Aspirin. An ab Initio Quantum-Mechanical Study of Conformational Preferences and of Neighboring Group Interactions

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The potential energy surface of acetylsalicylic acid, aspirin, has been explored at the RHF/6-31G* and B3LYP/6-31G* levels, and single-point calculations were performed at levels up to B3LYP/6-311G**//B3LYP/6-31G*. All conformational isomers have been located, the thermochemical functions have been computed, and relative energies and free enthalpies were determined. The conformational space of aspirin is spanned by three internal coordinates, and these are the carboxylic acid C—O conformation (s-trans preferred by about 7 kcal/mol), the C—COOH conformation (Z preferred unless there are H-bonding opportunities), and the ester C—O conformation (s-trans preferred by about 4 kcal/mol). There are nine aspirin isomers since one of the conformers realizes hydrogen-bonding structure isomerism as well. Neighboring group interactions are discussed with reference to the intrinsic properties of benzoic acid and phenyl acetate. The intrinsic conformational preference energies for benzoic acid and phenyl acetate are not additive. The acid s-trans preference energies differ by as much as 9 kcal/mol depending on the Ph—COOH and ester conformations. Similarly, the E-preference energies about the Ph—COOH bond vary by as much as 6 kcal/mol depending on the ester conformation. The structural discussion suggests an overall ortho repulsion between the functional groups in all aspirin isomers including the intramolecularly hydrogen-bonded isomers. The isodesmic reaction between the most stable conformers of benzoic acid and phenyl acetate is found to be endothermic by 2.7 kcal/mol and provides very compelling evidence for and a quantitative measure of ortho repulsion. The ortho repulsion of 2.7 kcal/mol is a lower limit, and the ortho repulsion can increase to as much as 6 kcal/mol in some aspirin isomers.

Introduction

Aspirin hardly needs an introduction.1–4 Acetylsalicylic acid was first synthesized by Bayer in 1897, and it was named Aspirin in 1899. The analgesic and antipyretic effects of salicylic acid had already been known. In the 18th century, Stone discovered the medical effects of the salicyc of willow bark, and salicylic acid was eventually recognized as the active ingredient. Salicin is enzymatically hydrolyzed to saligenin and glucose by β-glucosidase.5 Saligenin is then slowly oxidized to salicylic acid in the blood and in the liver.6 The medicinal effects of salicin require several hours to be felt and are then sustained for several hours. Salicin is available as an antirheumatic and analgetic drug under the trade name Assalix.7 More immediate effects can be achieved by ingestion of salicylic acid or its salts. The sodium salt of salicylic acid was used as a painkiller in the 19th century, even though salicylic acid caused stomach irritations, while salicin is entirely harmless to the gastrointestinal tract. Searching for less-irritating derivatives of salicylic acid, the Bayer chemist Felix Hoffmann synthesized acetylsalicylic acid (Scheme 1).

Aspirin turned out to be an extraordinary success. In a 1994 article8 of the Medical Sciences Bulletin it was written that “Americans consume about 80 billion aspirin tablets a year, and more than 50 nonprescription drugs contain aspirin as the principal active ingredient.” The Aspirin Foundation of America provides scientific, regulatory, legislative, and general educational information about aspirin to the medical community and the public, and this information can be accessed via the Internet.9

In 1971, Vane discovered that aspirin interferes with the biosynthesis of prostaglandins, and in 1982, he was awarded the Nobel Prize in medicine in recognition of

(2) Many facts about aspirin can be found at Bayer’s Aspirin web site at URL http://www.bayer.de.
(9) Home page of the “Aspirin Foundation of America” at URL http://www.aspirin.org/.
Garavito et al.\textsuperscript{10,11} discovered how aspirin interferes with prostaglandin synthesis. The biosynthesis of prostaglandins depends on the enzymes cyclooxygenase 1 (COX-1, aka PGH\textsubscript{2} synthase 1) and cyclooxygenase 2 (COX-2, aka PGH\textsubscript{2} synthase 2), and aspirin is an inhibitor of COX-1 and COX-2.\textsuperscript{12} COX-1 is employed for normal, physiological prostaglandin synthesis, and COX-2 makes prostaglandins in inflammatory cells. Aside from pain signaling, prostaglandins also are involved in a variety of other processes including platelet aggregation.

forms inversion-symmetric, hydrogen-bonded carboxylic acid dimers. Note that two positions are shown in Figure 1 for each of the hydrogen-bonding H-atoms (A). The crystal structure of aspirin thus suggests a carboxylic acid group in the s-trans conformation and about equal stabilities of the two Ph-COOH rotational isomers in the dimer. Aspirin also is involved in a second type of inversion-symmetric dimer, a dimer bonded by way of perfect dipole–dipole antiparallel alignment of the carboxyl groups of two ester functions (B). Each aspirin molecule partakes in a dimer of each kind, as shown in C, and one-dimensional extended chains result. Model D shows the arrangement of the chains in the crystal.

