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 to form aspirin and benzene is found to be endothermic by 2.7 kcal/mol and provides 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 previously been known. In the 18th century, Stone discovered the medical effects of the salicin 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 salicyclic 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 article[8] 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 interfers with the biosynthesis of prostaglandins, and in 1982, he was awarded the Nobel Prize in medicine in recognition of

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(2) Many facts about aspirin can be found at Bayer's Aspirin web site at URL http://www.aspirin.de.

(3) Aspirin, Molecule of the Month, February 1996. Featured as the second molecule at the MOTM site at URL http://www.bris.ac.uk/Depts/Chemistry/MOTM/aspirin/aspirin.htm.

(4) Moore, N.; Van Ganse, E.; Le Parc, J. M.; Wall, R.; Schneid, H.; Farhan, M.; Verrière, F.; Pelen, F. The PAIN Study: Paracetamol, Aspirin and Ibuprofen. *Clin. Drug Invest.* **1999**, *18*, 89.

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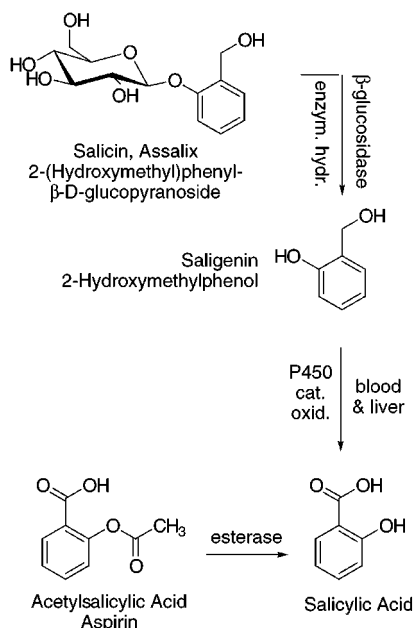
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(9) Home page of the "Aspirin Foundation of America" at URL http://www.aspirin.org/.

Scheme 1. Salicin, Saligenin, Salicylic Acid, and Aspirin

Salicin, Assalix
2-(Hydroxymethyl)phenyl-
β-D-glucopyranoside

β-glucosidase | enzym. hydr.

Saligenin
2-Hydroxymethylphenol

P450 cat. oxid. | blood & liver

Acetylsalicylic Acid
Aspirin

esterase

Salicylic Acid

Figure 1. Hydrogen-bonding and dipole alignment in the crystal structure of aspirin.

this work on the mechanism of action of aspirin. More recently, Garavito et al.[10,11] discovered how aspirin interfers with prostaglandin synthesis. The biosynthesis of prostaglandins depends on the enzymes cyclooxygenase 1 (COX-1, aka PGH_2 synthase 1) and cyclooxygenase 2 (COX-2, aka PGH_2 synthase 2), and aspririn is an inhibitor of COX-1 and COX-2.[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. With the knowledge of the structures of the enzymes, it is now possible to investigate in detail their interaction with aspirin. For example, the work by Lool, Picot, and Garavito[11b] showed that the closely related bromoaspirin bromoacylates Ser-530 of COX-1 while salicylic acid binds to Tyr-355 and Arg-120. Note that no structure has been determined of an intact aspirin (or a close relative) bound to a COX enzyme.

