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Structural Investigations in Organic Molecules and Crystals by Means of Molecular Mechanics and X-Ray Diffraction

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Molecular mechanics is an inductive method[1] in which a set of energy functions, deduced from a large amount of experimental data, is used for the prediction of observable properties of a series of molecules. The method was pioneered by Westheimer,[2] put in a form suitable for electronic computing by Hendrickson,[3] and recently reformulated carefully by Karplus and Warshel.[4] The energy of the molecule relative to the energy of a hypothetical strain-free molecule is calculated as the sum of four components

$$E = E_r(r) + E_\theta(\theta) + E_\phi(\phi) + E_{nb}(d)$$

where E_r and E_θ are bond length and bond angle deformations, E_ϕ is the torsional eclipsing energy, and E_{nb} is the nonbonded interaction energy. Sometimes the first term is split in two, $E_\sigma(r)$ and $E_\pi(r)$, related to σ and π bonds.

For each of the above terms, there are well-known expressions, and the only problem is one of choice. We calculated the π-electron energy by Hückel's theory (for a more sophisticated approach see ref 5). For E_σ and E_θ a harmonic potential was assumed: $E_\sigma(r) = 0.5k_r(r - r_e)^2$ and $E_\theta(\theta) = 0.5k_\theta(\theta - \theta_e)^2$, where appropriate experimental values for force constants and equilibrium geometrical parameters were included. The torsional energy for threefold barrier we took as $E_\phi(\phi) = (K/2)(1 + \cos 3\phi)$, where ϕ is the angle of twist and K was taken from experiment; the torsional energy for sixfold barriers was ignored. For nonbonded interactions initially we used Hendrickson's formulas and parameters. Later, wanting to make calculations with a simple set of formulas and parameters, we shifted to the potential given by Bartell.[6] These functions are similar to those used so successfully by Kitaigorodsky in his studies of the intermolecular interaction energies in organic crystals.[7]

Application of molecular mechanics has been successful in many areas of physical organic chemistry. Most of these areas, concerned with the study of properties of single molecules, have been reviewed recently in a paper[8] which assesses the predictive ability of molecular mechanics in calculations of structural parameters and enthalpies of formation of saturated hydrocarbons.

We were interested mainly in the conformation of organic molecules that, due to their size, are not suitable for microwave or electron diffraction investigation, or for *ab initio* quantum mechanical calcula-

tions. X-Ray diffraction data were collected for such molecules to determine conformation in the solid state. Although in general packing forces do not significantly change the geometry of organic molecules, and in particular do not change bond lengths, intermolecular forces in crystals can affect the angle of rotation around single bonds. Molecular mechanics was chosen as the most practical tool to obtain the conformation of the isolated molecules. Then we included intermolecular interactions for molecular crystals to determine if this would lead to the correct conformation in the crystal. The agreement between calculated and experimental conformation in the crystal would then give us confidence that the calculated geometry for the isolated molecule was in fact a good approximation. To support this indirect argument we used for the intermolecular atom–atom potential the same nonbonded interaction functions that were used in the isolated molecule calculations.

For such a problem, biphenyl is a classical example. The twist angle between the two phenyl rings is about 40° in the gas phase[9] and 0° in the crystalline phase.[10] Our calculations for the isolated molecule included as variable parameters the inter-ring distance r, the twist angle θ between the rings, and the CCH angle $\hat{X}$ for hydrogen atoms in ortho position.[11] The minimum of energy was obtained for $r = 1.51$, $\theta = 35°$, $X = 121°$. The experimentally observed values are $r = 1.49$ Å, $\theta = 40°$, and X is assumed to be 120°. The calculation for the crystal was made by locating the center of mass of molecules in the experimental position, so that only six variables were needed: the internal variables r, θ, $\hat{X}$, and three Euler angles, ϕ_1, ϕ_2, ϕ_3. At our minimum the molecule was planar, with $r = 1.518$ Å (observed value of 1.507 Å), and the orientation gave a discrepancy index, R, of 0.15, to be compared to the values 0.17 for the $h0l$ zone and 0.15 for the $0kl$ zone obtained by the experimentalist.