There are no benzene–benzene contacts; the lattice architecture optimizes dipole–dipole interactions, and arene–arene quadrupole–quadrupole interactions do not play a significant role. This crystal structure is the only crystal structure of aspirin, and no other polymorphs have been observed as yet.\textsuperscript{17} In light of these strong and directed specific interactions of aspirin in the solid state, it is clear that the X-ray data a priori do not allow for deductions as to the preferred conformation of molecular aspirin. The molecular structure of aspirin, surprisingly, has not received the attention one might reasonably expect. We are aware of only two ab initio studies of aspirin,\textsuperscript{17,18} and we will refer to these studies in the following discussion.

In this paper, we report on the conformational preferences of aspirin. We begin with a description of the...
Theoretical and Computational Methods

All structures were first optimized at the restricted Hartree-Fock level, RHF, of ab initio theory19 without any symmetry constraints, C1, and using gradient methods.20 For every structure, accurate second derivatives of the energy were computed to ascertain that a stationary structure had indeed been located and to obtain thermochemical data. The structure was refined subsequently using density functional theory, which is a cost-effective method to approximate electron correlation effects. We employed the B3LYP functional, which combines Becke’s three-parameter exchange functional21 with the correlation functional of Lee, Yang, and Parr.22,23 These are both nonlocal functionals whose combination is widely used and accepted. We will discuss the B3LYP/6-31G* structures in all subsequent discussions.

The π-density of the phenyl group presents a polarizable medium4 and may be sensitive to induced polarization. The C–O, C=O, and O–H bonds all are highly polar, and intramolecular polarization may be an important mechanism of electronic relaxation and stabilization. The split-valence and polarized 6-31G* basis set was employed in the geometry optimizations, and the vibrational analyses and this basis set can be expected to provide reliable results. We also carried out single-point calculations with the larger basis set 6-311G**. This basis set describes each valence atomic orbital with three basis functions and contains polarization functions on all atoms.

Total and relative energies are listed in Table 1. We report the total energies and the results of the vibrational analyses. The relative energies E_rel are given in kcal/mol with respect to the most stable isomer. Selected structural parameters are given in Figures 2–8, and complete structures are contained in the Supporting Information. Correlation effects on relative energies are significant (up to 4 kcal/mol), and they tend to reduce the relative energies; compare the RHF/6-31G* and B3LYP/6-31G* data in Table 1. Correlation effects on structures are minor; larger variations occur only for internal coordinates that are associated with very low curvatures (e.g., dihedral angles), and Table 1 shows that the relative energies computed at B3LYP/6-31G**//RHF/6-31G* and at B3LYP/6-31G* are virtually the same. Moreover, the relative energies computed with the larger basis set, B3LYP/6-311G**//RHF/6-31G* and B3LYP/6-311G**//B3LYP/6-31G*, are also virtually the same. In fact, all relative energies computed with the

(b) Leach, A. R. Molecular Modelling; Addison-Wesley Longman Limited: Essex, England, 1996.


Table 1. Total and Relative Energies of Aspirin, Benzonic Acid (BA), and Phenyl Acetate (PA)

