Molecular Recognition and Crystal Energy Landscapes: An X-ray and Computational Study of Caffeine and Other Methylxanthines

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Abstract: We introduce a new approach to crystal-packing analysis, based on the study of mutual recognition modes of entire molecules or of molecular moieties, rather than a search for selected atom–atom contacts, and on the study of crystal energy landscapes over many computer-generated polymorphs, rather than a quest for the one most stable crystal structure. The computational tools for this task are a polymorph generator and the PIXEL density sums method for the calculation of intermolecular energies. From this perspective, the molecular recognition, crystal packing, and solid-state phase behavior of caffeine and several methylxanthines (purine-2,6-diones) have been analyzed. Many possible crystal structures for anhydrous caffeine have been generated by computer simulation, and the most stable among them is a thermodynamic, ordered equivalent of the disordered phase, revealed by powder X-ray crystallography. Molecular recognition energies between two caffeine molecules or between caffeine and water have been calculated, and the results reveal the largely predominant mode to be the stacking of parallel caffeine molecules, an intermediately favorable caffeine–water interaction, and many other equivalent energy minima for lateral interactions of much less stabilization power. This last indetermination helps to explain why caffeine does not crystallize easily into an ordered anhydrous structure. In contrast, the mono- and dimethylxanthines (theophylline, theobromine, and the 1,7-isomer, for which we present a single-crystal X-ray study and a lattice energy landscape) do crystallize in anhydrous form thanks to the formation of lateral hydrogen bonds.

Keywords: caffeine · methylxanthines · molecular recognition · organic crystals · structure elucidation

Introduction

Caffeine (1,3,7-trimethylpurine-2,6-dione) is a widely used food and drug reagent, whose solid-state phase behavior is of interest to the manufacturing industry. The compound readily forms a hydrate, whose crystal structure has been determined by single-crystal X-ray diffraction. The hydrate may transform at ambient conditions to an anhydrous β-phase, which in turn converts to a second anhydrous α-phase at higher temperature. It appears that no fully ordered crystal phase has ever been isolated for pure caffeine;[1] these two phases still defy a complete structural determination, because only powders and disordered crystals are obtained. In view of the importance of the substance, its properties have been widely studied by spectroscopic and calorimetric methods.[2]

Why is it that pure, anhydrous caffeine does not form an ordered crystal? The molecule cannot form hydrogen bonds, but that may not be the only explanation: well ordered crystals are formed by related compounds, for example, methylated naphthalenes, azanaphthalenes, naphthoquinones, and coumarins. For its molecular surface of $S_M = 197$ Å^2, caffeine is expected to have a packing energy (the negative of the heat of sublimation) of $E = -(0.32S_M + 37) = -100$ kJ mol^{-1},[3] so that its bulk packing potential is not so weak. One has here a typical riddle encountered in the study of crystallization and phase transitions in organic crystals, a field where computer modeling is nowadays becoming more and more important. The main purpose of this paper is to illustrate two new concepts in the analysis and computer modeling of organic crystals: the first is the concept of structure determinants, or neighboring molecular pairs in the crystals, whose interaction energy is evaluated using the entire calculated molecular electron density[4] by the PIXEL approach,[5] as opposed to traditional atom–atom methods;[6] the second is the concept of landscape analysis, or a packing analysis that uses a large number of computer-generated crystal polymorphs to analyze the possible packing modes

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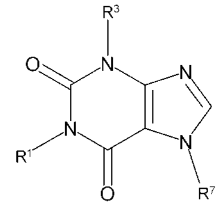
for a given compound, in terms of interaction energies dissected into coulombic, polarization, dispersion, and repulsion terms, also made possible by the PIXEL approach. We apply these concepts to investigate the recognition mechanisms of the caffeine molecule, in an attempt to provide an explanation for the difficulties encountered by these molecules during crystal nucleation and growth. In the process, a crystal structure is generated for anhydrous caffeine that lends support to experimental determinations based on powder diffraction. For comparison, we also consider a few other methylated xanthines (purine-2,6-diones): theophylline, or 1,3-dimethylxanthine,[7] theobromine, or 3,7-dimethylxanthine,[8] 3-methylxanthine,[9] whose crystal structures have previously been determined; and 1,7-dimethylxanthine (DMex17), for which we present a single-crystal X-ray structure determination. Unlike caffeine, these methylxanthines have a potential for in-plane N–H···O and N–H···N hydrogen bonding.



$R^1 = R^3 = R^7 = CH_3$ caffeine
$R^1 = R^3 = CH_3$, $R^7 = H$ theophylline
$R^3 = R^7 = CH_3$, $R^1 = H$ theobromine
$R^1 = R^7 = CH_3$, $R^3 = H$ 1,7-dimethylxanthine
$R^3 = CH_3$, $R^1 = R^7 = H$ 3-methylxanthine

