and discards duplicate structures; Minop: optimizes lattice energies with respect to cell parameters and rigid-body degrees of freedom. This submodule can also be used separately as a lattice energy minimizer. Energies are calculated by empirical atom-atom force fields (default: the UNI potentials).

Prom reads a molecular model with orthogonal cartesian coordinates for each atom, and generates crystal structures for that molecule, in the form of files with cell parameters, fractional atomic coordinates and space group operations. The lattice energy for each generated structure is calculated and the most stable ones can be identified. The molecule must be rigid, that is no intramolecular energies are ever considered. The space groups allowed are $P\bar{1}$, $P2_1$, $P2_12_12_1$, $P2_1/c$, $C2/c$ and $Pbca$. If the input molecular model has more than one fragment (more than one molecule in the asymmetric unit, clathrates, molecular complexes, salts, solvate crystals), their reciprocal positions remain fixed and no fragment-fragment energy is calculated. The methods used are purely from geometrical crystallography: briefly, the procedure consists in building dimers, ribbons and layers of molecules according to partial space group symmetry, selecting the most cohesive ones among such substructures, and applying further translation as required to obtain complete, but still approximately packed, three-dimensional crystal structures. This search is usually redundant, so that generated structures must be clustered and sorted to screen out duplicates. Optimization of these raw structures with respect to rigid-body molecular degrees of freedom and cell parameters is then performed.

Pixel module: calculates the coulombic, polarization, dispersion and repulsion energies between separate, rigid molecules. The Pixel module uses molecular electron densities which are calculated by some quantum chemical package (e.g GAUSSIAN). Two types of system are considered:

- a) clusters made of any number of molecules of up to two molecular species. The position of each molecule in the cluster is obtained by an orientation matrix constructed from three Euler angles, and by a displacement vector. These must be obtained by the user on visual inspection;
- b) a crystal made of only one molecular species, one molecule per asymmetric unit. The positions of molecules in the cluster that represents the crystal structure are generated automatically using cell parameters, space group matrices, and a cutoff threshold for the distance between centers of mass of the central and surrounding molecules. The minimization of the lattice energy can be carried out with a steepest-descent or Simplex algorithm.