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Theoretical and computational aspects of the potential energy surface analysis. Next, we describe the intrinsic features of benzoic acid and of phenyl acetate to lay a foundation for the discussion of aspirin. Then we report and describe the conformational isomers of aspirin, and we present a discussion of the structural effects of neighboring group interactions in aspirin. In the last section, we present and discuss conformational preference and energy and we establish the nonadditivity of these neighboring group interactions in aspirin. In the last section, we present and discuss conformational preference and energy and we establish the nonadditivity of these neighboring group interactions in aspirin. In the last section, we present and discuss conformational preference and energy and we establish the nonadditivity of these neighboring group interactions in aspirin. In the last section, we present and discuss conformational preference and energy and we establish the nonadditivity of these neighboring group interactions in aspirin.
The relative energies are determined with the total energies alone, that is, without any consideration of the thermal motions of the molecules. Even at 0 K, molecules vibrate, and all of the vibrational modes are in their vibrational ground states (ν = 0) and they add vibrational zero-point energy (VZPE) to the energy content of a molecule. At higher temperatures, the vibrational energy increases since some vibrational modes are excited because of translational and rotational motions. All of these contributions are collected in the thermal energy (TE) term in Table 1, and these terms are computed for standard room temperature (298.15 K). The enthalpies (H) also were evaluated. Hence, we can compute a free enthalpy for every molecule G = E_{total} + TE − 0.001TS, and the G_{rel} values are the differences with respect to the most stable isomer. We have not applied any scaling to the thermal energies. Vibrational frequencies are overestimated by about 10%, and they require scaling. Differences between vibrational zero-point energies and thermal energies, however, are hardly affected by the scaling. As can be seen from the data presented in Table 1, the relative free enthalpies G_{rel} closely parallel the relative total energies E_{rel}. We will be discussing relative total energies throughout the following discussion.

All calculations were carried out with the program Gaussian 94 on a Silicon Graphics PowerChallenge L minisupercomputer with 8 R10000 processors.

Results and Discussion

Intrinsic Features of Benzoic Acid and Phenyl Acetate. In Scheme 2 are depicted the Lewis structures of the s-cis and s-trans isomers of benzoic acid and of phenyl acetate. These rotational isomers are due to the hindered rotation about the C–O single bond of the carboxyl groups in carboxylic acids and esters.26 The s-cis,s-trans nomenclature of R–CO–OR’ describes whether R and R’ are on the same or opposite sides of the C–O bond, respectively. With a view to the resonance form that contains a C=O double bond between the carbonyl carbon and the OR’-oxygen, one might alternatively employ the E,Z nomenclature to describe the rotational isomers. The s-cis conformation thus corresponds to the E structure. We employ both of these nomenclatures, and we will employ them even if the respective groups are no longer coplanar.

The structure of s-trans benzoic acid is planar (Figure 2). A few remarks about bond angles of this structure are useful as reference values for the following discussions. Note first that α = ∠(C–C–O) = 125.0° is much larger than β = ∠(C–C–O) = 113.0°, and the difference between these angles is Δ = 12.0°. The ∠(O–C–O) angle is 121.9° in s-trans-benzoic acid, and this angle shows little variation; all the ∠(O–C–O) angles fall within the narrow range of 119.8°–121.9°. Because of this small variation of ∠(O–C–O) and because the angle is close to 120°, it can be seen that the space demand of the “C=O” fragment is higher than the space demand of the “HO–C” fragment of the carboxyl group. The angles γ and ε are a second pair of angles that are useful for the description of neighboring group effects. These are the ∠(C_{ortho}–C_{ipso}–C) angles and γ is the angle measured on the side of the carboxyl group whereas ε is measured on the side of the hydroxyl group. The angles γ and ε are within 4° for s-trans-benzoic acid (Figure 2), but more significant differences occur in the other isomers.

The structure of s-cis-benzoic acid is nonplanar because the carboxyl group is twisted with respect to the benzene plane by ∠(HO–C–C–C) = 22.2°. Obviously, this distortion serves to reduce steric H,H-repulsion between the hydroxy-H- and the O-atoms at the cost of reduced conjugation between the benzene and the carboxyl group (Scheme 3). But this nonplanarity is only one of the structural manifestations of this H,H-repulsion. The entire COOH group is bent in a way so as to reduce the H,H-repulsion, and this is accomplished by angular distortions: α is reduced, β is very much increased, γ is reduced, and ε is increased.

While sterical H,H-repulsion probably is the main reason for the twisting of s-cis-benzoic acid, there might also be some attractive features associated with this twisting to keep the relative energy comparatively low. Benzyl alcohol prefers the so-called endo structure in which the alcohol function is significantly moved out of the benzene plane, and the O–H bond points toward the region of the benzene π-density.27 This same feature occurs in s-cis-benzoic acid and will be seen again in all of the acid s-cis aspirin molecules except for those with an intramolecular H-bonding opportunity.


