

Molecular Mechanics in Crystalline Media

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A general, computationally easy method for minimizing the steric energy of a molecule, polymer, surface, or net within the field of a fixed, or periodically updated, crystal lattice has been devised. The goal has been obtained by coupling molecular mechanics (MM) to Kitaigorodsky's atom–atom pairwise potential (AAPP). The primary outcomes of such MMAAPP computations are the “solid state” conformation of the molecule, its intramolecular steric energy and its interaction energy with the surrounding lattice. These computations are ideally suited for studying relative stabilities of different polymorphs, plastic deformations of a whole crystal lattice, and molecular motions of flexible guest molecules in host crystal lattices. The proposed approach can help in understanding solid-state dynamics, factors controlling reactivity in crystal lattices, and crystals as “supramolecular entities”. In addition, the capability of building “hypothetical” crystals with sterically reasonable geometries can be exploited in the process of solving crystal structures from partial diffraction data.

We have been driven to molecular mechanics by our interests in the ligand stereochemistry of metal carbonyl clusters. Since these systems are characterized by a certain freedom for carbonyls to float about the metal cage (or, alternatively, by the freedom of the metal cage to librate within the ligand envelope),¹ we adopted Lauher's equal potential surface (EPS) concept² and showed that an EPS can be derived by maintaining a weakened concept of connectivity in the so-called local connectivity approach.³ However, the lack of a definite M–CO connectivity, which is intrinsic to the EPS approach, may result in sterically allowed but electronically unreasonable structures.⁴ As a consequence, we have limited the freedom of the carbonyl ligands about the metal cage by introducing a new component of the force field which addresses the fulfillments of the local electron bookkeeping and favors the conformations associated with a better spread of the total charge.⁵ Recently, we extended our force field to π ligands bonded to vertexes, edges, or faces of metal clusters using the “dummy” atom formalism.⁶

Since we have found many discrepancies between “theoretical” (ideally referring to the gas phase) and experimental stereochemistries (often referring to the solid state), we have developed a strong interest in ascertaining the role of the crystal lattice (i.e. of packing interactions) in addressing the actual stereochemistry of such flexible molecules. Accordingly, we decided to implement into a local version of Allinger's MM3 program,⁷ previously used for the above quoted computations, the possibility to optimize the conformation of a molecule within

the field of a fixed, or periodically updated, crystal lattice. A similar task was pursued by Osawa but never described in detail.⁸

The possibility of success of the present approach, hereafter MMAAPP, from coupling of molecular mechanics (MM) and Kitaigorodsky's atom–atom pairwise potential (AAPP)⁹ methods, in interpreting the solid-state dynamics of *flexible* molecules stands on the good parametrization of intra- and intermolecular interactions. Indeed, MM3 van der Waals (vdW) parameters have been shown to reasonably describe both *intra-* and *intermolecular* interactions.^{7c} Given the great successes of the AAPP method in rationalizing the dynamics of *substantially rigid* molecules,^{9–11} and the well-known capabilities of MM3 in dealing with organic systems at the molecular level we think that the present approach could be used quite safely to study the solid-state dynamics of flexible molecules and/or to evaluate the effects of a (rigid) host crystal lattice on a (flexible) guest molecule.

In the following, we will describe the proposed MMAAPP methodology using a few simple examples taken from the literature; however, the power of this approach has been previously proved in the cluster realm by rationalizing the solid-state dynamics of $\text{Fe}_3(\text{CO})_{12}$.¹²

The Program

All the computations have been done employing a local version of MM3 upgraded to deal with (i) carbonyl ligands in the local connectivity approach;³ (ii) formal local charge distributions;⁵ (iii) “dummy” atoms;⁶ and (iv) crystal lattices.¹²

The latter task is achieved by the combined usage of the two programs PACKMM, which builds up the model of the crystal and the whole input deck for MM3, and MM3, the actual molecular mechanics program. However, as we will see in the following, the approach is

(1) Johnson, B. F. G.; Roberts, Y. V. *Polyhedron* **1993**, *12*, 977.

(2) Lauher, J. W. *J. Am. Chem. Soc.* **1986**, *108*, 1521.

(3) Sironi, A. *Inorg. Chem.* **1992**, *31*, 2467.

(4) In a conventional MM study, the connectivity of the atoms is exactly defined (and is not allowed to change during the minimization), and, as a consequence, the number of valence electrons of each atom is also strictly controlled. However, within the EPS formalism, which allows variable connectivity of the metals, we lose control of the local number of valence electrons on each metal center.

(5) Sironi, A. *Inorg. Chem.* **1995**, *34*, 1432.

(6) Mercandelli, P.; Sironi, A. *J. Am. Chem. Soc.* **1996**, *118*, 11548.

(7) (a) Allinger, N. L.; Yuh, Y. H.; Lii, J.-H. *J. Am. Chem. Soc.* **1989**, *111*, 8551. (b) Lii, J.-H.; Allinger, N. L. *J. Am. Chem. Soc.* **1989**, *111*, 8566. (c) Lii, J.-H.; Allinger, N. L. *J. Am. Chem. Soc.* **1989**, *111*, 8576.

(8) Osawa, E. In *Reactivity in Molecular Crystals*; Ohashi, Y., Ed.; Kodansha: Tokyo, 1993; p 1.

(9) Pertsin, A. J.; Kitaigorodsky, A. I. *The Atom–Atom Potential Method*; Springer-Verlag: Berlin, 1987.

(10) Gavezzotti, A.; Simonetta, M. *Chem. Rev.* **1992**, *92*, 633.

(11) Braga, D. *Chem. Rev.* **1992**, *92*, 633.

(12) Sironi, A. *Inorg. Chem.* **1996**, *35*, 1725.

quite general, and once the proper model of the crystal has been generated by PACKMM, every MM program can be easily upgraded to deal with crystals.