The crystal structure of aspirin was determined first by Wheatley,[13] and it was later refined by Kim et al.[14] We obtained the crystal structure data from the Cambridge Crystallographic Database,[15] and some of the key features of this crystal structure are depicted in Figure 1. Packing diagrams of aspirin can be found in a recent article on the crystal morphology of aspirin.[16] Aspirin
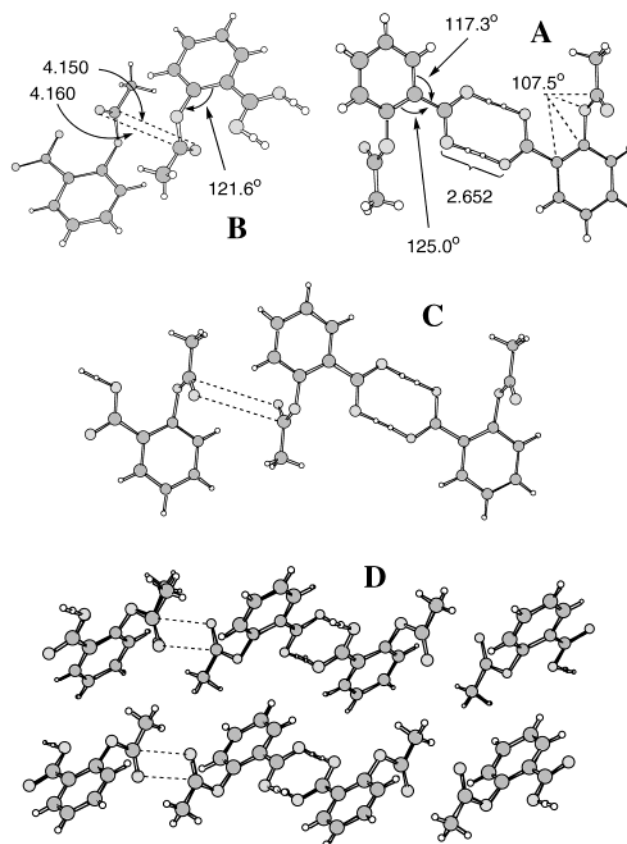
forms inversion-symmetric, hydrogen-bonded carboxylic acid dimers. Note that *two* positions are shown in Figure 1 for each of the hydrogen-bonding H-atoms (**A**). The crystal structure of aspirin thus suggests a carboxylic acid group in the *s-trans* conformation and about equal stabilities of the 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 carbonyl 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.[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,[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

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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 energies and we establish the nonadditivity of these preference energies. In particular, we present compelling evidence that the neighboring group interactions are repulsive irrespective of the presence or absence of intramolecular hydrogen-bonding.

Theoretical and Computational Methods

All structures were first optimized at the restricted Hartree−Fock level, RHF, of ab initio theory[19] without any symmetry constraints, C_1, 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 structures were 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 functional[21] 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 medium[24] 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*, also are virtually the same. In fact, all relative energies computed with the

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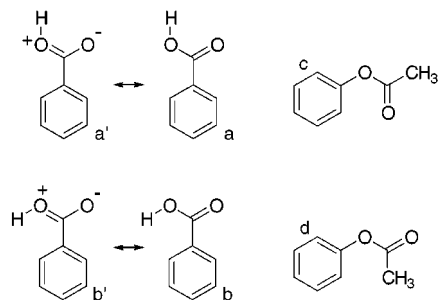
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Table 1. Total and Relative Energies[a−g] of Aspirin, Benzoic Acid (BA), and Phenyl Acetate (PA)

molecule	RHF/6-31G*						B3LYP/6-31G*// RHF/6-31G*		B3LYP/6-31G*		B3LYP/6-311G**// RHF/6-31G*		B3LYP/6-311G**// B3LYP/6-31G*	
	total energy	VZPE	TE	S	E_{rel}	G_{rel}	total energy	E_{rel}	total energy	E_{rel}	total energy	E_{rel}	total energy	E_{rel}
1a, Z,Z,Z	−644.964999	106.56	113.44	105.37	0.00	0.00	−648.689119	0.00	−648.694769	0.00	−648.870344	0.00	−648.873620	0.00
2a, Z,Z,E	−644.963268	106.53	113.45	106.33	1.09	0.81	−648.687844	0.80	−648.693470	0.82	−648.868963	0.87	−648.872190	0.90
3a, E,Z,Z	−644.952872	106.35	113.30	105.26	7.61	7.50	−648.678827	6.46	−648.684588	6.39	−648.860015	6.48	−648.863408	6.41
4a, E,Z,E	−644.955798	106.62	113.52	106.19	5.77	5.61	−648.683874	3.29	−648.690050	2.96	−648.865361	3.13	−648.869113	2.83
5a, E,Z,E	−644.955477	106.64	113.51	104.58	5.98	6.28	−648.682817	3.95	−648.688904	3.68	−648.863630	4.21	−648.867216	4.02
1b, Z,E,Z	−644.953965	106.51	113.37	104.58	6.92	7.09	−648.680875	5.17	−648.686678	5.08	−648.861657	5.45	−648.865089	5.35
2b, Z,E,E	−644.953554	106.58	113.35	105.02	7.18	7.20	−648.680593	5.35	−648.686404	5.25	−648.861403	5.61	−648.864796	5.54
3b, E,E,Z	−644.935696	106.19	113.19	106.96	18.39	17.66	−648.665828	14.62	−648.671611	14.53	−648.846877	14.73	−648.850228	14.68
4b, E,E,E	−644.947962	106.60	113.44	105.47	10.69	10.66	−648.677839	7.08	−648.683815	6.87	−648.858840	7.22	−648.862413	7.03
BA, s-trans	−418.325327	78.23	82.41	82.74	0.00	0.00	−420.818713	7.30	−420.822146	0.00	−420.93740	0.00	−420.939266	0.00
BA, s-cis	−418.311173	78.04	82.27	83.00	8.53	8.31	−420.807081	7.30	−420.810572	7.26	−420.925997	7.16	−420.927925	7.12
PA, s-trans	−457.346875	95.89	101.23	95.08	0.00	0.00	−460.121724	0.00	−460.125547	0.00	−460.244654	0.00	−460.247088	0.00
PA, s-cis	−457.338335	95.96	101.19	92.16	5.36	6.19	−460.115464	3.93	−460.118802	4.23	−460.237945	4.21	−460.239925	4.49
benzene	−230.703137	67.56	70.13	68.11			−232.247487		−232.248668		−232.307885		−232.308503	