We turned then to *p,p'*-bitolyl. The crystal structure determination[12] has shown that the monoclinic crystals contain two molecules in the asymmetric

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unit with the long molecular axes parallel to the b axis of the cell and with twist angles of 36 and 40°. Conformational energy calculations were carried out with center of mass and axes in the experimental position, assuming regular carbon and hydrogen hexagons and allowing four degrees of freedom to the system: namely, the angle of rotation ϕ_i ($i = 1-4$) around the molecular axes of the four phenyl rings.

The minimum energy was found for $\phi_1 = 20°$, $\phi_2 = 55°$, $\phi_3 = -18°$, $\phi_4 = -58°$ (experimental values $\phi_1 = 20°$, $\phi_2 = 55°$, $\phi_3 = -18°$, $\phi_4 = -58°$). It is gratifying that the orientation of the rings corresponds to within 1°. With para substituents, the packing is such that the two rings are twisted by about the same angle as in gaseous biphenyl while, as mentioned, biphenyl itself is planar in the solid state due to packing forces. As an example of a biphenyl derivative with only one substituent, we determined the crystal structure of p-nitrobiphenyl.[13] Crystals of this compound are orthorhombic, with eight molecules in the unit cell. For the isolated molecule the variables were the inter-ring distance r, the twist angle $\theta°$ between the phenyl rings, and the rotation angle $\psi°$ of the nitro group with respect to the phenyl ring.

At the energy minimum we found $r = 1.51$ Å, $\theta = 35°$, $\psi = 0°$. In crystal packing calculations, the reference molecule was given two degrees of freedom: namely, the dihedral angles ϕ' and ϕ'' of the first and second phenyl ring with respect to the same ring in the experimental conformation. The minimum obtains for $\phi' = 3°$, $\phi'' = 2°$. The dihedral angle between the phenyls is 32° (experimental value, 33°), and the molecule as a whole is only slightly rotated by 2.5° with respect to the experimental conformation. For this molecule we needed some new atom–atom potentials. These were taken from Kitaigorodsky's work,[14] except for the N $\cdots$ N, N $\cdots$ C, N $\cdots$ H interactions, where we used potentials recently proposed by Mirskaja and Nantchitel, as quoted by Ahmed and Kitaigorodsky.[15]

For comparison we note that disubstituted 4,4'-dihydroxybiphenyl[16] shows coplanarity of the two rings, although here formation of hydrogen bonds has some effect, the 4,4'-dinitrobiphenyl being rotated by about 35°.[17] So it seems reasonable to infer that the value of about 35° for the dihedral angle between phenyl rings is a rather typical feature of the isolated molecules of para-substituted biphenyls, regardless of the nature and number of substituents. In crystalline state, molecular packing can play a different role in different situations, and each crystal must be considered specially.

The crystal structure determination of 2-bromo-1,1-di-p-tolylethylene[18] has shown that a phenyl ring cis to the bromine atom is turned 69° out of the ethylene plane, while the second phenyl is 24° out of the same plane. In conformational calculations for the isolated molecule the minimum energy is obtained at

angles of 55 and 25°, respectively. However, if the optimum conformation is determined for the molecule in the crystal, the calculated twist angles very satisfactorily become 69 and 25°. Another example is 1,1-bis(p-nitrophenyl)ethylene, a monoclinic crystal with four molecules in the unit cell.[19] The calculated geometry for the isolated molecule shows the following features: $\theta_1 = \theta_2 = 35°$, $\phi_1 = \phi_2 = 0°$, $r_{C=C} = 1.336$ Å, $r_{C_{ethylene}-C_{1st\ phenyl}} = r_{C_{ethylene}-C_{2nd\ phenyl}} = 1.508$ Å, where θ's are the twist angles between phenyl rings and ethylenic fragments and ϕ's are twist angles for the nitro groups.