Molecular Systems. Space group labels, cell parameters, atom types, and crystallographic coordinates for all the atoms within the asymmetric unit (AU) are fed to the program PACKMM which builds up (i) the reference molecule (RM) (which can extend over several symmetry-related AUs, since we always “complete” an isolated molecule); (ii) the list of surrounding molecules (SMs) (i.e. those having at least one atom within a sphere of given radius from the RM); and (iii) the complete MM3 input file containing the usual topological description of the RM and all the (encoded) relevant information for generating its SMs. The transformations relating crystallographic to orthonormal coordinates (and symmetry operations)¹³ together with details on the coding procedure, which allows us to periodically update the crystal lattice,¹⁴ are reported in the Appendix.

Our model of the crystal is constituted by the ensemble of the RM and its SMs, i.e. by a cluster of molecules partially obeying (being finite) the space group symmetry of the crystal. The steric energy (E_s) per RM in the crystal, will be

$$E_s = E_{\text{intra}} + E_{\text{inter}}$$

where E_{intra} is the conventional (intramolecular) steric energy of the RM while E_{inter} (known as the potential packing energy, *PPE*, when dealing with rigid molecules) is the sum of all nonbonded interactions, van der Waals (vdW) and Coulombic, between the RM and SMs atoms. Note that the need for a detailed description of molecular topology (and force field) applies only to the RM while the SMs are nothing but a collection of individual atoms.¹⁵ Accordingly, once the proper atom list has been generated by PACKMM, every MM program can be upgraded (in order to deal with crystals) by extending the computation of nonbonded interactions (both for forces and energies) to these “isolated” atoms.

Polymeric Systems. Polymers are more difficult to deal with since intramolecular interactions extend all over the crystal. However, to compute the forces acting on the RM (which is not any more an individual molecule) only a relatively small subset of “connected” atoms is needed while the E_s per RM in the crystal can be properly computed by weighting the bonding (intramolecular) interactions. Accordingly, PACKMM builds up a model of the polymeric crystal partitioned in four non-overlapping parts (see Figure 1); namely, (i) the RM (which always reduces to the AU in the case of polymers); (ii) the connected environment (CE) (which is constituted by all the atoms which are needed to compute the valence forces acting on the RM atoms); (iii) the intramolecular environment (*IntraE*) (which is constituted by the atoms, within a sphere of given radius from the RM, belonging to the same chain or net of the RM); and (iv) the intermolecular environment (*InterE*) (which is constituted by the surrounding “molecules” having at least one atom within a sphere of given radius from the RM but not belonging to the same chain or net of the RM). To ensure an overall charge of zero, (CE \cup *IntraE*) and *InterE* are always constituted by an integral number of (symmetry-related) AUs.

To refine the conformation of the whole polymeric crystal, it is enough to compute the forces acting on the RM only. This requires a

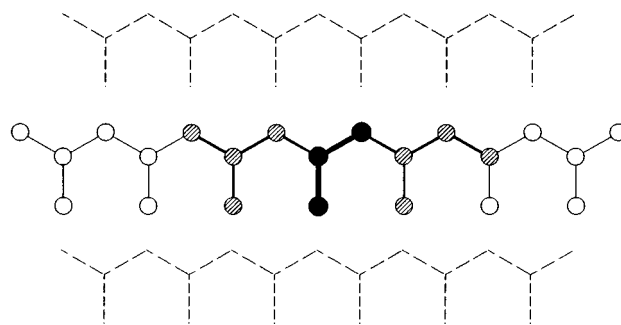


Figure 1. Our model of the crystal is constituted by the ensemble of the RM and its SMs, i.e. by a cluster of molecules partially (being finite) obeying the space group symmetry of the crystal. When dealing with polymers the partition between RM and SMs is not enough and in addition to (i) the RM (closed circles), which always reduces to the AU in the case of polymers, we must consider: (ii) the connected environment (CE, dashed circles), which is constituted by all the atoms which are needed to compute the valence forces acting on the RM atoms; (iii) the intramolecular environment (*IntraE*, open circles), which is constituted by the atoms belonging to the same chain or net of the RM; and (iv) the intermolecular environment (*InterE*, dashed line), which is constituted by the surrounding “molecules” having at least one atom within a sphere of given radius from the RM but not belonging to the same chain or net of the RM. In the case of molecular system obviously (RM \cup CE \cup *IntraE*) reduces to RM while *InterE* reduces to SMs.

full topological description of RM and CE but not of *IntraE* and *InterE* which, contributing only to the nonbonded energy, can be seen as a collection of individual atoms. Note that, since conventional force fields include at most 1,4 valence interactions the CE has to contain all the atoms having a 1,4 relationship with some RM atom at most. Moreover, the fact that some “external” CE atoms have some missing valences (being also connected to some *IntraE* atoms) has no relevance since we compute the forces on the RM atoms only.

Once the RM and CE have been properly defined and the computation of nonbonded interactions has been extended to *IntraE* and *InterE*, every MM program can handle polymeric crystals. However, to compute a correct E_s per RM we must partition the intramolecular interaction energies (i.e. those involving RM and (CE \cup *IntraE*)).¹⁶ In particular for an n atoms interaction $E(i_1, \dots, i_n)$ ($n = 4$ at most for torsional terms) the fraction of the energy belonging to the RM will be

$$w(i_1, \dots, i_n) = (1/n) \sum_{j=1}^n \text{mult}(i_j) \times \delta(i_j, \text{RM})$$

where $\text{mult}(i_j)$ is the normalized¹⁷ crystallographic site occupancy for the i_j atom and $\delta(i_j, \text{RM})$, Kronecker's delta, will be 1 or 0 depending if i_j belongs to the RM or not.

The (weighted) steric energy per RM will be

$$E_s = E_{w, \text{intra}} + E_{\text{inter}}$$

where $E_{w, \text{intra}} = \sum w(i_1, \dots, i_n) E(i_1, \dots, i_n)$, is the *weighted* intramolecular energy, and the summation runs over the usual n -body bonding (within RM \cup CE) and nonbonding interactions (between RM and RM \cup CE

(13) Note that, to deal with space group symmetry, the usual MM3 symmetry operation has been augmented with a translational component.