The C–O s-trans and s-cis isomers of phenyl acetate are shown in Figure 3. The former is more stable by $E_{\text{rel}} = 4.49$ kcal/mol. The most important structural feature of both phenyl acetates concerns the fact that the ester group is (almost) perpendicular with respect to the benzene plane (Figure 3). This is very different from phenyl alkyl ethers. Methoxybenzene, for example, assumes a C–O conformation that places the methyl C-atom in the benzene plane. The reason for the non-planarity of the s-trans isomer of phenyl acetate is by no means obvious while one could invoke steric factors to explain the avoidance of planarity in the case of the s-cis isomer. At the same time, there also is no obvious driving force that would provide a benefit for the planar structure.

Conjugation is not a reason for the assumption of a planar structure, and this is illustrated in Scheme 4; no resonance forms can be written that place positive charge on the benzene atoms. The actual structure of s-trans-phenyl acetate orients the acetate dipole moment toward the phenyl moiety (see side view in Figure 3), and it is possible that this structure benefits from intramolecular polarization. The structure of s-trans-phenyl acetate does not possess any symmetry plane and it is chiral. The ester and benzene planes are almost perpendicular in the RHF structure ($\angle(C–O–C–C) = 72.9^\circ$), and the deviation from orthogonality is larger in the B3LYP structure ($\angle(C–O–C–C) = 47.6^\circ$). The structure of s-cis-phenyl acetate does...
possess a plane of symmetry, the plane containing the ester group and bisecting the benzene ring.

**Conformational Isomers of Aspirin.** The conformational space of aspirin requires three labels to describe the C\(^{-}\)O conformation of the carboxylic acid, the C\(^{-}\)COOH conformation, and the C\(^{-}\)O conformation of the ester. The C\(^{-}\)COOH conformation describes the orientation of the carboxyl group relative to the acetate substituent. We use numbers to describe structures that differ with regard to their acid C\(^{-}\)O conformation and/or C\(^{-}\)COOH conformation. And we add the letter "a" and "b" to the structures to indicate the ester C\(^{-}\)O conformation; in Figures 4–7, the "a" and "b" structures are shown to the left and right, respectively. Structures 1 and 2 have the s-trans conformation with regard to the acid C\(^{-}\)O bond; that is, the hydroxyl-H atom and the phenyl group are in a trans arrangement with regard to the C\(^{-}\)OH single bond and they are shown in Figures 4 and 5. Structures 3–5 feature carboxylic acid groups with C\(^{-}\)O s-cis conformations, and they are shown in Figures 6–8. The two s-trans structures 1 and 2 are rotational isomers with regard to the Ph\(^{-}\)COOH bond. In structure 1, the hydroxyl group is as far away from the ester neighboring group as possible while the hydroxyl group is on the side of the ester functional group in 2. The stereochemical relation between 3 and 4 is the same as that between 1 and 2. In Table 1, we provide the three E,Z descriptors characterizing each structure, and these labels refer to the acid C\(^{-}\)O conformation, the Ph\(^{-}\)COOH conformation, and the ester C\(^{-}\)O conformation in that order. We begin the discussion with a consideration of the a structures, that is, the s-trans esters.

The isomers 3a and 4a show several interesting features. The carboxylic acid group of 3a is twisted with respect to the best plane of the benzene ring, and this distortion serves to reduce steric H,H-repulsion between the hydroxyl-H- and the o-H-atoms. The dihedral angle \(\angle (\text{HO-C-C-C})\) is 38.7°, and the pronounced deviation from planarity is well illustrated by the Newman projection of isomer 3a. The dihedral angle \(\angle (\text{H-O-C-C})\) remains close to 0°, and the O-H bond thus points toward the benzene π-cloud in a way that is reminiscent of benzyl alcohol\(^2\) (vide supra). The carboxylic acid group and the benzene ring also are not coplanar in the other isomer 4a but the torsion angle \(\angle (\text{O-C-C-C})\) = 9.5° is much less. Structure 4a allows for the formation of an intramolecular hydrogen bond between the hydroxyl H-atom and the phenolic O-atom of the ester. The hydrogen bond results in the formation of a six-membered ring, and the length of the H bond is 1.808 Å. As with 3a and 4a, structure 5a has the RCO\(^{-}\)OH s-cis conformation, and like 4a, this structure 5a has the acid hydroxyl group in proximity to the ester group and features an H bond between the neighboring groups. In contrast to 4a, however, it is the carbonyl-O atom that serves as the H-bond acceptor in 5a. The length of this H bond is 1.858 Å. The result of this H bonding is an eight-membered ring with a typical boat conformation.
For every one of the ester s-trans structures 1a–4a there exists an ester s-cis isomer 1b–4b. But there is no analogue 5b to 5a. We searched for a structure of type 5b beginning with an H-bonded structure with an eight-membered ring and with a chair conformation. All of these attempts at finding 5b led to 4b.