The C_2 axis along the double bond was not imposed, but resulted from the calculations. For the model crystal the results are: $\theta_1 = 36°$, $\theta_2 = 35°$, $\phi_1 = 0°$, $\phi_2 = 5°$, $r_{C=C} = 1.336$ Å, $r_{C-C} = 1.508$ Å. The experimental values are $\theta_1 = 38°$, $\theta_2 = 40°$, $\phi_1 = 12°$, $\phi_2 = 14°$, $r_{C=C} = 1.33$ Å, $r_{C-C} = 1.49$ Å. The results are not as good as usual, but a better analysis of librational motions should be carried out on X-ray data, since the direction of highest thermal libration for the oxygen atoms is the one normal to the N–O bonds.

Let us consider now 2-bromo-1,1-diphenylprop-1-ene. The structure had been solved earlier[20] and it was found, not unexpectedly, that the ring cis to bromine is rotated by 45° and the one cis to methyl by 71°. However, the geometry obtained at the end of least-squares refinement had two very unsatisfactory features: the double bond length was 1.31 Å and the $C_{ethylenic}-C_{methyl}$ bond length was 1.57 Å. We decided to see if conformational energy calculations could improve the situation.[21] First, the minimum energy geometry of the isolated molecule was calculated, and the interesting geometrical parameters were: $\theta_1 = 55°$, $\theta_2 = 65°$, $r_{C=C} = 1.35$ Å, $r_{C-C} = 1.52$ Å.

The packing forces were included in this model molecule, resulting in the following geometry in the crystal: $\theta_1 = 47°$, $\theta_2 = 66°$, $r_{C=C} = 1.35$ Å, $r_{C-C} = 1.52$ Å. We calculated for this geometry structure factors and a reliability index of $R = 8.6\%$, exactly the value we had obtained at the end of the least squares refinement. Thus the R function appears to have two minima of equal value, but for some reason the least-squares procedure always leads to the one with an unrealistic molecular geometry. Of course it is not surprising that carbon atoms in proximity to a bromine are difficult to locate by X-ray diffraction techniques.

In the following example, packing calculations helped us to refine a structure. In nucleophilic substitution reactions at aromatic carbons, a mechanism involving an activated complex or an intermediate as shown (I) was proposed a long time ago. In some special cases it has been possible to isolate the intermediate. One example is the reaction of symmetric trini-

I

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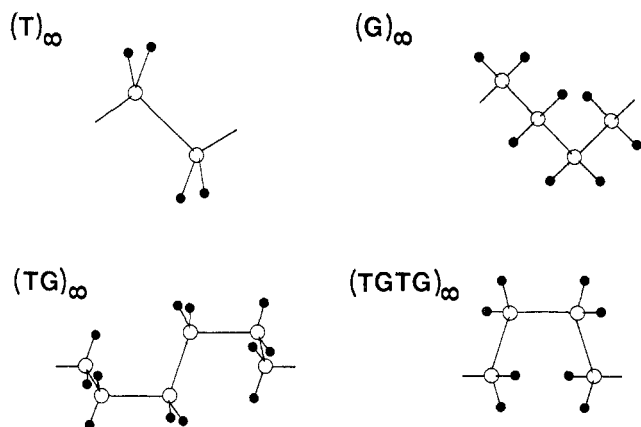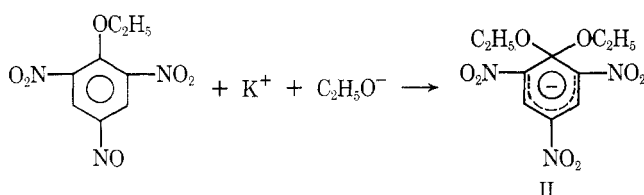(21) G. Casalone, C. Mariani, A. Mugnoli, and M. Simonetta, *Theor. Chim. Acta*, 8, 228 (1967).