(14) Actually, PACKMM encodes all the symmetry information needed to obtain the SMs atoms from the RM ones as a list of integers (one for each atom). This allows, using the proper decoding routine, to periodically update (during the minimization process) the SMs on the base of the actual RM. The underlying assumption for these procedure is that relatively small deformations of the RM do not lead any “new” molecule to join or any “old” one to leave the actual SMs cluster. This assumption can be checked by verifying that the minimized coordinates fed into PACKMM afford the same SMs cluster (in term of symmetry operator) of the starting coordinates.

(15) This is not true if the electrostatic energy is approximated by the dipole interaction energy computed throughout bond dipoles (since we would also need to memorize the bonding pattern of the SMs). For this reason we have restored an older option (available in MM2), and we compute the charge interaction energy instead.

(16) Note that this weighting scheme must be used only to compute the *weighted* intramolecular energy but *not* to compute the forces acting on each atom. Indeed, it is possible to demonstrate that these *unweighted* forces are the derivatives of the *weighted* intramolecular energy.

(17) To obtain the energy per RM, the normalization factor is the reciprocal of the maximum crystallographic site occupancy (CSO) within the RM. For instance, in the following example of cubic diamond, where the RM is constituted by just one C atom with CSO = 1/24, the normalization factor will be 24 and $\text{mult}(\text{C})$ will be 1.

∪ *IntraE*), while E_{inter} is the nonbonding interaction energy between RM and *InterE*.¹⁸

Minimization Strategies. E_s can be minimized essentially within two different assumptions depending on whether the crystal lattice is periodically updated on the base of the actual RM conformation. The former assumption allows us to reach the closest minimum on the (crystal) potential energy surface and/or to study correlated motions, i.e. plastic deformations of the whole crystal lattice. On the contrary, the latter assumption allows to study uncorrelated processes occurring (randomly) to individual molecules within the (fixed) crystal lattice field.

Note that, after a minimization step under the latter assumption the conformation of the SMs is not anymore similar to that of the RM. Thus, to sample the energy profile of a relevant reaction coordinate (i.e. in order to minimize the RM under the constraints of the particular reaction path and of the fixed crystal lattice, normally starting from the RM conformation computed for the previous point in the energy profile), we must allow in general for a difference between the RM and SM conformations. More generally, we allow even for a different molecular nature of the RM and the SMs, thus studying the conformation and/or the dynamics of a guest molecule (GM) in a host crystal lattice.

Conventional AAPP methods can easily afford energy barriers against reorientation of a single rigid molecule in a rigid crystal environment.¹⁹ Since we deal with flexible RMs we should be able to study more elaborated molecular motions. However, for sake of generality, we also allow for some cooperation between the RM and a shell of nearest neighbors, the enclosure shell (ES), provided that the set of SMs is large enough to contain a second shell of rigid next-nearest-neighbors to ensure that the ES is not allowed undue freedom of motion. This task is easily fulfilled for molecular systems (no GM) since the RM and the ES molecules, despite having different conformations, share the same topological description. Thus it is enough to periodically swap the coordinates of the RM and the ES molecules to allow for cooperative motions and/or deformations of the ES molecules.²⁰

A few words about the meaning of the steric energies computed here may be in order. The E_s directly refers to a *local* property of the RM (or GM) molecule and must be used to compute potential energy profiles for their reorientation and/or deformation. However, to compare computed steric energies with *global* properties of the crystal, the correct value to be considered is

$$E_s^* = E_{\text{intra}} + (1/2)E_{\text{inter}}$$

For instance, E_s^* is related to sublimation enthalpies by the following relation:

$$\Delta H_s = E_s^* - E_g$$

where E_g is the steric energy of an isolated RM in the gas phase conformation. This expression is not quite correct, since the calculation (which ideally refers to RT) yields in principle the sublimation internal energy, that is the energy difference between a molecule in the crystal and a molecule in the vapor, both at rest. A detailed analysis of the energetic aspects of crystal packing has been reported by Gavezzotti and Filippini.²¹ Noteworthy, E_s^* values are meaningful only when the RM is representative of the global structure, for instance, in the case of plastic deformation of the crystal.

Dealing with polymers, even if it is impractical to speak of or to measure ΔH_s , it is still useful to define E_s^* as

(18) Note that, when an atom of the RM lies on a special position even its intermolecular interaction energy must be weighted with its normalized crystallographic site occupancy.

(19) For instance, OPEC by A. Gavezzotti.

(20) If there is cooperation, however, we must also take into account the ES reorganization energy.

(21) Gavezzotti, A.; Filippini, G. In *Theoretical Aspects and Computer Modeling of the Molecular Solid State*; Gavezzotti, A., Ed.; Wiley: Chichester, 1997; p 61.

$$E_s^* = E_{\text{w,intra}} + (1/2)E_{\text{inter}}$$

since it can be used to compare different polymorphs.

Results and Discussion

Molecular Mechanics of Carbon Lattices. Laqua et al. recently reported some force field calculations (MM2) of carbon lattices mimicked by carbon clusters of growing complexity.²² The individual computations were clearly biased by surface effects; however, the authors, by extrapolating their results to infinity, eventually reported extrapolated lattice strain energies. In the following, to show the capabilities of our approach in dealing with polymers, we will compute the “exact” (MM3) lattice strain energies for the three sp^3 carbon lattices considered by Laqua et al., namely, cubic diamond (CD), hexagonal diamond (HD), and γ -silicon diamond (BC-8) (see Figure 2).

Such an example is particularly well suited for our purposes since it is both topologically complex (dealing with 3D nets) and numerically simple (the RM being constituted by just one atom), thus allowing even a paper and pencil check. Indeed, it is straightforward to verify that, according to the proposed partition of intramolecular interactions (there are no intermolecular interactions in these carbon lattices), the program eventually takes into account four stretching (each weighted $1/2$), 18 bending (each weighted $1/3$), 72 torsion (each weighted $1/4$), and a large number²³ of vdW interactions (each weighted $1/2$) per carbon atom.