Computational Methods

For the molecular structures, all hydrogen atom positions were renormalized according to standard geometrical criteria.[6a] Prior to the crystal-structure determination, a molecular model for DMex17 was obtained by deleting the methyl group at the nitrogen atom in the 3-position of the caffeine molecule, and replacing it with a hydrogen atom. Molecular, valence-only electron densities, for all of the compounds mentioned, were calculated[4] at the MP2/631G** level with a grid step of 0.08 Å, using the unoptimized molecular structure found in the crystal. For comparison with localized models, atomic-charge parameters were determined by the POP=ESP procedure embedded in the GAUSSIAN package.[4] All other calculations were carried out with the computer program package, OPiX.[10] A first module identifies crystal-structure determinants, that is, nearest neighbor molecular pairs described by a symmetry operator, a distance between centers of mass, a dihedral angle between molecular planes, and a molecule–molecule interaction energy. Another module[11a] uses a rigid molecular model to generate crystal structures in the most common space groups, with lattice energies being calculated by the UNI atom–atom potentials,[6] with the optional addition of point-charge coulombic terms. This module also includes a lattice energy minimizer. A third module uses the calculated molecular electron density and the SCDS-PIXEL procedure[5] to calculate coulombic, polarization, dispersion, and repulsion energies between neighboring molecules. Very briefly, the method is as follows. The elementary cubes in the electron density are called charge pixels. The total coulombic energy is calculated by sums over pixel–pixel, pixel–nucleus, and nucleus–nucleus coulombic terms. A local polarizability is assigned to each pixel using additive atomic polarizabilities, and the electric field generated at each pixel, by pixels and nuclei in surrounding molecules, is calculated. The polarization energy is then evaluated through the linear polarization formula. A London-type formula is used to evaluate dispersion energies, again as a summation over pixel pairs, through the local polarizabilities and the molecular ionization potential, which is taken as the energy of the highest occupied molecular orbital. Finally, the overlap between molecular densities is calculated by numerical integration, and the exchange-repulsion energy is evaluated as proportional to the overlap integral raised to a power of between 0.9 and 1.0. The whole procedure requires no more than four empirical parameters, the numerical values of which were taken here from previous work.[12]

Results and Discussion

Packing analysis of the caffeine monohydrate crystal structure: The crystal structure of caffeine monohydrate[1] is available from the Cambridge Structural Database (refcode CAFINE01). The water molecules are disordered and incommensurate, and the distance between water oxygen atoms in the channel is only 2.5 Å. The following discussion refers only to interactions among caffeine molecules. The caffeine–water interaction will be investigated separately.

Figure 1 shows the motif in the *bc* plane. The channel in which water molecules stay and through which they diffuse is evident; the distances between the nitrogen or methyl carbon atoms across the channel is around 7.0 to 7.5 Å, so that the diameter of the channel is around 4 Å, just matching the molecular cross section of a water molecule, and water diffusion is not severely hindered by exchange repulsion. The *bc* layers are stacked at the short translational distance of 3.97 Å, corresponding to the *a* axis.

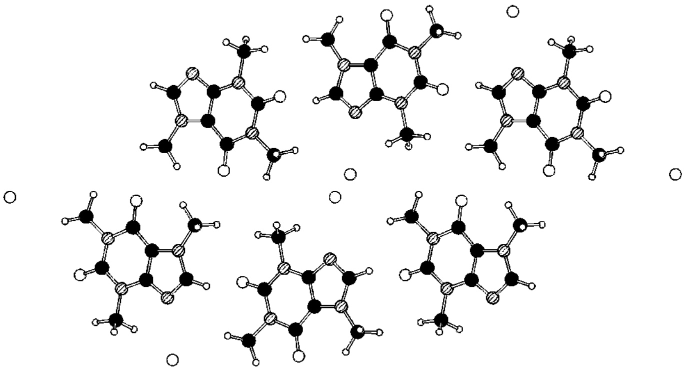


Figure 1. The crystal structure of caffeine monohydrate, *bc* projection. The isolated circles denote the position of water oxygen atoms. The water channel runs perpendicular to the plane of this projection. Filled circles denote C atoms, striped circles denote N atoms, large open circles denote O atoms, and small open circles denote H atoms. Adapted from reference [1].

For a quantitative discussion, the structure determinants in the caffeine monohydrate crystal are listed in Table 1. The leading interaction, energetically speaking, is the stacking motif. It consists mainly of a dispersive contribution, whereas the coulombic part is less important (note the

Table 1. Nearest neighbor molecular pairs (structure determinants) in the experimental crystal structure of caffeine monohydrate.

Symmetry[a]	Distance[b] [Å]	Angle[c] [°]	E_{qq}[d] [kJ mol^{-1}]	E_{coul}[e] [kJ mol^{-1}]	E_{pol}[e] [kJ mol^{-1}]	E_{disp}[e] [kJ mol^{-1}]	E_{rep}[e] [kJ mol^{-1}]	E_{tot}[e] [kJ mol^{-1}]
T (stack)	3.97	0	+3.65	−4.3	−7.1	−59.2	30.8	−39.8
I (D···D)	8.45	0	−9.5	−13.8	−6.1	−10.4	13.8	−16.3
I	7.65	0	−7.4	−7.4	−1.5	−7.0	2.4	−13.5
G (E···AB)	8.94	9	−13.6	−19.5	−6.1	−8.0	20.8	−13.0
G	7.63	9	0.0	−0.6	−2.3	−10.6	5.0	−8.6

[a] Symmetry codes: T = translation, I = inversion center, G = glide mirror plane, S = screw axis. [b] Distance between molecular centers. [c] Dihedral angle between aromatic molecular planes. [d] Coulombic interaction energy calculated by point-charge atom–atom model. [e] Coulombic (E_{coul}), polarization (E_{pol}), dispersion (E_{disp}), repulsion (E_{rep}), and total (E_{tot}) energies from the PIXEL calculation.