(T)∞   (G)∞

(TG)∞   (TGTG)∞

Figure 1. Conformations for polyethylene chains.

trophenetole with alkali ethoxide, leading to a Meisenheimer salt (II).

$$O_2N-\bigcirc(OC_2H_5)(NO_2) + K^+ + C_2H_5O^- \longrightarrow O_2N-\bigcirc(C_2H_5O)(OC_2H_5)(NO_2)(NO_2)$$

II

The crystal structure of phenetole was solved first.[22] The nitro group para to the ethoxy group is almost coplanar with the benzene ring, while the two ortho groups are rotated by 32 and 61°, the oxygen is in the plane of the ring, and the two carbons in the ethoxy group lie in the plane perpendicular to the ring through the oxygen atom.

The structure of the Meisenheimer salt shows two molecules in an asymmetric unit.[23] Both were located, but we could determine the position of only three of the four ethoxy groups; the fourth group was apparently disordered. On a difference-Fourier synthesis a large positive region appeared instead of definite peaks. Again, packing calculations were the remedy. We assumed normal bond lengths and angles in the ethoxy group, and after locating all the other atoms in the asymmetric unit in their known positions, we allowed rotation of the C_2H_5 group around the C–O bond and of the CH_3 group around the O–C bond and calculated the repulsion energy of all pairs of non-bonded atoms whose distance was less than the touching distance. This energy surface showed two minima of about the same value. We assumed that each ethoxy group of that kind had a 50–50 chance to be in one or the other of these two positions. We put half the C atoms in positions corresponding to the energy minima and successfully proceeded with our least-squares refinement, which finally led us to an R value of 6.4% and to reasonable bond angles and lengths for all atoms, including the disordered ethoxy chain. The three nitro groups are roughly in the plane of the ring, in both molecules.

We also applied the method to study the conformation of crystalline polyethylene.[24] The calculation

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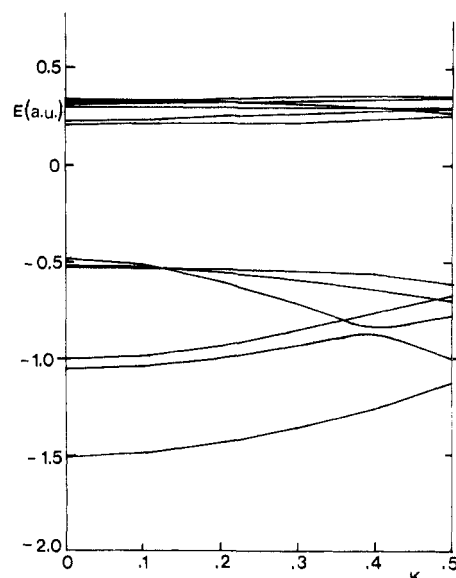(24) G. Morosi and M. Simonetta, *Chem. Phys. Lett.*, 8, 358 (1971).

Figure 2. Energy levels for polyethylene as a function of the wave number.

was carried out in two steps. First, we determined the most stable geometry of a single chain by a quantum mechanical computation, using the SCF–MO method in its CNDO approximation.[25] Initially we assumed all angles to be tetrahedral, allowing variation of bond lengths, and we found for the configuration suggested by spectroscopic evidence the following order of stability: $(T)_\infty > (TG)_\infty > (TGTG')_\infty > (G)_\infty$ (see Figure 1). When the energy for the most stable conformation was calculated, including variation of bond angles in the minimization procedure, the following geometry was found: $r_{C-C} = 1.52$ Å, $r_{C-H} = 1.13$ Å, $\angle CCC = 114°$, $\angle HCH = 105°$. Bond angles satisfy orthogonality conditions.

Figure 2 shows the energy levels as a function of wave number k, in atomic units per CH_2 group. Filled and vacant orbitals are well separated, as expected for a good insulator. In the second step, the energy for the crystal energy was minimized for $(T)_\infty$ chains of different geometry as a function of the orthorhombic unit cell parameters a and b and of θ, the angle between axis a and the projection on the ab plane of the C–C bond through the origin. As expected, the most stable conformation of the chain in the crystal turned out to be the same as for the isolated chain; the calculated lattice parameters were $a = 7.078$ Å, $b = 4.97$ Å, and $\theta = 42°$, to be compared with experimental values $a = 7.478$ Å, $b = 4.97$ Å, and $\theta = 42°$. The packing energy per CH_2 unit is 1.95 kcal/mol, while the experimental heat of fusion was found to be of the order of 1 kcal/mol.