References

- [1] Pertsin, A. J.; Kitaigorodsky, A. I.: *The Atom-Atom Potential Method*, Springer-Verlag, Berlin 1987.
- [2] Filippini, G.; Gramaccioni, C. M.; Simonetta, M.; Suffritti, G. B.: Lattice-dynamical calculations on some rigid organic molecules. *J. Chem. Phys.* **59** (1973) 5088–5101.
- [3] Jorgensen, W. L.; Maxwell, D. S.; Tirado-Rives, J.: Development and testing of the OPLS-all atom force field on conformational energetics and properties of organic liquids. *J. Am. Chem. Soc.* **118** (1996) 11225–11236.
- [4] Gavezzotti, A.: Are crystal structures predictable? *Acc. Chem. Res.* **27** (1994) 309–314.
- [5] Lommerse, J. P. M.; Motherwell, W. D. S.; Ammon, H. L.; Dunitz, J. D.; Gavezzotti, A.; Hofmann, D. W. M.; Leusen, F. J. J.; Mooij, W. T. M.; Price, S. L.; Schweizer, B.; Schmidt, M. U.; van Eijck, B. P.; Verwer, P.; Williams, D. E.: A test of crystal structure prediction of small organic molecules. *Acta Cryst.* **B56** (2000) 697–714.
- [6] Gavezzotti, A.: The crystal packing of organic molecules: challenge and fascination below 1000 dalton. *Crystallography Reviews* **7** (1998) 5–121.
- [7] Gavezzotti, A.; Filippini, G.: Energetic aspects of crystal packing: experiment and computer simulations. In: *Theoretical aspects and computer modeling of the molecular solid state* (Ed. A. Gavezzotti). Wiley and Sons, Chichester, 1997.
- [8] Filippini, G.; Gavezzotti, A.: Empirical intermolecular potentials for organic crystals: the 6-exp approximation revisited. *Acta Crystallogr.* **B49** (1993) 868–880.
- [9] Gavezzotti, A.; Filippini, G.: Geometry of the intermolecular X–H...Y (X, Y=N, O) hydrogen bond, and the calibration of empirical hydrogen-bond parameters. *J. Phys. Chem.* **98** (1994) 4831–4837.
- [10] Chickos, J. S.: Heats of sublimation, In: *Molecular Structure and Energetics*, Vol. 2 (Eds. Liebman, J. F.; Greenberg, A.) VCH: New York, 1987.
- [11] Gavezzotti, A.; Dunitz, J. D.: Electrostatic energies in the 1,4-dichlorobenzene polymorph crystals: the role of charge density overlap effects in crystal packing analysis. *Helv. Chim. Acta* **85** (2002) 3949–3964.
- [12] van Eijck, B. P.; Kroon, J.: Coulomb energy of polar crystals. *J. Phys. Chem.* **101** (1997) 1096–1100.
- [13] Dunitz, J. D.; Gavezzotti, A.: Intermolecular recognition and adhesion in organic crystals: persistent bonding, elusive bonds. *Angew. Chem. Int. Ed.* **44** (2005) 1766–1787.
- [14] Gavezzotti, A.: The calculation of intermolecular interaction energies by direct numerical integration over electron densities. I. Electrostatic and polarization energies in molecular crystals. *J. Phys. Chem.* **B106** (2002) 4145–4154.
- [15] Gavezzotti, A.: Calculation of intermolecular interaction energies by direct numerical integration over electron densities. 2. An improved polarization model and the evaluation of dispersion and repulsion energies. *J. Phys. Chem.* **B107** (2003) 2344–2353.
- [16] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, Jr.; J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Menonucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A.: *Gaussian 98*, Revision A.7, Gaussian, Inc., Pittsburgh PA. (1998)
- [17] Miller, K. J.: Additivity methods in molecular polarizability. *J. Am. Chem. Soc.* **112** (1990) 8533–8542.
- [18] Gavezzotti, A.: Towards a realistic model for the quantitative evaluation of intermolecular potentials and for the rationalization of organic crystal structures. I. Philosophy. *Cryst. Eng. Comm.* **5** (2003) 429–438.
- [19] Gavezzotti, A.: Towards a realistic model for the quantitative evaluation of intermolecular potentials and for the rationalization of organic crystal structures. II. Crystal energy landscapes. *Cryst. Eng. Comm.* **5** (2003) 439–446.
- [20] Mitchell, J. B. O.; Price, S. L.: A systematic nonempirical method of deriving model intermolecular potentials for organic molecules: application to amides. *J. Phys. Chem.* **A104** (2000) 10958–10971.
- [21] Volkov, A.; Coppens, P.: Calculation of electrostatic interaction energies in molecular dimers from atomic multipole moments obtained by different methods of electron density partitioning. *J. Comput. Chem.* **25** (2004) 921–934.
- [22] Pisani, C.: *Molecular Crystals*, in *Handbook Molecular Physics*, (Ed. S. Wilson and R. McWeeny). Wiley, Chichester, 2001.
- [23] Ferenczy, G. G.; Angyan, J. G.: Intra- and intermolecular interactions in crystals of polar molecules. A study by the mixed quantum mechanical/molecular mechanical SCMP-NDDO method. *J. Comput. Chem.* **22** (2001) 1679–1690.
- [24] Raabe, G.: The use of quantum chemical semiempirical methods to calculate the lattice energies of organic molecular crystals. Part. I: the three polymorphs of glycine. *Z. Naturforsch.* **55a** (2000) 609–615.
- [25] Rovira, C.; Novoa, J. J.: A density functional study of crystalline acetic acid and its proton transfer polymorphic forms. *J. Chem. Phys.* **113** (2000) 9208–9216.
- [26] Price, S. L.: Applications of realistic electrostatic modelling to molecules in complexes, solids and proteins. *J. Chem. Soc., Faraday Trans.* **92** (1996) 2997–3008.
- [27] Mooij, W. T. M.; van Duijneveldt, F. B.; van Duijneveldt-van de Rijdt, J. G. C. M.; van Eijck, B. P.: Transferable ab initio intermolecular potentials. 1. Derivation from methanol dimer and trimer calculations. *J. Phys. Chem.* **A103** (1999) 9872–9882.
- [28] Gilli, G.; Gilli, P.: Towards a unified hydrogen-bond theory. *J. Mol. Struct.* **552** (2000) 1–15.
- [29] Carlucci, L.; Gavezzotti, A.: Molecular recognition and crystallization for caffeine and other methylxanthines. To be submitted.
- [30] Demartin, F.; Filippini, G.; Gavezzotti, A.; Rizzato, S.: X-ray diffraction and packing analysis on vintage crystals: Wilhelm Koerner's nitrobenzene derivatives from the School of Agricultural Sciences in Milano. *Acta Crystallogr.* **B60** (2004) 609–620.
- [31] Gavezzotti, A.: OPiX, A computer program package for the calculation of intermolecular interactions and crystal energies, University of Milano, 2003. The package is available upon request at angelo.gavezzotti@unimi.it for a nominal fee.