Dealing with isomeric lattices, we can make a direct comparison between steric energies and we do not need to compute strain energies which will follow the very same trend. Obviously, within the cluster approximation (each cluster being a different molecule) this is not true and Laqua et al. had to resort to strain energies. Accordingly we will compare our steric energies (E_s in Table 1) with their (extrapolated) strain energies (SE in Table 1).

As far as the geometrical aspects are concerned, our results are very close to the experimental ones (CD and HD lattices) and substantially similar to those reported by Laqua et al. (CD and BC-8 lattices). However, while the CD and HD lattices have similar extrapolated energies (within 0.5 kcal mol⁻¹), they differ for 2.5 kcal mol⁻¹ in our “exact” computations. This discrepancy cannot be attributed to either the different force field used in the “exact” computations (MM3 vs MM2), since it persists (and even increases to 3.6 kcal mol⁻¹) when MM2 parameters are used,²⁴ or to the extrapolation procedure (which seems to be sound) but are attributed instead to the cluster sampling technique. In particular, we feel that the HD lattice, which contains two different kinds of cages,²⁵ despite being

(22) Laqua, G.; Musso, H.; Boland, W.; Ahlrichs, R. *J. Am. Chem. Soc.* **1990**, *112*, 7391.

(23) More than 5000 within the radius of 16 Å. As a matter of fact, even the CD and HD lattices have a slightly different number of atoms in the *IntraE* because of some automatism of PACKMM which does not take the minimum cluster of atoms containing a sphere of the given radius but only checks that such a sphere is really contained in the *IntraE*. However, this has no consequences since the vdW interaction energies have converged to their actual values (within 0.05 kcal mol⁻¹) for that radius. The problem would be more serious if Coulombic interactions were also considered (but this is not the case for carbon lattices) since they converge much slower.

(24) Note that the relative instability of the HD lattice with respect to the CD one is due to 1,4 interactions, which are however differently parametrized in MM2 and MM3. Indeed, with MM3 the instability arises from torsional terms while with MM2 it arises from 1,4 vdW interactions.

(25) Namely, iccane- and bicyclo[2.2.2]octane-like cages, in a 1:1 ratio, the former being almost unstrained while the latter heavily strained.

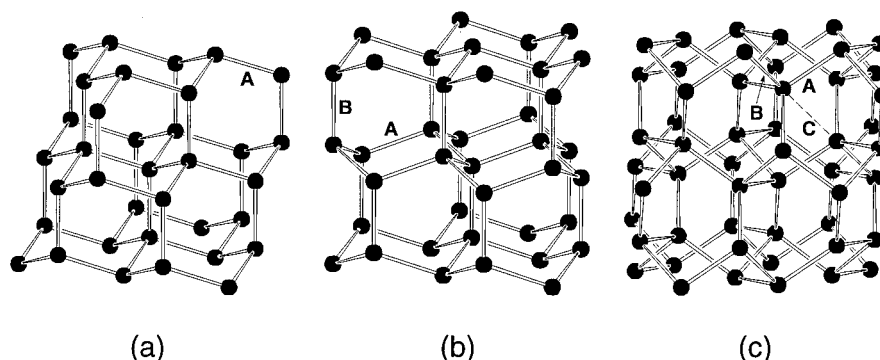


Figure 2. Fragments of the (a) cubic diamond, (b) hexagonal diamond and (c) BC-8 carbon lattices. Letters A, B, and C address different C—C bond distances whose actual values are reported in Table 1.

Table 1. Comparison of Calculated Data for Carbon Lattices with Previous Works

structural parameters		A ^f	B	C	E _{stretch} ^g	E _{bend}	E _{tors}	E _{vdW}	E _s	SE ^h
CD ^a	a = 3.567 ^b	1.545			0.24	0.00	3.20	0.96	4.40	0.00
HD	a = 2.522; c = 4.119; z = 0.0625 ^b	1.544	1.545		0.24	0.00	5.47	1.20	6.91	0.48
BC-8	a = 4.293; x = 0.1036 ^c	1.54	1.54	2.18	0.15	10.75	8.35	7.71	26.96	
	a = 4.420; x = 0.0975 ^d	1.60	1.49	2.34	2.46	8.07	8.23	4.89	23.65	11.23
	a = 4.432; x = 0.0961 ^e	1.608	1.475	2.363	3.21	7.53	8.23	4.55	23.52	

^a CD: $Fd\bar{3}m$ $8b(1/8, 1/8, 1/8)$; HD: $P6_3/mmc$ $4f(1/3, 2/3, z)$; BC-8: $Ia\bar{3}$ $16c(x, x, x)$. ^b Ownby, P. D.; Yang, X.; Liu, J. *J. Am. Ceram. Soc.* **1992**, *75*, 1876. ^c Johnston, R. L.; Hoffmann, R. *J. Am. Chem. Soc.* **1989**, *111*, 810. ^d Reference 22. ^e This work. ^f C—C bond distances A, B, and C (Å) are defined in Figure 2. ^g All energy values are in kcal mol⁻¹. ^h Strain energy *per* carbon atom, as reported in ref 22.

assembled from topologically equivalent C atoms, was perhaps sampled without taking into account the correct ratio (1:1) between these differently strained cages, thus affecting the extrapolation procedure with a systematic error.

Note that Laqua et al. have obtained their “optimal” lattice parameters from the inner shell geometry of their clusters which, for reasonably large clusters, is insensitive to surface effects, extrapolation procedures and sampling techniques. Thus it is not surprising that their “optimal” geometries were substantially correct despite the errors in the extrapolated energies. In particular, even if Laqua et al. have underestimated the strain energy of the BC-8 lattice by ca. 10 kcal mol⁻¹,²⁶ they have obtained an “optimal” geometry which is substantially identical with ours.²⁷

The above computations on carbon lattices probably have little value from a theoretical viewpoint since “molecular” MM3 parameters were not thought for covalent 3D nets. Indeed, we probably overestimate the relative energy (2.5 kcal mol⁻¹) of lonsdaleite (HD) with respect to diamond (CD), given that Fahy and Louie,²⁸ using plane-wave pseudopotentials with Hedin—Lundquist exchange correlation, computed a much smaller value (0.7 kcal mol⁻¹, this value being only by chance similar to that obtained within the “cluster” approach). However, independently from their possible contribution to chemical physics of carbon lattices, our computations clearly convey the information that our approach to polymers (surfaces and nets) is faster and easier to use than the more usual “cluster” methodology, since it straightforwardly affords, without the need to extrapolate results, geometries and energies which are unaffected by “surface” effects.