Since molecular mechanics had proved to be such an effective tool in understanding the relationships between conformations of isolated and packed molecules, we turned to the solution of a crystal structure by means of intermolecular potentials. We started with a very interesting molecule, 1,6:8,13-propane-1,3-diylidene[14]annulene. [14]Annulene is a molecule with a ring made of 14 C–H groups. However, the molecule is not stable in this configuration owing to the overlap of the hydrogen atoms pointing inside the ring. Professor Vogel very elegantly managed to

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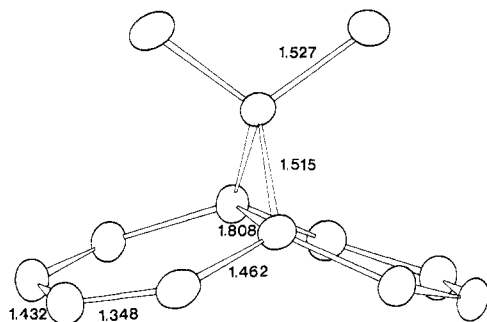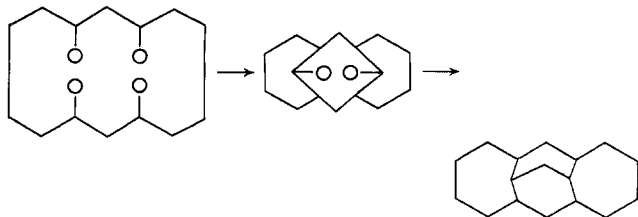
Figure 3. Bond lengths in 11,11-dimethyltricyclo[4.4.1.0^{1,6}]undeca-2,4,7,9-tetraene.

relieve the strain by introduction of two CH$_2$ bridges, and to further relieve the strain between the bridges (again due to hydrogen overlap) by means of a third CH$_2$ group. He kindly supplied us with a few crystals

of this precious compound, and we undertook the crystal structure determination. In the meantime, we calculated the geometry of an isolated molecule by the usual method.

Bond distances and angles involving H atoms were always assumed. We also assumed *mm2* symmetry for the molecule and the same value (1.397 Å) for all the C–C bond lengths in the annulene ring. The carbon skeleton then has nine degrees of freedom. The energy was minimized with respect to all of them. The orientation of the molecular model in the orthorhombic unit cell was determined by comparing overlap of Patterson functions calculated for different orientations with the same function as obtained by X-ray experimental data.

The position of the reference molecule in the unit cell was determined by shifting the oriented molecule along the axes *x* and *y* (*z* is a polar axis) and calculating at each point the sum of nonbonded interactions between each atom of the model and each atom of molecules generated by symmetry around the reference molecule. One very clear minimum was found. From this point, the structure was refined by the least squares technique, to a final *R* of 0.06%.[26] The annulene ring is aromatic, in accordance with its chemical and spectroscopic behavior. Bond lengths in the ring are between 1.38 and 1.41 Å (mean value 1.395 uncorrected, 1.401 corrected), and molecular *mm2* symmetry is preserved within experimental error. Experimental and calculated (by the Schomaker–Trueblood method[27]) thermal parameters are in good agreement for all 17 carbon atoms. The ring is not planar, but the distance from the best plane is <0.6 Å. Torsional angles around the C–C bond in the ring reach the maximum value of 28°.