[a] Total energies in atomic units. *[b]* All thermochemical data are reported as computed and unscaled. *[c]* Vibrational zero-point energies (VZPE) in kcal/mol computed for standard temperature (298.15 K). *[d]* Thermal energies (TE) in kcal/mol. *[e]* Entropies (S) in cal mol^{-1} K^{-1} computed for standard temperature. *[f]* Relative energies (E_{rel}) in kcal/mol specify differences in total energy. *[g]* Relative free enthalpies (G_{rel}) in kcal/mol.

Scheme 2. Single-Bond Rotational Isomers of Benzoic Acid and of Phenyl Acetate[a]

[a] Structures a, a′, and c are *s-trans* and structures b, b′, and d are *s-cis* isomers.

B3LYP method, using either basis set and with either one of the optimized structures, differ less than 0.5 kcal/mol. In the following discussion all relative energies are those determined at the highest level employed, B3LYP/6-311G**//B3LYP/ 6-31G*.

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 ($v = 0$) and they add vibrational zero-point energy (VZPE) to the energy content of a molecule. At higher temperatures T, the vibrational energy increases since some vibrational modes are excited and 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 contributions of vibrational, rotational and translational motions to the molecular entropy (S) also were evaluated. Hence, we can compute a free enthalpy for every molecule $G = E_{total}$ + TE − $0.001 TS$, 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[25] 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

Scheme 3. Resonance Forms of *s-trans*-Benzoic Acid
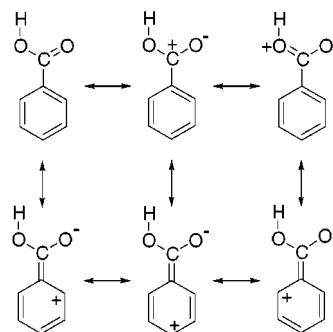
carbonyl carbon and the OR′-oxygen, one might alternatively employ the *E,Z* nomenclature to describe the rotational isomers. The *s-cis* conformation thus corresponds to the *E* structure. We employ both of these nomenclatures, and we will employ them even if the respective groups are no longer coplanar.

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 $\alpha = \angle(C−C=O) = 125.0°$ is much larger than $\beta = \angle(C−C−O) = 113.0°$, and the difference between these angles is $\Delta = 12.0°$. The $\angle(O−C−O)$ angle is 121.9° in *s-trans*-benzoic acid, and this angle shows little variation; all the $\angle(O−C−O)$ angles fall within the narrow range of 119.8°−121.9°. Because of this small variation of $\angle(O−C−O)$ 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 $\angle(C_{ortho}−C_{ipso}−C)$ angles and γ is the angle measured on the side of the carbonyl 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 $\angle(HO−C−C−C) = 22.2°$. Obviously, this distortion serves to reduce steric H,H-repulsion between the hydroxyl-H- and the *o*-H-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 steric 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.

