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Polymorphism and Isomorphism as Tools to Study the Relationship Between Crystal Forces and Molecular Conformation

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Polymorphism and isomorphism in molecular crystals are due to subtle energy differences and similarities in crystal structures. A compound may crystallize in more than one crystal structure, with different conformations, a phenomenon known as *conformation polymorphism*. In other cases chemically similar compounds may crystallize with nearly identical (isomorphic) structures. The investigation of polymorphism and isomorphism by structural and computational techniques leads to an understanding of the phenomena themselves and to the development of the techniques for studying them. Examples, citing recent results on benzylideneaniline systems, are given.

Although chemists have been aware of polymorphism for over 150 years,[1] relatively little use has been made of the phenomenon in studies of the organic solid state. The unique characteristic of a polymorphic system is that it provides two or more different crystalline environments in which the properties of a particular chemical entity (e.g., chemical reactivity, spectral properties, thermal behavior, electrical conductivity) may be studied and compared.

Experimental calorimetric studies indicate that in most cases, energy differences between polymorphs do not exceed 2–3 kcal/mole, which is also

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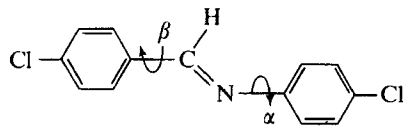
the energy domain for torsional conformation parameters in many organic molecules. This suggests the possibility that molecules with torsional degrees of freedom may adopt different conformations in different polymorphs, a phenomenon known as *conformational polymorphism.*[2] In such cases the differences in molecular conformation must be directly related to intermolecular or "crystal" forces since the difference in environment is the *only* variable in the system. Hence cases of *conformational polymorphism* provide excellent opportunities for investigating the relationship between crystal forces and molecular conformation.

A complete investigation of this type involves four basic steps:[3]

1) full crystal structure analyses to determine precise molecular conformations and intermolecular geometrical relationships
2) estimation of energetic differences in the observed molecular conformations by some appropriate computational procedure
3) determination of lattice energetics in the observed structures, again by computation
4) detailed analysis of 2) and 3) which is assisted by a "partitioning" of the total lattice energy into its individual atomic contributions.

Our first complete study of *conformational polymorphism* was carried out on a benzylideneaniline, in particular N-(*p*-chlorobenzylidene)-*p*-chloroaniline (**1**) and illustrates the approach and kind of information obtainable



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from such investigations.[3] The molecule is relatively small, and hence may be reasonably compared with similar model compounds which are amenable to *ab initio* calculations or may be treated with reasonable precision by presently available semi-empirical methods. The molecular conformation is a function of a small number of conformational parameters, in this case the two exocyclic torsion angles, α and β. The crystal structures contain no molecules of solvation; hence only interactions between like molecules determine the structures, and it is those interactions which we wish to study.

As a result of the first step, we find that the molecular conformations in the two polymorphs differ significantly. In one form (triclinic space group $P\bar{1}$,[4] Figure 1a) the molecule is essentially planar while in the second form (orthorhombic space group *Pccn*,[5] Figure 1b) the exocyclic torsion angles (α, β) are $\pm 24.8°$, with the rings rotated in opposite senses with respect to the plane of the four atoms in the central bridge.

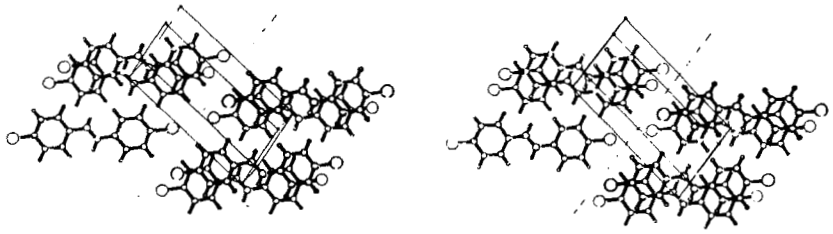


FIGURE 1a Stereoview of the triclinic structure as viewed on the best plane of the molecule. The unit cell origin is at the upper right; the direction of the *a* axis is diagonally to the lower right; *b* is essentially out of the plane of the paper; *c* is the remaining axis.