A second example of solution of a crystal structure by means of the atom–atom potential approach was 11,11-difluoro-1,6-methano[10]annulene.[28] The
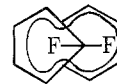
method of solution followed the same route as for the preceding compound. The molecule shows chemical and spectroscopic aromatic behavior. C–C distances in the ring range from 1.33 to 1.47 Å. The compound could valence-isomerize to a bisnorcaradiene structure. However, no evidence to support this was found, since one "double bond" is 1.44 Å and the C$_1$–C$_6$ distance is 2.25 Å. We also determined, this
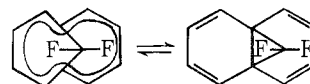
time by conventional techniques, the crystal structure of a compound in which the bisnorcaradiene form obtains, namely, 11,11-dimethyltricyclo[4.4.-1.0^{1,6}]undeca-2,4,7,9-tetraene.[29] The crystal is triclin-

ic, space group $P1$, with two moleles in the asymmetric unit. The average molecular structure is shown in Figure 3. Chemical and spectroscopic behavior support this finding.[30]

Now the question arises: why is the difluoro compound an annulene and the dimethyl not? In the latter compound there is a cyclopropane ring, with a very long C–C bond, perhaps the longest C–C bond ever found. In the fluoro derivative, the bond has disappeared. In both cases, there is a strong internal strain acting on this bond. In our opinion, the difference in the two compounds is due to electron substituent effect. Using the Walsh model for describing orbitals in a cyclopropane ring, Hoffmann has shown through molecular orbital analysis that π-electron-attracting substituents weaken the adjacent bonds and strengthen the opposite one, while π-electron donors weaken all bonds in the ring.[31] To substantiate such qualitative arguments we made an *ab initio* MO calculation, using the SCF-GTO-3G technique proposed by Pople.[32] This is a complete SCF calculation including all valence electrons. The valence shell orbitals are expressed as linear combinations of three gaussians, with coefficients and exponents that make the orbital as close as possible to a Slater orbital. We considered cyclopropane and 1,1-difluoro- and 1,1-dimethylcyclopropanes. Although the effects are weak, the results are in complete agreement with the qualitative predictions.[29]

Another example of the use of molecular mechan-

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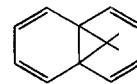(27) V. Schomaker and K. N. Trueblood, *Acta Crystallogr., Sect. B*, 24, 63 (1968).

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ics to study the conformation of organic crystals is 1,6:8,13-butane-1,4-diylidene[14]annulene.[33] The isolated molecule was assumed to have point group symmetry $2C_2$, and all bond lengths in the ring were taken as 1.397 Å. The energy was minimized with respect to the eleven internal degrees of freedom of the C-atom skeleton. Standard values were assumed for the C–H bond length, and the direction of these bonds was determined by the orthogonality conditions for the hybrid carbon orbitals. The minimum energy was found to correspond to $mm2$ symmetry. In view of this symmetry and of the fact that the space group was $Fmm2$ with four molecules in the unit cell, we had only to find which axis was polar and to check two possible orientations of the molecule, rotated by 90° with respect to each other. Only for one position was the packing energy reasonable (−2.5 kcal/mol); for all others some contacts were too short to be admissible. The R index was 0.24, a good starting point for least squares refinement. The final molecular parameters are shown in Figure 4. The molecule was expected to behave like a rigid body in undergoing thermal libration. The tensors **T, L, S,** corresponding to vibrations along a straight line, along an arc, and along a helical path, were computed. Agreement between the observed and the calculated anisotropic thermal factor coefficients, B_{ij}'s, was good.

This time we also tried to utilize further the atom–atom potential, comparing experimental anisotropic thermal parameters with the mean-square amplitudes calculated by means of the lattice dynamics model suggested by Pawley.[34] The results were encouraging. For example, for a carbon atom in position 2 we have[35]

	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
exptl	26	61	157	−7	−4	−9
calcd	18	52	117	−3	−2	−1

Agreement for all other atoms is of this order. Thus we see a potential new field of application for atom–atom potential functions, in the calculation of the dynamical matrix for molecular crystals. Calculations of "crystallographic" temperature factors have been carried out for a number of rigid organic molecules with satisfactory results.[36]