scarcely realistic repulsive coulombic contribution calculated in the more approximate point-charge model). We then label the interaction zones in the molecular plane as follows (Figure 2): methyl–carbonyl "bay" areas A, B, C, D; the acidic hydrogen atom region E; and the methyl–nitrogen "bay" area F. The next interaction, in order of importance in the crystal, is one between two D-type bay areas in coplanar molecules, related by a center of symmetry, with a confrontation of positively charged methyl-hydrogen zones and negatively charged carbonyl oxygen atoms. Then comes another centrosymmetric interaction, the coulombic stabilization resulting from a general effect diffuse over a large molecular zone, in which it is not easy to identify any particular approach of opposite charges or opposite dipoles. The next interaction is between the acidic hydrogen zone E and the carbonyl oxygen atom between the A and B bay areas, mainly sustained by the coulombic term, which produces a string of glide-related molecules (however, there is no simple explanation for the almost impossibly short H···O distance of 2.16 Å found in the X-ray crystal structure analysis). The whole crystal is built of parallel molecules, as the dihedral angle between planes of screw- or glide-related molecules is only 9°. Judging from this crystal structure, the caffeine molecule has no propensity for the formation of T-shaped dimers.

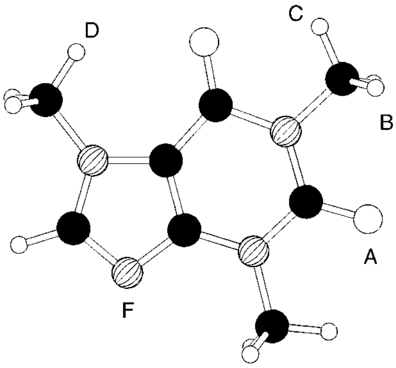


Figure 2. Labeling of sites for lateral interactions in the caffeine molecule.

Table 2. Crystal forms of caffeine.

Space group	a [Å]	b [Å]	c [Å]	α [°]	β [°]	γ [°]	V[a] [Å^3]	
$P2_1/c$, $Z=4$	3.97	16.75	14.80	–	95.8	–	245.1	X-ray[b]
$P2_1/c$, $Z=4$	3.94	15.45	14.51	–	97.5	–	218.8	opt, charges[c]
$P2_1/c$, $Z=4$	3.88	13.98	15.84	–	93.3	–	214.2	opt, no charges[d]
$R3$, $Z=3$	14.97	14.97	3.47	–	–	120	224	α-phase[e]
$P\bar{1}$, $Z=2$	6.98	8.86	9.41	109	105	109	238	β-phase[f]
Cc, $Z=20$	43.04	15.067	6.953	–	99.0	–	222.7	α-phase[g]

[a] Cell volume per molecule. [b] Hydrate crystal structure. [c] Optimized from the hydrate after removing water, UNI potentials plus ESP charge parameters. [d] *Idem*, optimized by UNI potentials. [e] Anhydrous, reference [1]. [f] Anhydrous, reference [1], reduced cell. [g] Anhydrous, reference [14]. Crystal structure determinations for anhydrous phases are critical due to lack of suitable single crystals.

When water escapes from the crystal lattice of caffeine hydrate, the substance recrystallizes into an anhydrous β-form. A possible computational equivalent of the dehydration process is the relaxation of the hydrate crystal structure after removal of the guest water molecule. In this way the lattice energy minimizer in the OPiX computer program package readily produces a stable crystal form, in which the channel space has been filled thanks to a relatively small molecular displacement and to a reduction in cell dimensions. The results (Table 2) are not too different whether or not charge parameters are included in the potential, but the optimization without charges produces a higher density (more close-packed) crystal.

A study of molecular recognition modes: Independently from the neighboring pairs found in the crystal, dimerization energies for various plausible arrangements of two caffeine molecules, or a caffeine molecule and a water molecule, were calculated a priori by the Pixel module of the OPiX package. For comparison, the atom–atom UNI energies and the point-charge coulombic energies were also evaluated. The results are summarized in Table 3.

For the caffeine–water dimer, the calculated interaction energy of 27.1 kJ mol^{-1} and the equilibrium O···N distance of 2.97 Å match the corresponding heat of dehydration (31.3 kJ mol^{-1}) and the O···N distance (2.82 Å) found in the hydrate crystal[1] rather well. The interaction between caffeine and water is essentially electrostatic in nature, with a

Table 3. Interaction energies[a] [kJ mol^{-1}] in several caffeine dimers.

Dimer	Type[b]	E_{qq}	E_{coul}	E_{pol}	E_{disp}	E_{rep}	E_{tot}
stack, antiparallel		−13.7	−47.1	−19.5	−92.5	91.1	−68.1
stack, parallel		+2.4	−18.8	−14.8	−72.4	66.1	−39.9
water		−18.6	−39.2	−17.7	−10.1	40.0	−27.1
methyl···N	F···F	−6.0	−11.2	−3.9	−13.2	13.0	−15.2
methyl···O	A···A, B···B, C···C	−5/−6	−6/−7	−2/−4	−5/−8	+5/+9	−8/−10
	D···D	−12.1	−14.3	−3.2	−8.4	7.7	−18.1
H···O	E···AB	−8.6	−11.2	−2.7	−5.0	6.6	−12.2
H···N	E···F	−13.4	−24.6	−6.8	−11.1	20.1	−22.3

[a] Definitions of six energy terms are given in Table 1. [b] See Figure 3 for definitions of interaction types.

significant polarization component and a smaller dispersion contribution.