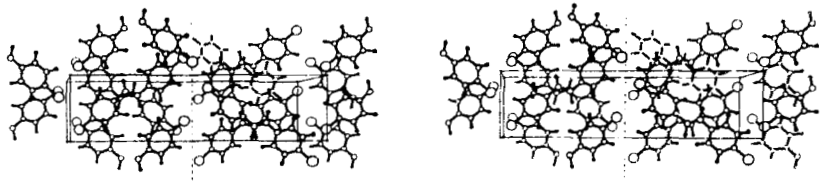
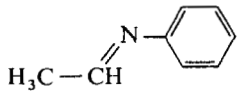


FIGURE 1b Stereoview of the orthorhombic structure as viewed along the *c* crystallographic axis. *a* is horizontal and *b* is vertical. Reproduced with permission from reference 3.

In the second step (molecular energetics) we applied *ab initio* molecular orbital methods to the two model compounds in **2**, **3**, which should provide



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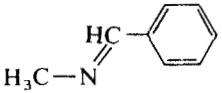

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good estimates of the energetics about the exocyclic bonds. In these studies the relative, rather than the absolute, energies between conformations and between crystal structures are the important quantities, since we are concerned with energetic differences between them. Hence, considering the planar molecule (triclinic structure) as the zero energy (Figure 2) the conformation found in the orthorhombic structure ($\alpha = -\beta = 24.8°$) is *ca* 0.7 kcal/mole more favorable (depending on basis set employed).

The third step is carried out by performing lattice energy minimizations on the two crystal forms to obtain their relative energetics. Here both the form of the potential function in the atom · · · atom potential and the nonbonded parameters used in the potential may bias the results. To minimize such a bias we routinely employ three different potential functions in all lattice energy minimizations: "6-12," "6-9" and Williams' exponential functions (Table I) which have been shown to account well for a variety of crystal

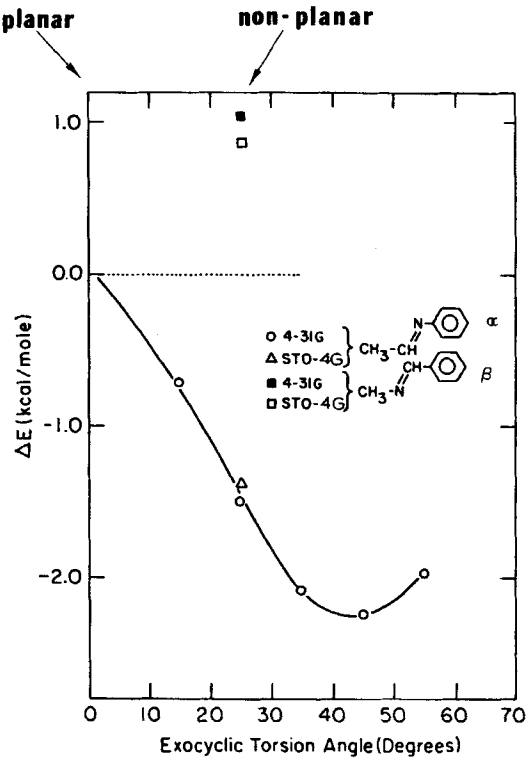


FIGURE 2. Summary of *ab initio* calculations on **2** and **3**. The points labelled STO-4G were obtained using a minimum basis set while those labelled 4-31G were obtained using an extended basis set in GAUSS 70[18] and GAUSS 100[19] respectively.[21] The ordinate represents energy differences between the planar conformation (0°) and non-planar ones. The points at *ca.* 25° represent the non-planar conformation found in the orthorhombic structure, which clearly is not the minimum energy conformation. On the basis of these calculations the minimum energy conformation for benzylideneaniline would correspond to $\alpha \approx 45°$, $\beta \approx 0°$. Reproduced with permission from reference 3.

structures and sublimation energies.[6,7] The results for the lattice energy minimizations on the two polymorphs with the three different potential functions are given in Table II. In all three cases the triclinic structure is favored over the orthorhombic one, and by an energy difference which is compatible with both the *ab initio* molecular orbital calculations, and with expected energy differences between polymorphs.[8] The triclinic form *must* have a lower lattice energy than the orthorhombic form in order to stabilize the more highly energetic planar conformation found therein.