The same atom–atom potential has been used to evaluate vibrational frequencies, dispersion curves along principal directions, and the density of states. Where available, experimental data are in good agreement with the results of our calculations. A careful study of the mathematical techniques in current use in the interpretation of thermal motion in molecular crystals of rigid molecules has shown that serious difficulties may arise, and that a lattice-dynamical treatment, when feasible, is to be preferred. Sampling the Brillouin zone turned out to be a point of paramount importance for a correct dynamical
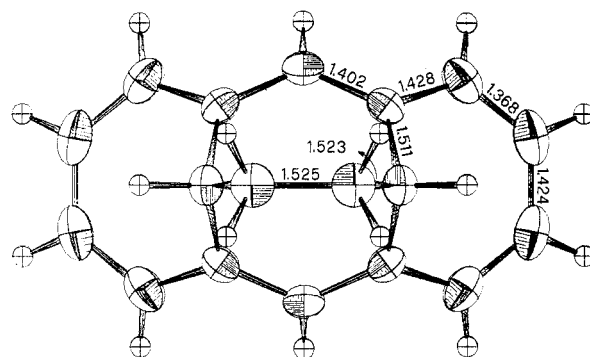

Figure 4. Bond lengths in 1,6:8,13-butane-1,4-diylidene[14]annulene.

treatment.[37] From frequencies obtained for all sampled points a density of states can easily be constructed, from which it is possible to calculate a number of thermodynamic functions for the molecular crystal, such as enthalpy of sublimation, specific heats at constant volume or pressure, entropy, free energy, and vapor pressure.[38]

It is gratifying that the atom–atom potentials that have been calibrated to fit structural parameters of isolated molecules or of static crystal structures lead to satisfactory values for dynamical observables, such as infrared and Raman vibration frequencies, anisotropic temperature factors, and thermodynamic functions. On the other hand, experimental data of this kind could be used to calibrate the functions for atoms other than carbon and hydrogen, where reliable potentials are still needed. Here we made the same observation that occurred to Schleyer, et al.,[8] in their work in the area of isolated molecules: the choice of the potential function is not of crucial importance to obtain good agreement between calculated and experimental data.

I will now mention our work on 7-methoxycarbonyl-*anti*-1,6:8,13bismethano[14]annulene.[39] Since
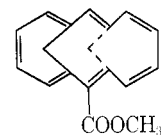
the hydrocarbon has a low melting point, Professor Vogel kindly provided us with good crystals of the methoxycarbonyl derivative. Starting from [14]annulene, the strain was relieved this time by means of two CH_2 bridges placed on different sides of the ring. Spectral data and chemical behavior predict a nonaromatic structure. The crystal structure was solved by direct methods to a final $R = 0.051$,[40] and the final geometry for the molecule is shown in Figure 5. The striking feature is the systematic succession of long and short bond distances in the annulene perimeter, at variance with the results found for similar annulenes.