The recognition energy between two caffeine molecules is a complex function of distance and orientation. We have identified a few clearly relevant motifs on the basis of elementary steric and electrostatic reasons (Figure 3): the stacked dimer, parallel or antiparallel; the four possible homodimers over methyl and carbonyl-oxygen bay areas A, B, C, D (i.e., considering only the interaction between two identical sites in molecules related by a center of symmetry); the centrosymmetric dimer over the methyl–nitrogen bay area F; the centrosymmetric, E-hydrogen atom to F-nitrogen atom dimer; and the E-hydrogen atom to AB-oxygen atom dimer. For the stacked dimers, the positional variables in the search for energy minima were a vertical distance and an offset distance between molecular centers; the other dimers were coplanar, and the variables were one or two in-plane displacements.

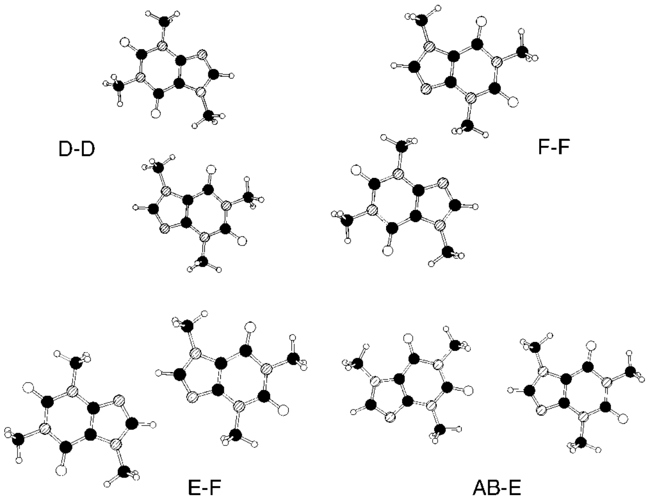


Figure 3. Lateral recognition modes for caffeine. See Figure 2 for labels.

We now proceed to use the breakdown of PIXEL energies over crystal structure determinants to rationalize the formation of the hydrate crystal structure of caffeine and its reluctance to form an ordered anhydrous phase. The most evident result in Table 3 is the overwhelming prevalence of the antiparallel-stacking interaction over all other interaction modes. The fact that this mode is not used in the hydrate crystal may be explained by observing that the sum of the parallel-stacking and water interaction modes (67 kJ mol^{-1}) is just equal to the binding energy of the antiparallel mode. Both stacking modes are quite reasonably driven by the dispersive contribution, but the coulombic energy is largely in favor of the antiparallel one. These results are in broad agreement with experimental evidence in water,[13] pointing to the aggregation of caffeine molecules exclusively by plane-to-plane stacking.

Of the four possible dimers over the methyl···O bay areas, three (A···A, B···B, C···C) involve the formation of an eight-membered ring and are energetically very nearly equivalent, as expected. The fourth (D···D mode) involves the formation of a ten-membered ring; it is the one with the highest attachment energy and is also the only one observed in the hydrate crystal. The C···C and D···D energy valleys are connected by a parallel displacement of the two molecules, and the energy maps reveal that a molecular displacement of more than 1 Å meets a barrier of only 1 kJ mol^{-1}. The advantage of the D···D recognition mode is essentially electrostatic, but it is not easy to recognize why this is so on the basis of simple atomic point-charge arguments. This is further confirmation of the need for reasonably accurate quantitative arguments in any discussion of relative recognition energies.

The E-hydrogen atom to AB-oxygen atom dimerization mode is used by caffeine in the hydrate crystal form, although with small geometrical changes with respect to the Pixel-calculated minimum energy arrangement. The close contact between H and O atoms is commonly called a C–H···O "hydrogen bond", but the total interaction energy of this last molecule–molecule recognition mode is far from predominant, so that it is not proper to assign a special structure-driving importance to such a bond. The formation of a dimer over the methyl···N bay area F is forbidden in the presence of water, against which it cannot compete because the corresponding interaction energies are −15.2 compared to −27.1 kJ mol^{-1}. The E-hydrogen atom to F-nitrogen atom mode could almost compete with hydration on the basis of binding energies, but the hydration mode might be kinetically favored, because the mobility of the water molecule is larger than that of the caffeine molecule.

In conclusion, the packing of the hydrate crystal structure of caffeine shows many of the most energetically favorable molecule–molecule arrangements, except the most stable of all, the antiparallel dimer, which is substituted by the sum of a parallel dimer and a caffeine–water interaction. The next logical step in the rationalization of this observation relies on an analysis of the crystal energy landscape for pure caffeine. We therefore generated a number of anhydrous caffeine crystal structures containing the antiparallel dimer motif, to determine their relative stability.

Generation of crystal structures for anhydrous caffeine: While the prediction of a crystal structure is still far from being routinely feasible,[11b] the procedures for the geometrical generation of many crystal structures from a given molecular structure are well established,[11a] at least as far as the molecular model is fairly rigid and does not include too much conformational freedom. This feature is the basis of the energy-landscape concept, because even if the experimental crystal structure is not easily found or located among the ones that have been generated, the procedure generates a collection of all reasonable packing modes for the given molecule, yielding very valuable information.

The molecular model extracted from the crystal structure of the hydrate phase was packed into a large number of tentative anhydrous crystal structures in the most common space groups, using the appropriate module in the OPiX package. After the usual merging, sorting, and optimization procedures, 99 crystal structures were retained, of which 12 in $P\bar{1}$, seven in $P2_1$, nine in $P2_12_12_1$, 63 in $P2_1/c$, and eight in $C2/c$. The lattice energies were calculated by the UNI parameters and by the Pixel method, and the point-charge coulombic energies over ESP charges were also calculated. Crystal data of the most stable structures are collected in Table 4, and energies are shown in Table 5.