(26) Possibly for reasons analogous to those discussed above, but now the correct sampling does not refer any more to cages (which are all equivalent in BC-8) but to rings. Indeed, in the BC-8 structure there are two differently strained kind of rings: one moderately unstrained, a six-membered twist-boat, the other heavily strained, an eight-membered chair with a very short next-nearest-neighbor contact.

(27) MM2 is substantially similar to MM3 whenever the geometrical aspects alone are concerned.

(28) Fahy, S.; Louie, S. G. *Phys. Rev.* **1987**, *B36*, 3373.

Supramolecular Interactions. The major pitfall of any AAPP approach is the assumption of spherically symmetric nonbonded potentials about each atom. Indeed, there is an abundance of evidence showing that intermolecular atom—atom nonbonded interactions are highly directional or, according to Bondi,²⁹ that many atoms are “pear-shaped”. For instance, it is well-known that the A—H···B angle tends to be close to 180° in intermolecular hydrogen bonds and that the approach of a proton to a base B is preferentially along a lone pair direction. More generally, for most donor···acceptor intermolecular interactions, the electron acceptors accept preferentially along the extension of an (the) existing σ bond while electron donors donate along their lone pair directions.³⁰ These directional intermolecular interactions could however be handled in our MMAAPP approach by explicitly considering them in the definition of the atom—atom connectivity. Depending on the actual topology of these “new” bonds, the original molecular crystal transforms either into a molecular crystal with a more complex RM (like in most “dimeric” carboxylic acids) or into a 1–3D polymer.³¹ These directional intermolecular interactions obviously require to be parametrized for MM3 but this task, even if achievable, is outside of our actual aims. However, given that the number of directional intermolecular interactions *per* RM is normally small, the CEs should be reasonably simple and the pertinent steric energies are expected to be quickly computed and easily interpretable.

Molecular Motion in *ansa*-Titanocenes. Edwards et al. recently elucidated structures and dynamics of a family of crystalline *ansa*-metallocenes, [(C₅H₄)₂C₂Me₄]TiX₂ (X = F, Cl, Br, I), by the joint application of solid-state NMR and single-crystal X-ray diffraction.³² They showed that the solid-state

(29) Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441.

(30) Dunitz, J. D. *The Crystal as a Supramolecular Entity. Perspectives in Supramolecular Chemistry*; Wiley: Chichester, 1996; Vol. 2, p 1.

(31) The recognition of these weak, directional, intermolecular forces has, indeed, greatly contributed to the thought of crystals as supramolecular entities.

(32) Edwards, A. J.; Burke, N. J.; Dobson, C. M.; Prout, K.; Heyes, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 4637.

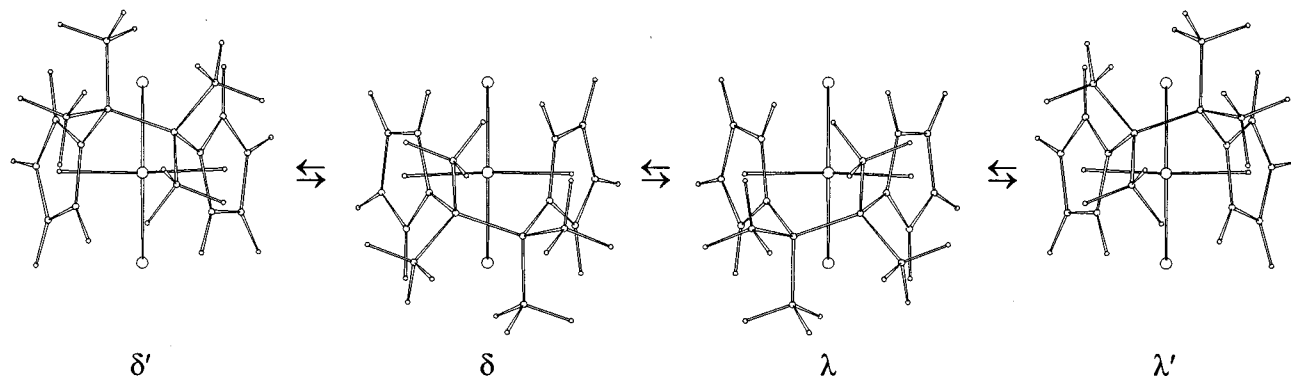


Figure 3. A sketch of the enantiomeric exchange for *ansa*-titanocenes lacking of C_2 symmetry. In solution, the process involves four conformations $\delta' \rightleftharpoons \lambda'$ which, due to the facile rotation of the bridging ligand framework around the metal to ring centroid axis ($\delta' \rightleftharpoons \delta$ and $\lambda' \rightleftharpoons \lambda$), can easily interconvert leading to an averaged C_{2v} molecular symmetry which explains the solution ^{13}C NMR spectra. In the solid state, due to the very different steric demand of δ'/λ' with respect to δ/λ conformations, only the $\delta \rightleftharpoons \lambda$ enantiomeric exchange occurs (see text).

dynamic processes detected for the Cl, Br, and I derivatives are not the expected enantiomeric exchange process, which is observed to be facile in solution (see Figure 3), but a 180° reorientation about the pseudo- C_2 axis, bisecting the X–Ti–X interbond angle, combined with a small polytopal relaxation about the metal center. However, it was impossible, with the conventional AAPP approach,¹⁹ either to check if the enantiomeric exchange process was really forbidden (because it implies some internal molecular flexibility) or to “prove” the proposed reaction path (given the lack of “real” cylindrical symmetry of the complex rotating molecules). In the following we will show that the MMAAPP approach allows for a deeper understanding of the experimental results.