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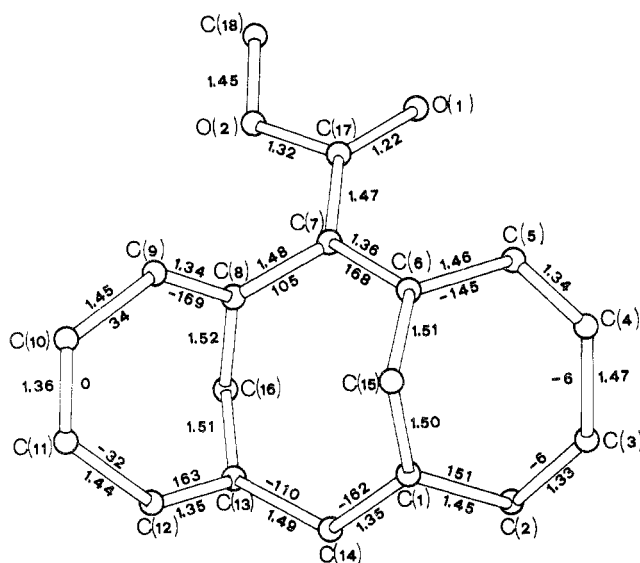
Figure 5. Geometrical parameters in 7-methoxycarbonyl-*anti*-1,6:8,13-dimethano[14]annulene.
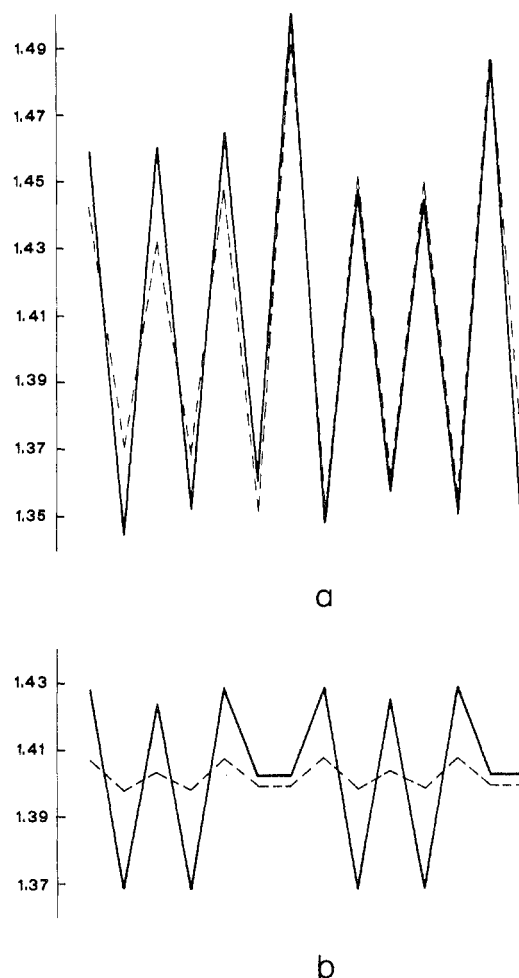

a

b

Figure 6. Experimental (solid line) and calculated (dashed line) bond lengths (Å) for bonds C(1)–C(2) to C(14)–C(1) in the annulene ring: (a) 7-methoxycarbonyl-*anti*-1,6:8,13-dimethano[14]-annulene; (b) 1,6:8,13-butane-1,4-diylidene[14]annulene.

We compared six annulenes with known crystal structures. The difference in bond length along the perimeter could not be attributed to a more pronounced deviation from planarity of the perimeters. Butano[14]annulene, which shows the highest deviation from planarity, does not show the highest deviation in bond lengths. The olefinic or aromatic behavior can instead be attributed to the misalignment angles ϕ_{ij} between the directions of adjacent $2p_z$ orbitals on carbon atoms i and j in the ring. The maximum value is shown in the anti derivative. The reliability of our assumption was substantiated by means of Hückel molecular orbital calculations for the π electrons in the ring in which the angles ϕ_{ij} were kept constant and equal to the experimental value; the C–C distances were initially assumed all equal to 1.4 Å, and the exchange integral β was taken as $\beta = \beta_0 S/S_0$, where S is the overlap integral in the considered geometry and S_0 is the overlap integral for two Slater $2p_z$ carbon orbitals with parallel axes at a distance of 1.4 Å. At the end of the calculation, C–C bond orders and hence bond distances were evaluated, and new β integrals were calculated. The calculation was repeated (always with the experimental ϕ_{ij}) till consistency obtained. The results shown in Figure 6 for the anti compound and butano[14]annulene are in very satisfactory agreement with experiment, suggesting the adequacy of the proposed explanation.

In conclusion, we wish to point out two new areas where one may confidently apply molecular mechanics when intermolecular interactions are added to the intramolecular potential. Such intermolecular interactions can be evaluated by means of the usual intramolecular nonbonded potential functions. The first area is crystal and molecular structure determination by X-ray diffraction; molecular mechanics can be used as an aid (to avoid false minima[21] and to take

care of disorder[23]) or as an alternative (to solve the crystal structure *ab initio*[26,33]) to the traditional techniques. In this context molecular mechanics can be used to relate the structure of an organic compound, as measured in a crystal, to the structure of the isolated molecule. Molecular mechanics seems also to be an extremely powerful technique in the field of lattice dynamics and for the calculation of thermodynamic functions of molecular crystals. Results already obtained for a number of hydrocarbons[35–38,41] are quite satisfactory.

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