Table 4. Top-ranking crystal structures in the polymorph search for anhydrous caffeine.

Structure	a [Å]	b [Å]	c [Å]	α [°]	β [°]	γ [°]	V[a] [Å^3]
1) $P\bar{1}$	6.52	8.26	8.92	63	80	83	210
2) $P2_12_12_1$	6.49	8.28	15.4	–	–	–	207
3) $P2_1$	8.39	6.50	8.83	–	63	–	214
4) $P2_12_12_1$	6.61	8.99	14.32	–	–	–	213
5) $P\bar{1}$	6.49	8.33	8.87	63	86	86	212
6) $P2_1/n$	8.98	6.50	14.69	–	87	–	214

[a] Cell volume per molecule.

Table 5. Lattice energies[a] [kJ mol^{-1}] of the crystal structures in Table 4.

Structure	E_{UNI}[b]	E_{qq}	E_{coul}	E_{pol}	E_{disp}	E_{rep}	E_{tot}
1)	−130.3	−24.4	−55.1	−22.9	−133.8	106.6	−105.1
2)	−132.9	−25.4	−55.1	−20.1	−136.4	106.6	−105.0
3)	−127.8	−25.5	−52.7	−20.8	−129.5	98.4	−104.7
4)	−127.0	−21.3	−52.5	−17.7	−126.5	91.9	−104.7
5)	−127.8	−25.2	−55.3	−22.7	−132.7	106.2	−104.4
6)	−127.4	−25.8	−53.3	−21.3	−130.1	100.6	−104.1
minimized dehydrate, charges	−120.4	−25.8	−51.3	−21.3	−121.3	99.5	−94.4
id, no charges	−124.8	-	−40.0	−19.3	−120.5	89.3	−90.5

[a] Definitions of energy terms in columns three to eight are given in Table 1. [b] Lattice energy calculated by the UNI atom–atom potentials.

The calculated lattice energy for the most stable, anhydrous caffeine polymorph is −105.1 kJ mol^{-1} by Pixel or −132.9 kJ mol^{-1} by UNI, against an experimental heat of sublimation of 110–115 kJ mol^{-1} for the β-phase and 114–119 kJ mol^{-1} for the α-phase, at 298 K.[2] The Pixel estimate of the lattice energy of caffeine is good. Data in Table 5 also show that the hypothetical crystal phase, generated by rearrangement of the hydrate crystal structure after loss of water, is thermodynamically unfavorable. This explains nicely why the dehydration process is not a single-crystal to single-crystal process and does not produce an ordered daughter phase simply related to the mother phase. The uncertainties that the caffeine molecule must experience when packing into a crystal are reflected by the fact that six crystal structures in four different space groups rank together within a range of only 1 kJ mol^{-1}.

All of the most stable crystal structures calculated include antiparallel-stacked dimers, obtained either by a center of inversion or by a screw axis perpendicular to the molecular plane. This stacking motif is reflected in the 6.5–6.6 Å lattice parameter found in no less than four different space groups (Table 4). Figure 4 shows the typical columnar arrangement that results, in which intercolumn attachment points include a variety of interactions among those portrayed in Figure 3. Of our computational polymorphs, the most stable one with parallel stacking has a lattice energy of only −97.8 kJ mol^{-1} and a buckled structure with interplanar angles of 61° or 66°.

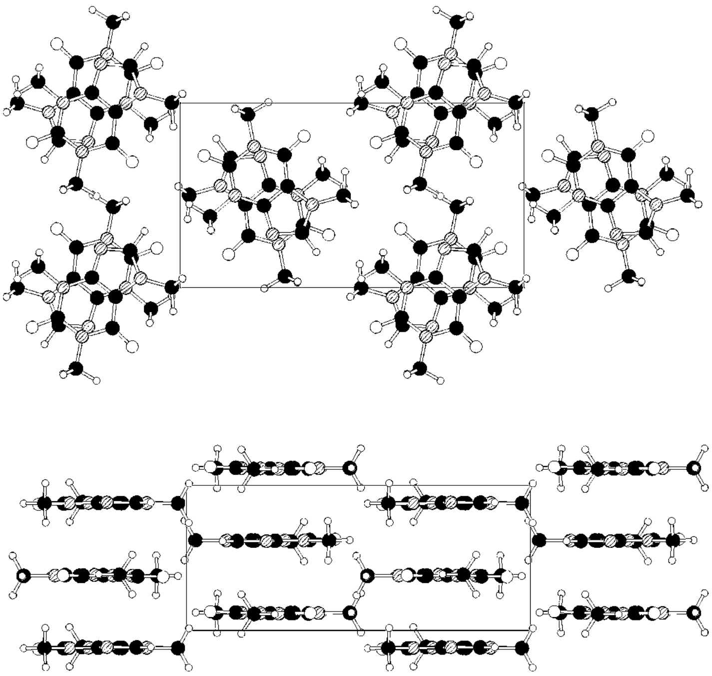


Figure 4. The best calculated crystal structure of anhydrous caffeine: projections perpendicular (below) and parallel (above) to the stacking direction.