Our computations³³ on the iodine derivative show that the enantiomeric exchange process is indeed allowed even in the solid phase, with a calculated enthalpy of activation of $9.5 \text{ kcal mol}^{-1}$, to be compared with a value of $4.8 \text{ kcal mol}^{-1}$ in the gas phase. In the crystal phase both the λ and δ conformers are present in different enantiomeric sites (the crystals being centrosymmetric) but on *each* site, due to the *locally* chiral crystalline environment, the λ and δ conformers do not have the same energy, and we compute a ΔH of $2.9 \text{ kcal mol}^{-1}$. This difference, leading to an occupancy of only 0.7% for the minor isomer at room temperature, is consistent with the observed ordered X-ray structure.

The reorientation about the pseudo- C_2 axis has been studied using a “rotational driver” i.e. by applying a rotational driving force (about the X–Ti–X bond angle bisector) to all the

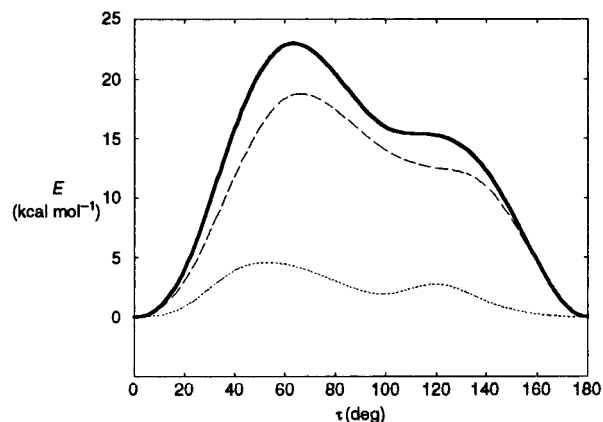


Figure 4. Potential energy profiles for the rotation of $[(\text{C}_5\text{H}_4)_2\text{C}_2\text{Me}_4]\text{-TiI}_2$ about its pseudo-2-fold axis. The full, dashed and dotted lines are polynomial fits to E_s , E_{inter} , and E_{intra} , respectively. τ is the dihedral angle between the actual and the starting TiI_2 planes.

atoms,³⁴ and periodically relaxing the molecule to intermediate conformations, by dropping the rotational force and constraining the TiX_2 moiety in its actual plane. The computed potential energy profile and the molecular conformation in a few selected points along the rotational path are reported in Figures 4 and 5, respectively. The ΔH^\ddagger value of 23 kcal mol^{-1} , in good agreement with the experimental value of 21 kcal mol^{-1} , is essentially determined by intermolecular interactions, while intramolecular terms seem to be of minor importance. However, the flexibility of the molecule is of extreme importance to the mapping of the potential energy barrier; indeed, due to the lack of C_2 symmetry, if the molecule would have been rotated rigidly the initial and final states would be different. Moreover, it is only its flexibility which allows the molecule to fit into the cavity during the rotational process thus lowering the computed barrier.

To further check our approach we have also computed the rotational barriers for the reorientation about the pseudo- C_2 axis of the fluorine and chlorine derivatives. For the fluorine derivative the “rotational driver” method cannot follow the whole path since the energy rises too much and the local geometry about the metal atom becomes heavily distorted. This is in good agreement with the observed lack of solid-state dynamics.

(33) All the computations have been done employing the following parameters: stretch Ti-D_{Cp} , $k = 1.529$, $r_0 = 2.00 \text{ \AA}$; stretch Ti-X , $k = 0.834$, $r_0 = 1.86$, 2.24 , and 2.74 \AA for fluorine, chlorine, and iodine, respectively; bend $\text{D}_{\text{Cp}}\text{-Ti-D}_{\text{Cp}}$, $k = 0.348$, $\theta_0 = 120^\circ$; bend $\text{D}_{\text{Cp}}\text{-Ti-X}$, $k = 0.278$, $\theta_0 = 103^\circ$; bend X-Ti-X , $k = 1.320$, $\theta_0 = 99$, 98 , and 94° for fluorine, chlorine, and iodine, respectively; bend $\text{Ti-D}_{\text{Cp}}\text{-C}_{\text{Cp}}$, $k = 0.486$; Cp bond order weakening constant $k_w = 0.87$. D_{Cp} and C_{Cp} refer to dummy centroid and carbon atoms of the cyclopentadienyl ring, respectively; X refers to fluorine, chlorine, or iodine atom. Units for the force constants: stretch mdyn \AA^{-1} , bend mdyn \AA rad^{-2} . All the force constants have been taken from Doman, T. N.; Hollis, T. K.; Bosnich, B. *J. Am. Chem. Soc.* **1995**, *117*, 1352; reference distances and angles have been optimized in order to reproduce the observed solid-state molecular structures. Solid-state computations have been done within a cutoff of 16 \AA and employing the following optimized cell constants, to maintain consistency with MM3 van der Waals parameters: $a = 12.07 \text{ \AA}$, $b = 8.52 \text{ \AA}$, and $c = 7.75 \text{ \AA}$, $\alpha = 108.9^\circ$, $\beta = 111.9^\circ$, and $\gamma = 91.2^\circ$ for the fluorine derivative (triclinic, $P1$); $a = 13.22 \text{ \AA}$, $b = 18.17 \text{ \AA}$, and $c = 14.37 \text{ \AA}$, $\beta = 116.5^\circ$ for the chlorine derivative (monoclinic, $P2_1/a$); $a = 24.70 \text{ \AA}$ and $c = 14.37 \text{ \AA}$ for the iodine derivative (rhombohedral, $R3c$).

(34) The rotational driving force applied to atom i have been computed according to $\mathbf{F}_i \propto \mathbf{r}_i \times \mathbf{n}$, where \mathbf{n} is the versor of the rotation axis and \mathbf{r}_i is the vector passing through the atom i and perpendicular to \mathbf{n} .