The fourth question is investigated by "partitioning" the minimized total energies in Table II into individual atomic contributions. The individual atomic contributions to the total energy are obtained as a natural consequence

TABLE I

Three different potential functions employed

$V(r) = \left[-2\left(\frac{r^*}{r}\right)^6 + \left(\frac{r^*}{r}\right)^{12}\right]\varepsilon_{ij} + \frac{q_i q_j}{rij}$	**6–12**
$V(r) = \left[-3\left(\frac{r^*}{r}\right)^6 + 2\left(\frac{r^*}{r}\right)^9\right]\varepsilon_{ij} + \frac{q_i q_j}{rij}$	**6–9**
$V(r) = -Ar^6 + B\exp(-ar) + \frac{q_i q_j}{rij}$	**6**–exp
attractive term	repulsive term	electronic term

TABLE II

Minimized crystal lattice energies

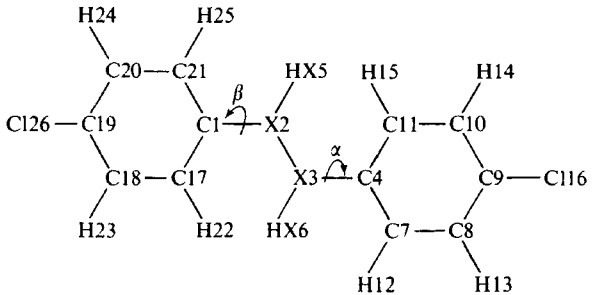
	Crystal energy in kcal/mole potential employed		
	6–12	6–9	Exponential
Triclinic			
E_{tot}	−22.73	−45.71	−23.99
E_{nb}	−23.28	−46.64	−24.84
E_{elec}	0.56	0.93	0.86
Orthorhombic (per molecule)			
E_{tot}	−21.68	−42.73	−22.34
E_{nb}	−22.41	−44.24	−23.27
E_{elec}	0.73	1.51	0.93
ΔE(tric-orth)	−1.05	−2.98	1.65

of the calculation, which is a sum over all intermolecular atom · · · atom interactions. While this approach seems rather obvious and straightforward, we believe we are among the first to apply it to a real system. The results for the dimorphic **1** are presented in Table III. Naturally, in dealing with individual atomic contributions to the total energy, the numbers involved are quite small, and we do not attach a great deal of significance to any particular atomic contribution. However, we do look for consistent trends, which are indeed present, and we can make the following points.

a) The *relative* role of each atom's contribution to the overall energy is remarkably insensitive to the potential function used and is in fact identical for the 6–12 and exponential potentials for both structures.

b) The order of the relative contributions of the partial atomic energy to the total energy is the *same* for both crystal forms. This is an indication that

TABLE III



Partition of the minimized crystal energy into individual atomic contributions[a]

Atom	Orthorhombic 6–12	Orthorhombic 6–9	Orthorhombic exp	Triclinic 6–12	Triclinic 6–9	Triclinic exp	Δe_t(tric-orth) 6–12	Δe_t(tric-orth) 6–9	Δe_t(tric-orth) exp
C1	−0.15(10)	−1.53(8)	−0.21(10)	−0.24(10)	1.87(8)	−0.32(10)	−0.09	−0.34	−0.11
X2	−1.91(2)	−3.71(1)	−1.87(2)	−2.04(2)	−3.81(1)	−2.01(2)	−0.13	−0.10	−0.14
HX5	0.04(11)	0.36(11)	0.03(11)	0.01(11)	0.36(11)	0.00(11)	−0.03	0.00	−0.03
C7	−1.18(5)	−3.00(5)	−1.39(5)	−1.13(5)	−2.99(5)	−1.36(5)	0.05	0.01	0.03
C8	−0.98(6)	−2.58(6)	−1.14(6)	−1.00(6)	−2.70(6)	−1.21(6)	−0.02	−0.12	−0.07
C9	−0.84(7)	−2.57(7)	−1.09(7)	−0.95(7)	−2.70(7)	−1.10(7)	−0.11	−0.13	−0.09
C10	−1.36(4)	−3.25(4)	−1.60(4)	−1.47(4)	−3.49(2)	−1.73(4)	−0.11	−0.24	−0.13
C11	−1.52(3)	−3.43(2)	−1.74(3)	−1.47(3)	−3.48(3)	−1.77(3)	−0.05	−0.05	−0.03
H12	−0.40(9)	0.04(10)	−0.32(9)	−0.49(9)	−0.20(10)	−0.49(9)	−0.09	−0.24	−0.17
H13	−0.62(8)	−0.43(9)	−0.50(8)	−0.68(8)	−0.39(9)	−0.63(8)	−0.06	−0.04	−0.13
H14	0.17(12)	0.76(12)	0.36(12)	0.20(12)	0.82(12)	0.37(12)	0.03	−0.06	0.01
H15	0.43(13)	1.22(13)	0.58(13)	0.39(13)	1.04(13)	0.54(13)	−0.05	−0.18	−0.04
Cl16	−2.45(1)	−3.28(3)	−2.38(1)	−2.52(1)	−3.46(4)	−2.41(1)	−0.07	−0.18	−0.03

[a] Entries are in kcal/mole. The number in parentheses gives the ranking of the atomic contribution in increasing energy. Due to symmetry only half of the atoms in the molecule are given.

the environments of the atoms in the two crystal forms do not differ drastically in terms of energetics.

c) No single atom makes an outstanding contribution to stabilizing the triclinic structure over the orthorhombic one; rather, the mode of stabilization is nonspecific in that nearly all atoms make a small stabilizing (Δe_i(tric-orth) < 0) contribution. This is true in spite of the fact that there are rather striking differences in the spatial arrangement of the molecules in the two structures (Figures 1a, 1b).