On the basis of the above results, we predict with some confidence that stable crystal structures for anhydrous caffeine must include antiparallel-stacked dimers with a 6.5 to

7.0 Å periodicity. The latest experimental structure determination,[14] in space group *Cc* (Table 2), includes that stacking periodicity along *c*, while five independent molecular rigid bodies were necessary to model the disorder due to variable orientation in the *ab* plane. The picture obtained in the *ab*-plane projection is quite similar to the layer motif seen in our Figure 4, in which our calculated periodicity of 15.4 Å agrees with the experimental one of 15.067 Å, and our calculated periodicity of 8.28 Å coincides with 43.04/5 = 8.61 Å. Thus, our computational crystal structure is an ordered equivalent of the disordered crystal structure found experimentally.

Our specification of interaction regions A to F in the previous paragraph intentionally dispenses with a consideration of special atom–atom distances, that is, weak C−H···O or C−H···N "bonds", and the like. In fact, for all the 99 crystal structures in our crystal energy landscape, we have calculated OH- and NH-bond indicators as the sum of differences between actual O···H or N···H distances in a crystal structure and the sum of atomic radii (2.68 and 2.74 Å, respectively).[15] A large value for this index, therefore, designates a structure with many short O···H or N···H distances. Figure 5 is a typical example of the complete scatter that results when the total or any of the partitioned lattice energies are plotted against the OH-bond factor. All crystal structures in our sample, within an energy window of 30 kJ mol^{-1} between the most and the least stable, contain short O···H distances, which do not seem to have any special relevance as far as selectivity is concerned. An analysis of angular dependence when methyl hydrogen atoms are involved would be even more problematic. Analogous results are obtained when the NH-bond factor is plotted. We conclude that short O···H distances are not a discriminating factor in the crystal packing of caffeine. This result is strictly analogous to those obtained for other polar crystals.[12b]

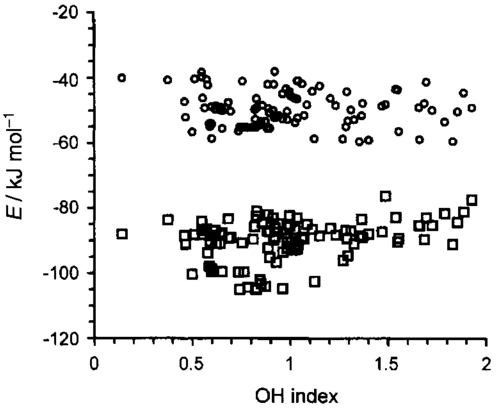


Figure 5. Coulombic (circles) and total (squares) lattice energies in 99 computational caffeine polymorph crystals as a function of the OH index, a measure of how many short O···H distances are present in the crystal structure.

Crystal structures and phase behavior of other methylxanthines: No single crystals of anhydrous caffeine have ever been grown. Of the dimethylxanthines, anhydrous theobromine and theophylline were crystallized, although not without difficulty, by vacuum sublimation.[7,8] The hydrate crystals are also known.[16] Crystals of 3-methylxanthine were obtained, apparently without too much difficulty, from an aqueous solution;[9] so for this compound hydration is not a very favorable or competitive process. The 1,7-dimethyl isomer, here called DMex17, is the least studied one, being less common in nature. Anhydrous and hydrate crystal forms are known, the melting point of the former being 572 K.[17] All of these methylxanthines have rather high melting points for organic substances of their size, especially notable for caffeine, which cannot form hydrogen bonds (however, in this case, the high melting point could be due to a low melting entropy because of disorder in the crystal).

When we started this study, the crystal structure of DMex17 was not available. For the analysis of the lattice energy landscape and a mild attempt at crystal structure prediction, using the same protocols as for caffeine, 99 crystal structures were generated for DMex17 by the Prom module of OPiX, of which 18 were in $P\bar{1}$ and 81 were in $P2_1/c$. We were then able to obtain crystalline material of sufficient quality, by ordinary recrystallization and without much difficulty, for single-crystal X-ray analysis (see Experimental Section). For comparison, the anhydrous crystal structures of theophylline (refcode BAPLOT01),[7] theobromine (refcode SEDNAQ),[8] and 3-methylxanthine (refcode FADCUI)[9] were retrieved from the Cambridge Structural Database.

Theophylline forms stacked dimers, but the crystal structure has no layers and the interplanar angle between adjacent molecules is 43°. There are strings of N−H···N hydrogen bonds between non-coplanar molecules. Theobromine forms an almost centrosymmetrical molecular dimer (the two molecules in the asymmetric unit) over a cyclic N−H···O=C hydrogen-bond system; molecular layers are then stacked at a distance of 3.8 Å. The packing also uses several favorable in-plane dimer arrangements among those sketched in Figure 3 (notably the F···F and E–AB ones). The 3-methylxanthine anhydrous crystal also finds an excellent packing motif comprising, at the same time, N−H···N, N−H···O hydrogen bonds and an almost perfect A···A methyl–carbonyl embrace.

For 1,7-dimethylxanthine, contrary to previous literature data,[17] we find that the anhydrous material can be cropped by slow recrystallization, in the form of thin, colorless platelets, while the hydrated crystals can be collected by fast recrystallization, in the form of thin, colorless needles. The freshly recrystallized, anhydrous material of this isomer forms a centrosymmetric dimer over N−H···O hydrogen bonds, but antiparallel stacking forms the main contribution to the lattice energy. On the whole, the crystal structure consists of a buckled sequence of molecular layers (Figure 6).