The 5b structures reveal an interesting conformational feature in that the carboxyl groups in 1b and 2b are no longer coplanar with the benzene rings! Twisting about the Ph–COOH bond is thus not limited to acid s-cis conformations and steric causes, but twisting can occur as the result of the presence of the ester group in the ortho position as the result of electrostatic effects. Any torsion about the Ph–COOH bond reduces the parallel alignment of the acid carbonyl group and the C–OCOMe bond and this distortion reduces dipole–dipole repulsion.

In their search for polymorphs of aspirin, Payne et al. assumed that the carboxy group remains coplanar with the benzene ring.17 Our results suggest that this assumption might not hold. We find significant twist angles in
all acid s-cis structures and also in some of the acid s-trans isomers.

**Structural Manifestations of Neighboring Group Interactions in Aspirin.** With the knowledge of the structures of benzoic acid and of phenyl acetate, one can compare the respective parameters in aspirin and analyze for neighboring group effects. It can be seen that the proximity of the neighboring groups leads to angular distortions in all aspirin structures that serve to increase the distance between the functional groups. In structure 1a these angular effects are small but clearly noticeable and they are cumulative. The carboxyl group is bent away from the ester; the γ-angle is greater than 120°, α = 126.7°, and this α-angle is even higher than in s-trans benzoic acid. Similarly, the ester is bent away from the carboxylic acid group. This bending can be described by the \( \angle(C-C-O) \) angle, and this angle \( \phi = 122.0^\circ \) in 1a. In structure 2a, the hydroxyl group is placed in proximity of the ester and the O,O-repulsion is much larger because β is intrinsically smaller than α (Figure 3). Consequently, a pronounced bending occurs of the carboxylic acid (e = 126.2°) and of the ester (\( \phi = 122.6^\circ \)) away from each other.

In light of the above discussion, the structural distortions in 3a can be recognized as the result of a balance between two driving forces, and these are the H,H- and O,O-repulsions. In s-cis-benzoic acid, the H,H-repulsion is minimized by a modest torsion by \( \angle(HO-C-C-C) = 22.2^\circ \) and a bending of the entire COOH group (vide supra). In 3a, such a bending is met by resistance by the concomitantly increasing O,O-repulsion between the carboxyl-O- and the phenolic O-atoms. An increase in the torsion angle becomes the best option, a reduction of H,H-repulsion is achieved while allowing for a minimization of the O,O-repulsion at the same time (\( \alpha, \gamma, \phi \) all are increased). The increase in the torsion reduces the possibility for conjugation between the benzene ring and the carboxyl group and this loss apparently is more than compensated for by the reduction in steric interactions. One may also note at this time that the ester group as a whole is an electron-withdrawing group and any donation from benzene to the carboxyl group should be diminished in aspirin as compared to benzoic acid (Scheme 3).

There is clear structural evidence for steric repulsion between the neighboring groups in the s-cis aspirin structure 4a. This statement might come as a surprise

**Figure 7.** Conformational isomers 4a and 4b of aspirin with s-cis conformation about the acid C–O bond and E-conformation about the C––COOH bond. Intramolecular H-bonding forms a six-membered ring.

**Figure 8.** Conformational isomers 5a of aspirin with s-cis conformation about the acid C–O bond and E-conformation about the C––COOH bond. Intramolecular H-bonding forms an eight-membered ring.
to many because the intramolecular H-bond is usually considered as bonding between the neighboring groups. It is better to view this H-bond as an attractive component of an overall repulsive neighboring group interaction. The ϕ- and ω-angles are greatly widened in 4a. Even with these angles widened, the O,O-distance between the H-bond acceptor and hydroxy-O-atoms remains too short to realize a coplanar and as much as possible linear H-bonding geometry. As far as the conformation of the ester group is concerned, it can be seen that the dihedral angle \( \angle(C-O-C-C) \) is 127.2° in 4a while this dihedral is between 60° and 80° for 1a–3a. All of these angles deviate from 90° by about the same amount and in opposite directions and this magnitude of the deviation from perpendicular is mostly intrinsic. The direction of the C–OOCMe twist is easily rationalized considering the orientation of the lone pairs of the phenolic O-atom. In 1a–3a the twist reduces O,O-lone pair repulsion while one of the phenol O-lone pairs is oriented to optimize this atom's H-bond acceptor capability in 4a.