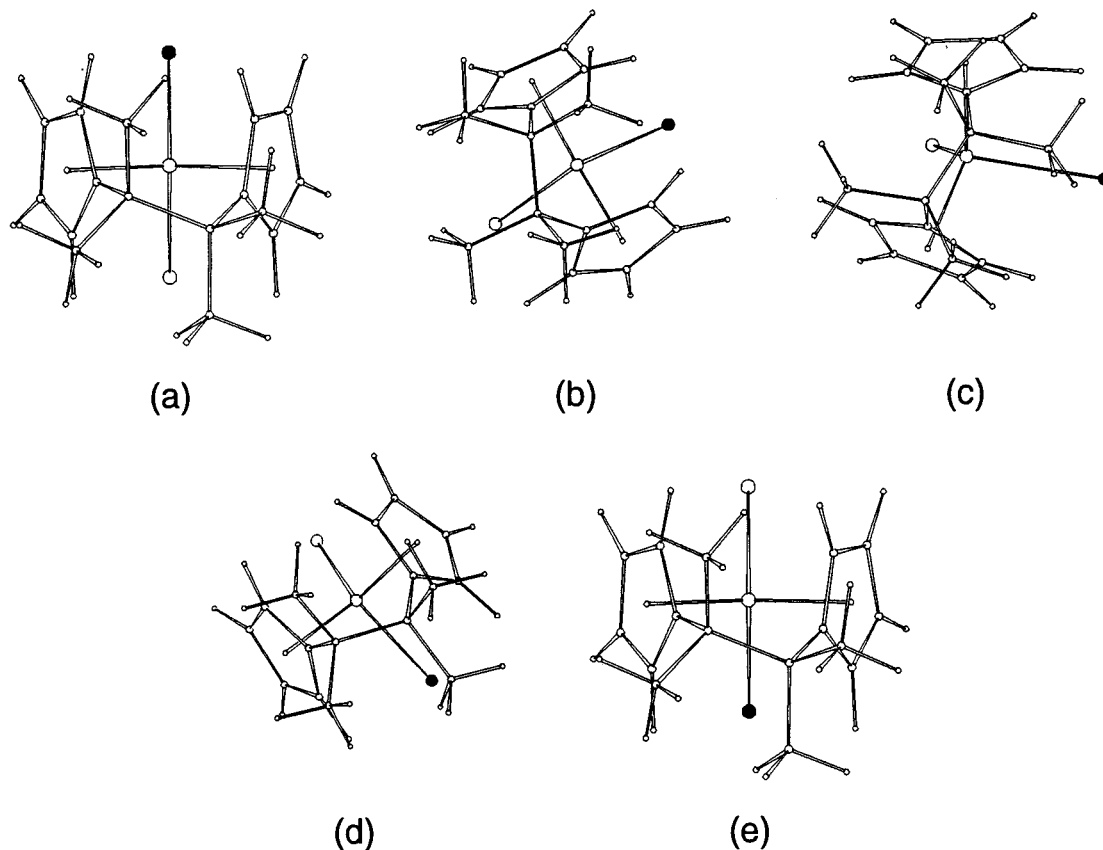


Figure 5. Molecular conformations along the reaction path described in Figure 4. (a) $\tau = 0^\circ$, (b) $\tau = 60^\circ$, (c) $\tau = 100^\circ$, (d) $\tau = 140^\circ$, (e) $\tau = 180^\circ$. I(1) is highlighted by partial shading.

The chlorine derivative has two distinct molecules A (generating a layer of equal molecules at $z = 0$) and B (generating a layer of equal molecules at $z = 0.5$) in the asymmetric unit. Solid-state NMR suggests the mobility of one of this molecules and the rigidity of the other. We compute for the two independent molecules very different potential energy barriers: 23 and 35 kcal mol⁻¹ for A and B, respectively. It is noteworthy that this result allows us to unambiguously label the identity of the dynamic molecule in the structure of [(C₅H₄)₂C₂Me₄]TiCl₂, a goal which was impossible to reach on grounds of qualitative packing considerations only.

Our MMAAPP approach allows for a better modeling, hence a deeper insight, of the solid state dynamics of flexible molecules. This eventually can afford a clearer interpretation of joint solid-state NMR and diffraction experiments on crystalline media. In this context it is worth noting that a dynamic process can be inferred by diffraction methods only if it leaves a track in the atomic displacement parameters (ADPs) and/or gives rise to some disorder. However, since a diffraction experiment maps (according to Boltzmann's statistics) only the bottom of the local minima of potential energy profile many possible sources of misunderstanding are present. Indeed, as previously shown for the solid-state dynamics of Fe₃(CO)₁₂,¹² the presence of a soft vibrational mode (determining the ADPs shape) cannot exclude the occurrence of a more energetic, but still allowed, process along a different reaction path (not leaving tracks on the ADPs). Analogously, when Boltzmann statistic assigns a negligible population to a reaction "intermediate", as for the λ (or δ , depending on which site has been considered) enantiomer of [(C₅H₄)₂C₂Me₄]TiI₂, the failure to observe it cannot be used as an argument for excluding the occurrence of the dynamic process under scrutiny.

Conclusions

In this paper we have shown that it is possible, in a quite general (and computationally easy) way, to minimize the steric energy of a molecule, polymer, surface, or net within the field of a fixed, or periodically updated, crystal lattice. The primary outcomes of such computations are the "solid state" conformation of the molecule, its intramolecular steric energy, and its interaction energy with the surrounding lattice. These computations are ideally suited for studying relative stabilities of different polymorphs, plastic deformations of whole crystal lattices, and molecular motions of flexible guest molecules in host crystal lattices. The proposed approach can help in understanding solid-state dynamics as obtained from MAS and CPMAS NMR experiments, factors that control reactivity in crystal lattices,³⁵ and crystals as supramolecular entities.