The computational crystal structures for 1,7-dimethylxanthine include a variety of layers of molecules held together by N−H···N or N−H···O hydrogen bonds, or combinations of these, or even bifurcated hydrogen bonds. Although the lat-

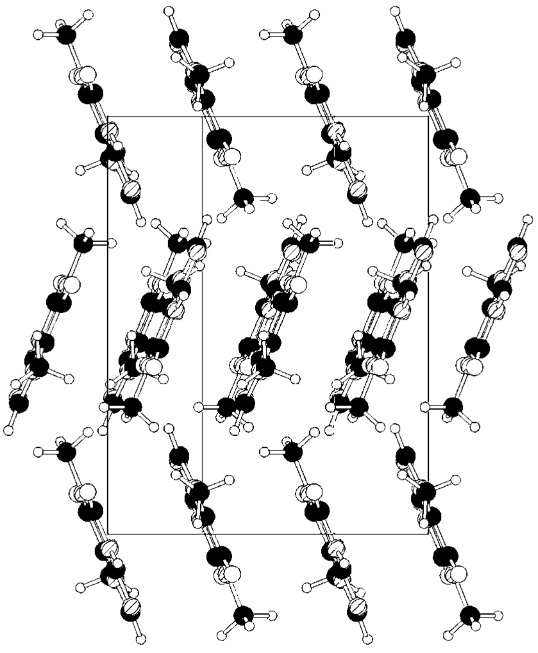


Figure 6. The crystal structure of 1,7-dimethylxanthine. The hydrogen-bonded dimers are seen edge-on.

tice energies of the computational forms (Table 6) are nearly identical to that of the experimental form, there is no agreement between the calculated and the experimental structures, a rather common result in crystal structure prediction attempts reported so far.

Table 6 collects the calculated lattice energies. The coulombic component is large in all structures, and, due to the presence of the penetration energy, the value calculated by PIXEL is, as usual, much larger than that calculated by the point-charge model.[12] The coulombic contribution and, concomitantly, the polarization contribution increase on going from caffeine to the dimethylxanthines to 3-methylxanthine; in spite of a parallel reduction of the dispersion and increase of repulsion terms, the lattice energy is more stabilizing for the hydrogen-bonding compounds, as expected. The same trend is observed in the two experimental sublimation enthalpies available. All of this data confirms an increasing stabilization of the crystal lattice with decreasing number of methyl groups in the molecule. The Pixel estimate of the sublimation heat of theophylline is fairly good, probably an underestimate, as already discussed for hydrogen-bonded systems,[12a] and it coincides with an estimation made by a carefully calibrated force field including distributed multipoles (119.8 kJ mol^{-1}).[18]

We finally exploit the crystal energy landscapes for caffeine and for 1,7-dimethylxanthine (Figure 7) to illustrate the overall differences in packing forces between a non-hydrogen-bonding compound and its hydrogen-bonding analogue. The caffeine landscape shows that dispersion energies increase with crystal density, and that the total lattice energy is dominated by dispersion, while coulombic and polarization terms are less important. These features are typi-

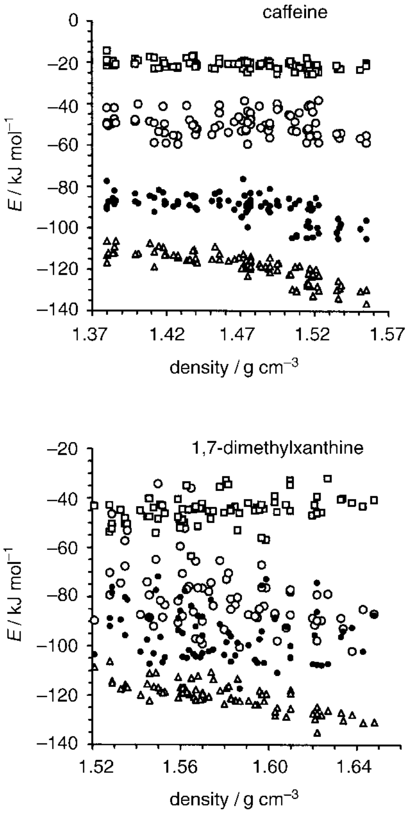


Figure 7. The lattice energy landscape for caffeine: total energies (full circles) are much more stabilizing than coulombic energies (open circles) due to the predominance of dispersion energies (triangles). In the lattice energy landscape for 1,7-dimethylxanthine, coulombic energies are more stabilizing than for caffeine, and are within the same range as total energies. Open squares: polarization energy.

Table 6. Lattice energies[a] [kJ mol^{-1}] of the anhydrous methylxanthines.

Structure	E_{qq}	E_{coul}	E_{pol}	E_{disp}	E_{rep}	E_{tot}	ΔH_{subl}[b]
caffeine, best calcd	−25.4	−55.1	−22.9	−133.8	106.6	−105.1	109–115[c]
DMex17, exptl	−54.0	−95.9	−38.7	−112.0	133.1	−113.4	–
DMex17, calcd $P\bar{1}$	−46.7	−100.4	−46.0	−122.3	151.5	−117.2	–
DMex17, calcd $P2_1/c$	−38.3	−89.6	−46.0	−127.2	155.2	−107.5	–
theophylline	−50.4	−94.3	−43.6	−104.9	122.8	−120.1	133–144[c], 126[d]
theobromine	−55.2	–	–	–	–	–	–
3-methyl	−70.2	−126.0	−53.3	−107.0	161.3	−125.0	–

[a] Definitions of energy terms in columns two to seven are given in Table 1. [b] Heat of sublimation. [c] Reference [2]. [d] Reference [18].

cal of a moderately polar crystal, and, in fact, the landscape is not too different from that of naphthalene.[12b] In contrast, in the DMex17 landscape, dispersion plays a less important role, and the sum of coulombic and polarization energies is almost equal to the total lattice energy. There is no relationship between total energies and crystal densities, and the most stable crystal structure is one that reaches a high coulombic stabilization at the smallest price in repulsion energy.