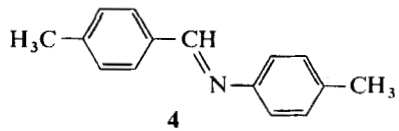
d) It is quite common, in the analysis of crystal structures, to make note of interatomic distances (or "contacts") which are shorter than the sum of van der Walls radii. These presumably are among the important or dominant factors in determining the packing mode. In the triclinic structure there is a short Cl · · · Cl distance of 3.42 Å,[4] while the shortest one of this type found in the orthorhombic structure is 3.79 Å[5] and is slightly greater than the sum of the van der Waals radii. Hence, in these terms we might have expected that the contribution of chlorines in the triclinic form would be a major one in stabilizing that structure over the orthorhombic one. The analysis by partitioning for these two structures suggests that this is not the case here, a surprising result indeed.

This summarizes an example of the utilization of the phenomenon of conformational polymorphism in investigating the relationship between crystal structure and molecular conformation. Studies employing lattice energy minimizations are often carried out on a single system in the manner described above. Clearly the true test of any computational technique is its transferability to other systems and its general applicability in predicting certain structural or conformational properties of a substance. To extend this general approach we have investigated, both structurally and computationally, chemical systems which resemble that of **1**. In this approach we look for isomorphism, or the lack thereof, among the molecules in question.

Isomorphism involves a series of chemically similar species, members of which crystallize with essentially identical structures. If the chemical series also contains a non-isomorphous structure in which molecular conformational changes are observed as well, then this phenomenon provides an additional potential tool for investigating the relationship between crystal forces and molecular conformation. Here we may pose the kind of question raised in studies of conformational polymorphism but in a negative way: namely, "why doesn't the molecule in question crystallize in the same crystal structure with the same conformation as other members of the chemically analogous series?" Investigations of this sort involve many of the same steps as above, with some modifications, but also include "computational substitution" in which the molecule under study is substituted into the "expected" structure and the lattice energy is calculated. Such a procedure yields

information as to why certain molecules do not crystallize in the expected crystal structure. Furthermore, since in any single study we always employ a number of potential functions of different form, these kinds of studies provide a test of the various potential functions used both for their internal consistency and their predictive capability.

In the particular example we have studied in detail the principal question is why **1** does not pack in a crystal in which the intramolecular energy is a minimum. In general this would be an extremely difficult problem to attack, as there is no information available as to the "nonexistent" favorable packing mode of the low energy form. In this molecular system, however, if both



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chlorines are substituted by methyls, **4**, the structure of one of the three resulting polymorphic forms[9b] contains the low energy conformation ($\alpha = 41.7°$, $\beta = -3.0°$), and does not exhibit crystallographic disorder. Since the size of a chlorine atom does not differ appreciably from that of a methyl group,[10] this would appear to be a reasonable packing for the dichloro derivative as well.

Using coordinates obtained from the crystal structure analysis of form II of the dimethyl compound[9b] (Figure 3) we generated coordinates for chlorine atoms to replace the methyl groups with idealized trigonal geometry at the