Presently, we cannot make ab initio predictions of possible molecular crystal structures because we need the previous knowledge of an initial AU (to be fed to PACKMM) and we lack a general strategy to foreseeing suitable AUs (which are the real outcome of an ab initio prediction). Moreover, we are forced to start from reasonably good AUs which, using a pertinent set of radii to recognize "bonds", eventually afford single crystals with a sound atomic connectivity.³⁶ However,

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(36) This request is not as stringent as it could appear at a first sight. Indeed, since anomalous contacts normally arises from atoms on the surface of the molecule (mainly hydrogens), it is often enough to drop all the H-H "bonds" from the connectivity table generated on the base of covalent radii, to lower the *criteria* for a well-behaved AU. Accordingly, it is possible to instruct PACKMM to refuse (or to accept) anomalously short (or long) contacts between selected atoms or atom types, to deal with rough AUs (or with supramolecular contacts).

once one well-behaved AU (or a part of AU) has been found or proposed, our MMAAPP approach becomes a powerful tool for building "hypothetical" crystals with sterically reasonable geometries (i.e. it becomes a powerful crystal builder), and this capability can be exploited in the process of solving crystal structures from partial diffraction data. Such as, in the rationalization of the molecular disorder present in poorly diffracting single crystals, in the interpretation of fiber diffraction data or even in the *ab initio* crystal structure determination from powder diffraction data.³⁷ Noteworthy, these applications are relatively free from the need of an extremely accurate force field since, according to Gavezzotti and Filippini, while the energy ordering of polymorphs depends on the force field, the location of minima in the potential energy hypersurface does not.³⁸ Hence within the constraints of a given unit cell and/or of a partial framework of atoms, only a few (if not one) reasonable structural/conformational alternative are possible.

At last we would like to comment that our way to deal with crystal is, from a computational point of view, superior to the more usual cluster approach since (i) the burden of the whole MM3 force field applies only to the RM (or RM \cup CE in the case of polymers), which is far less complex than a cluster of molecules; (ii) the computation of the vdW and Coulombic interactions can be easily extended to large cutoff radii (15–20 Å) at a moderate computational cost; and (iii) it straightforwardly affords, without the need to extrapolate results, geometries and energies which are unaffected by "surface" effects.

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Appendix

Transformations Relating Crystallographic to Orthonormal Coordinates. Crystallographic fractional coordinates can be orthonormalized to a Cartesian space in infinite ways.³⁹ By choosing, for example, the \mathbf{e}_y Cartesian versor along \mathbf{b} , \mathbf{e}_z along \mathbf{c}^* , and \mathbf{e}_x perpendicular to \mathbf{e}_y and \mathbf{e}_z so as to complete a right-handed reference frame, a given crystal vector \mathbf{r} can be transformed into its corresponding Cartesian vector \mathbf{r}^c (herein-after a superscript "c" will indicate Cartesian space elements) by means of the equation

$$\mathbf{r}^c = \mathbf{D}\mathbf{r}$$

where matrix \mathbf{D} takes the form

$$\mathbf{D} = \begin{bmatrix} a \sin \gamma & 0 & [c(\cos \beta - \cos \alpha \cos \gamma)]/\sin \gamma \\ a \cos \gamma & b & c \cos \alpha \\ 0 & 0 & [c(1 - \cos^2 \alpha - \cos^2 \beta - \cos^2 \gamma + 2 \cos \alpha \cos \beta \cos \gamma)^{1/2}]/\sin \gamma \end{bmatrix}$$

Indicating with \mathbf{O}_i and \mathbf{t}_i the rotational and translational components (including lattice centering when required) of the space group symmetry operator \mathbf{S}_i , the symmetry related vector \mathbf{r}_i can be expressed as

$$\mathbf{r}_i = \mathbf{S}_i \mathbf{r} = \mathbf{O}_i \mathbf{r} + \mathbf{t}_i$$

The same symmetry operation can be performed directly in Cartesian space instead of transforming \mathbf{r}_i into its Cartesian counterpart \mathbf{r}_i^c . Indeed,

$$\mathbf{r}_i^c = \mathbf{D}\mathbf{r}_i = \mathbf{D}(\mathbf{O}_i \mathbf{r} + \mathbf{t}_i)$$

Remembering that $\mathbf{r} = \mathbf{D}^{-1}\mathbf{r}^c$ and substituting in the previous equation,

$$\mathbf{r}_i^c = \mathbf{D}(\mathbf{O}_i \mathbf{D}^{-1}\mathbf{r}^c + \mathbf{t}_i) = (\mathbf{D}\mathbf{O}_i \mathbf{D}^{-1})\mathbf{r}^c + \mathbf{D}\mathbf{t}_i$$

Recognizing that $\mathbf{O}_i^c = \mathbf{D}\mathbf{O}_i \mathbf{D}^{-1}$ and $\mathbf{t}_i^c = \mathbf{D}\mathbf{t}_i$, i.e. the symmetry operator is now working in Cartesian space, one can write

$$\mathbf{r}_i^c = \mathbf{O}_i^c \mathbf{r}^c + \mathbf{t}_i^c$$

Encoding of the Lattice Atoms. With reference to the *origin* unit cell (i.e. the cell having $x, y, z \in [0,1]$), the symmetry generation of atoms can be encoded within a 4-byte long integer using the following algorithm:

$$\text{ICODE} = \text{NAT} \times 2^{21} + \text{ISHX} \times 2^{16} + \text{ISHY} \times 2^{11} + \text{ISHZ} \times 2^6 + \text{NOP}$$

where NOP is the symmetry operator number (less or equal to 48) referring to PACKMM internal list for the actual space group; NAT is the current atom number of the RM (less or equal to 2048); and ISHX is the number of translational steps along [100] (comprising symmetry and lattice translations) relative to the minimum translation observed along this crystallographic direction (ISHX is scaled to fit the interval [0, 31] with a maximum of 15 steps in the negative or positive direction). The same holds for ISHY and ISHZ in the [010] and [001] crystal directions, respectively.

Using the reverse decoding procedure MM3 is thus able to quickly read in all information needed to build the SM's from the RM whenever requested by the energy minimization process.

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