Conclusions

We propose a new approach to crystal-packing analysis, based on a study of the mutual recognition modes of entire molecules or of molecular moieties, rather than on a search for relevant atom–atom contacts, and based on the study of many computer-generated polymorphs, rather than on a quest for the one most stable crystal structure. One thus obtains valuable information on the packing modes and on the possible polymorphism of a given molecular material. The calculation of reliable relative energies is an essential ingredient, as was apparent ever since the beginning of quantitative crystal-packing studies,[19] while geometrical patterns alone or investigations based on weak atom–atom "hydrogen bonds" appear, in this case, to be scarcely selective and hence not very informative. We conclude that the SCDS-PIXEL method provides a picture of crystal packing qualitatively and quantitatively superior to atom–atom models: the partitioning into coulombic and dispersion stabilizations provides a closer link between molecular constitution and aggregation modes. The increase in computational cost is not prohibitive: the calculation of the energy of a molecular dimer takes seconds of CPU time, and that for a complete crystal structure takes a few minutes.

Based on our present results, we draw some conclusions on the phase behavior of caffeine in comparison with that of other methylxanthines. When caffeine crystallizes in the presence of water, the caffeine–water complex is probably already present before crystals are formed. The solvent is then retained as a surrogate for solute–solute hydrogen bonding and for weak and scarcely selective lateral interactions. By the same reasoning, when caffeine monohydrate loses water, it cannot simply recrystallize by closing the voids. If there is enough energy to break the water–caffeine bond, there is also enough energy to break the weak intercolumn interactions. A possible explanation of why caffeine cannot easily crystallize in the absence of water is that once the leading recognition mode, stacking, has been satisfied, there is uncertainty among a number of energetically almost-equivalent, lateral interactions among the A to F sites. Although the details of the disorder might be questionable, the postulated disordered structure[14] is altogether plausible as a result of this uncertainty. In particular, the signature of a centered cell detected experimentally is compatible with our columnar structure in Figure 4, allowance being made for the random orientation of the molecules within a column. Thus, the observed disorder is the result of kinetic factors in crystal growth, rather than of an intrinsic thermodynamic instability of the material. Computer modeling in the absence of kinetic energy (static modeling), in fact, readily produces a number of thermodynamic equivalents of the kinetic structure actually formed.

The dimethylxanthines crystallize rather well in the anhydrous form. As soon as one methyl group is substituted by a hydrogen-bonding donor H atom, the uncertainty is largely reduced, and strong lateral hydrogen-bonding interactions take over. In the monomethylxanthines, the lateral anchoring points are even stronger, and 3-methylxanthine forms a stable crystal, so strong that it decomposes before melting.

Experimental Section

1,7-Dimethylxanthine was purchased in anhydrous form from Fluka and recrystallized from hot water with fast and slow cooling rates. Single crystals of the anhydrous form, suitable for the diffraction analysis, were obtained with slow cooling rates as thin, colorless platelets . Two data sets were collected, one at 293(2) and one at 150(2) K, on two different crystals of dimensions 0.6×0.28×0.02 mm and 0.28×0.12×0.02 mm, respectively, mounted on a Bruker SMART CCD area detector with graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). Empirical absorption corrections (SADABS) were applied for the data collections. The structures were solved by direct methods (SIR97)[20] and refined by full-matrix least-squares on F^2 (SHELX-97).[21] Anisotropic thermal parameters were commonly assigned to all the non-hydrogen atoms. The hydrogen atoms were placed in the idealized positions and refined riding on their parent atoms for the room-temperature structure, and found from difference Fourier maps and refined isotropically for the low temperature structure.

Crystal data at 150(2) K: $C_7H_8N_4O_2$, $M_r = 180.17$, monoclinic, $a = 7.4047(8)$, $b = 13.4370(15)$, $c = 8.1951(9)$ Å, $\beta = 113.225(2)°$, $V = 749.31(14)$ Å^3, space group $P2_1/n$ (no. 14), $Z = 4$, $\rho_{calcd} = 1.597$ g cm^{-3}, $\mu = 0.122$ mm^{-1}, 7022 ($R_{int} = 0.0367$) reflections collected within the θ range 3°–27°. Least-square refinement, based on 1163 reflections with $I > 2\sigma(I)$ and 150 parameters, led to final $R1 = 0.0381$, $wR2 = 0.0886$, GoF = 1.002. Crystal data at 293(2) K : $C_7H_8N_4O_2$, monoclinic, $a = 7.412(2)$, $b = 13.697(4)$, $c = 8.139(3)$ Å, $\beta = 112.359(5)°$, $V = 764.1(4)$ Å^3, space group $P2_1/n$ (no. 14), $Z = 4$, $\rho_{calcd} = 1.566$ g cm^{-3}, $\mu = 0.120$ mm^{-1}, 5070 ($R_{int} = 0.0599$) reflections collected within the θ range 3°–25°. Least-square refinement, based on 873 reflections with $I > 2\sigma(I)$ and 119 parameters, led to final $R1 = 0.0651$, $wR2 = 0.1671$, GoF = 1.053. CCDC 239467 and 239468 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

Files with crystallographic coordinates and cell parameters of all crystal structures generated for caffeine and for 1,7-dimethylxanthine are available from the authors upon request.

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