The same structural arguments apply to the structure 5a and they also apply in complete analogy to the ester C–O bond conformational isomers 1b–4b. In all cases, the structural characteristics indicate neighboring group repulsions.

**Conformational Preference Energies of Aspirin.**

The most stable aspirin isomer is structure 1a and the energies of all other structures are given relative to this isomer. The s-trans structure 2a is only slightly less stable with \( E_{rel} = 0.90 \text{ kcal/mol} \). On the other hand, all of the s-cis structures 3a–5a are significantly less stable than either one of the s-trans isomers. The least stable s-cis structure is isomer 3a with \( E_{rel} = 6.41 \text{ kcal/mol} \). Benzoic acid itself shows an s-trans preference energy of 7.12 kcal/mol. Hence, the s-trans preference energy is diminished slightly by the presence of the ester group. The two other s-cis structures both benefit from intramolecular H-bonding with the ester group; 4a and 5a have relative energies of 2.83 and 4.02 kcal/mol, respectively, and they are almost isoequic. One would be tempted to suggest that the H-bonding energies thus are about 3 kcal/mol. However, this deduction would assume that the s-trans preference is the same for rotational isomers about the C–COOH bond, and that assumption is probably not true.

The ester s-trans preference energy of phenyl acetate is 4.49 kcal/mol, and we find ester s-trans preference energies for every (a,b)-pair of 1–4. But the ester s-trans preference energies are rather isomer-sensitive: 1b vs 1a 5.35 kcal/mol, 2b vs 2a 4.64 kcal/mol, 3b vs 3a 8.27 kcal/mol, and 4b vs 4a 4.20 kcal/mol. The s-trans preference energies differ by as much as 4 kcal/mol. Even the most stable s-cis ester remains more than 5 kcal/mol less stable than the best s-trans ester 1a.

The Z-preference energy about the Ph–COOH bond is about 1 kcal/mol in favor of 2a over 1a. In the ester C–O s-cis isomers, this Z-preference energy drops to almost nothing and Z–1b is favored over E–2b by only 0.2 kcal/mol. For the structures that allow for intramolecular hydrogen bonding in the E-conformation, there exists an E-preference with regard to the Ph–COOH bond. This E-preference is about 3.6 kcal/mol for 4a over 3a, and it is about 7.7 kcal/mol in favor of 4b over 3b. Clearly, nonadditivity is a major issue in this case as well.

In their vibrational analysis of aspirin, Binev et al. computed a structure of type 2b. Our results suggest that

**Neighboring Group Interaction Energy.** We have argued above on structural grounds that the overall neighboring group interaction between the carboxylic acid and the ester groups is repulsive. We have also argued that this remains true even in the presence of the attractive H-bonds in 4 and 5. The conformational preference energies show that 4 and 5 are less stable than other isomers and that simple fact shows immediately that there is more neighboring group repulsion in 4 and 5 than in 1 and 2. Binev et al. reported previously that the ortho repulsion is more effective than the H-bond formation.

The remaining task is the quantification of the neighboring group interaction in the most stable isomer of aspirin, 1a. We considered the formal reaction between s-trans-benzoic acid and s-trans-phenyl acetate to form aspirin isomer 1a and benzene, and we found this isodesmic reaction to be endothermic by 2.65 kcal/mol! Hence, the neighboring group interaction is a neighboring group repulsion in all isomers.

**Conclusion.**

The aspirin molecule in the crystal structure exhibits the conformation of the most stable aspirin isomers 1a and 2a. The small energy difference of about 1 kcal/mol between 1a and 2a explains why the doubly H-bonded aspirin dimer shows rapid H-position exchange. The torsion angle between the benzene and ester planes is enlarged in the crystal; this adjustment optimizes the ester–ester dipole–dipole interaction with hardly any energetic disadvantage for aspirin. Since all other conformers of aspirin are substantially higher in energy, the only hope for an aspirin polymorph essentially consists of packing isomers of 1a and 2a and there are no obvious alternatives. When it comes to aspirin–enzyme interactions, many more conformational options are possible. In particular, the ester carboxyl-oxygen presents a strong H-bond acceptor, and its specific interaction with a suitable enzyme H-donor group might well make accessible the ester s-cis conformational space of aspirin to enzyme binding. Our study reveals very clearly the nonadditivity of the preference energies for the individual conformational options.

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**Supporting Information Available:** Pdb files of stationary structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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