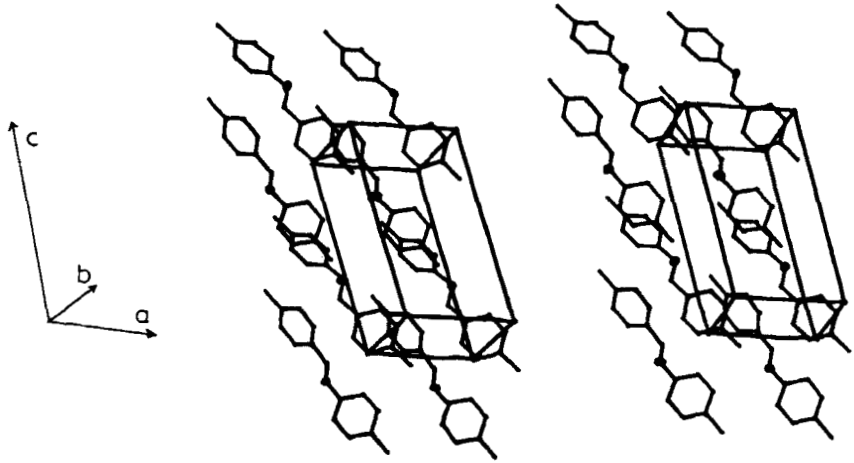


FIGURE 3 Stereoview of the crystal structure of form II of **4**. The view is on the plane of the benzylidene ring. The heavy dot denotes the nitrogen atom. Reproduced with permission from reference 11.

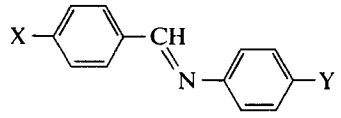
TABLE IV

Comparison of intramolecular and intermolecular energies

Structure	Exocyclic angles $\alpha(^0)$	$\beta(^0)$	Intramolecular contribution (kcal/mole) α	β	Total	Intermolecular energies (kcal/mole) 6–12	exponential	6–9
$P2_1$	41.7	−3.0	−2.1	0	−2.1	−20.13	−20.75	−41.23
Pccn	24.8	−24.8	−1.7	1.0	−0.7	−21.68	−22.34	−42.73
$P\bar{1}$	0.4	0.4	0	0	0	−22.73	−23.99	−45.71

substituted carbon and C—Cl bond length of 1.735 Å. The resulting structure was minimized using the same potentials and techniques as above.[11] All potentials showed the structure of the dichloro compound to be less stable than either the stable P*ccn* or metastable $P\bar{1}$ observed by 1.4 and 2.5 kcal/mole, respectively. The analysis of terms of the partial atomic energies showed the relative lack of stability to arise from the relatively unfavorable energetic environments of the aniline ring (including its Cl) as compared with its environment in the observed crystals.[11] Finally, comparison of the total energies (lattice plus intramolecular energy as obtained by molecular orbital calculations) Table IV, accounted for the "observed nonexistence" of the structure with the low-energy conformation. Thus we demonstrated that the approach outlined above appears to be quite general in investigating and understanding the relationship between crystal structure and molecular conformation on a detailed quantitative basis.

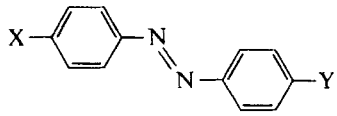
The example of substituting the dichloro compound **1** into one of the dimethyl **4** polymorphs is but one of many possibilities for such an approach. The lack of a true molecular inversion center or a true two-fold axis means that compounds **I–IX** are chemically different systems. However, in crystallographic terms, and consequently in molecular and lattice energetic terms,



	x	*y*
1	Cl	Cl
4	Me	Me
III	Br	Br
IV	Br	Me
V	Me	Br
VI	Cl	Me
VII	Me	Cl
VIII	Br	Cl
IX	Cl	Br

a number of these compounds are isomorphous; and we have investigated the pattern of polymorphism and isomorphism in this system to extend the studies outlined above.

We noted above that **1** is dimorphic and **4** is trimorphic but there is no isomorphism between these two materials. We have not observed polymorphism in **III**,[12] nor is it isomorphic with **1** or **4**. However **III** is isomorphous with its azobenzene analogue **X**[13] and one of the polymorphs of **4**[9a] is isomorphous with its azobenzene analog **XI**.[14] Neither polymorph of **1** is isomorphous with **XII**,[15] but **XII** is isomorphous with **XI** (and consequently



	X	*Y*
X	Br	Br
XI	Me	Me
XII	Cl	Cl

with Form III of **4**). Compounds **IV**–**VII** are all isomorphous within the group (again no evidence for polymorphism) but not isomorphous with any of the other analogous compounds shown here. The two "hybrid" compounds **VIII**, **IX** are apparently isomorphous with **I** and **III** respectively. The full crystal structures[16] and energetics[17] will be published elsewhere, and will reveal details of similarities and differences among these structures. However, the cell constants and space group information already suggest that these details are quite subtle, and unravelling them provides a stringent but good test for the applicability of the structural and computational techniques, together with polymorphism and isomorphism, to the study of crystal forces and molecular conformation.

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19. Extension of GAUSS 70 (ref. 18) by J. Baudet and G. N. H. Port.
21. The STO-YG point for molecule **3** was inadvertently misplaced in reference 3. It has been corrected here.