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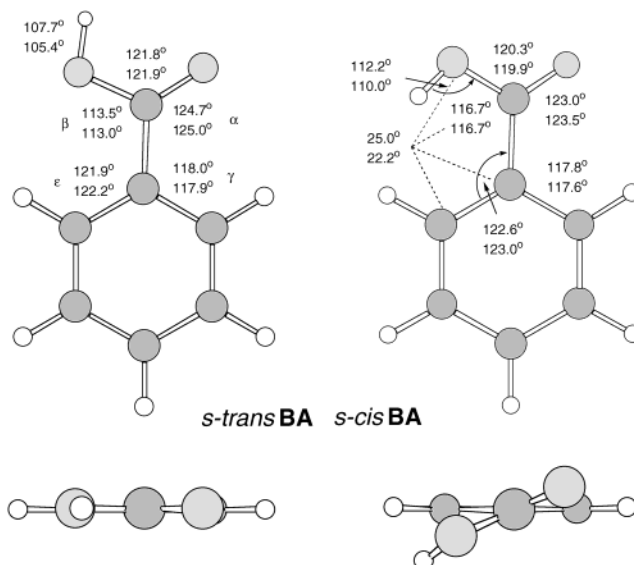(27) Glaser, R.; Nichols, G. R. *J. Org. Chem.* **2000**, *65*, 755−766.

Figure 2. Conformational isomers of benzoic acid. The molecular models are depicted with the benzene planes coinciding with the paper plane and Newman projections are shown on the bottom.
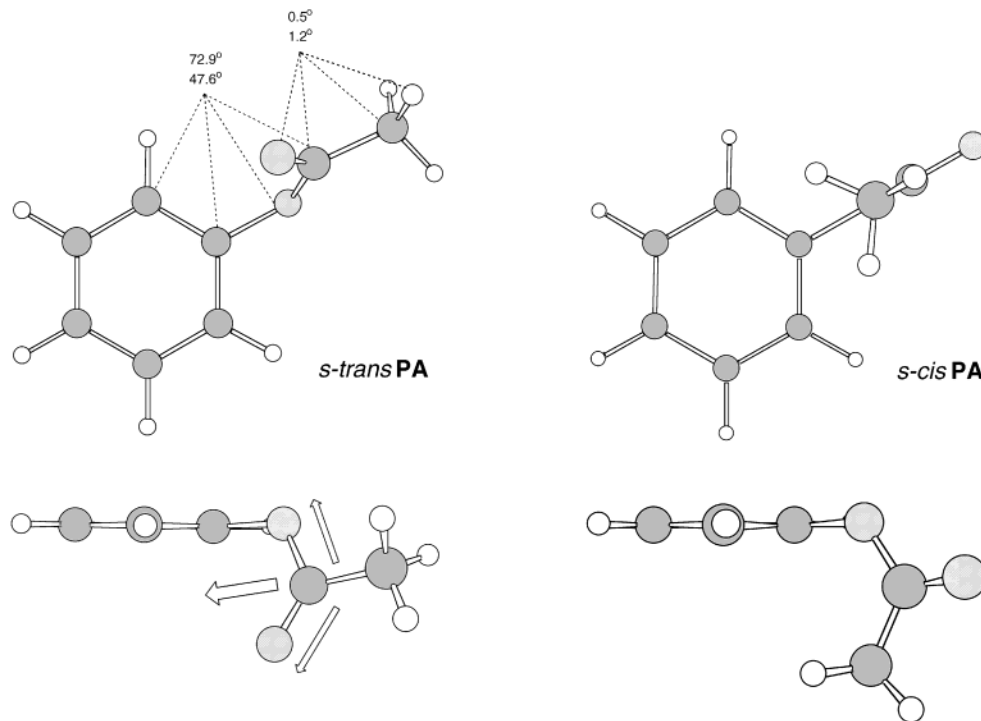

Figure 3. Conformational isomers of phenyl acetate. In each case, the molecular model was rotated by 30° about the horizontal axis and a Newman projection is shown on the bottom.

The C—O *s-trans* and *s-cis* isomers of phenyl acetate are shown in Figure 3. The former is more stable by E_{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 nonplanarity of the *s-trans* isomer of phenyl acetate is by no means obvious while one could invoke sterics 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) is 72.9°), and the deviation from orthogonality is larger in the B3LYP structure ($\angle$(C—O—C—C) is 47.6°). The structure of *s-cis*-phenyl acetate does
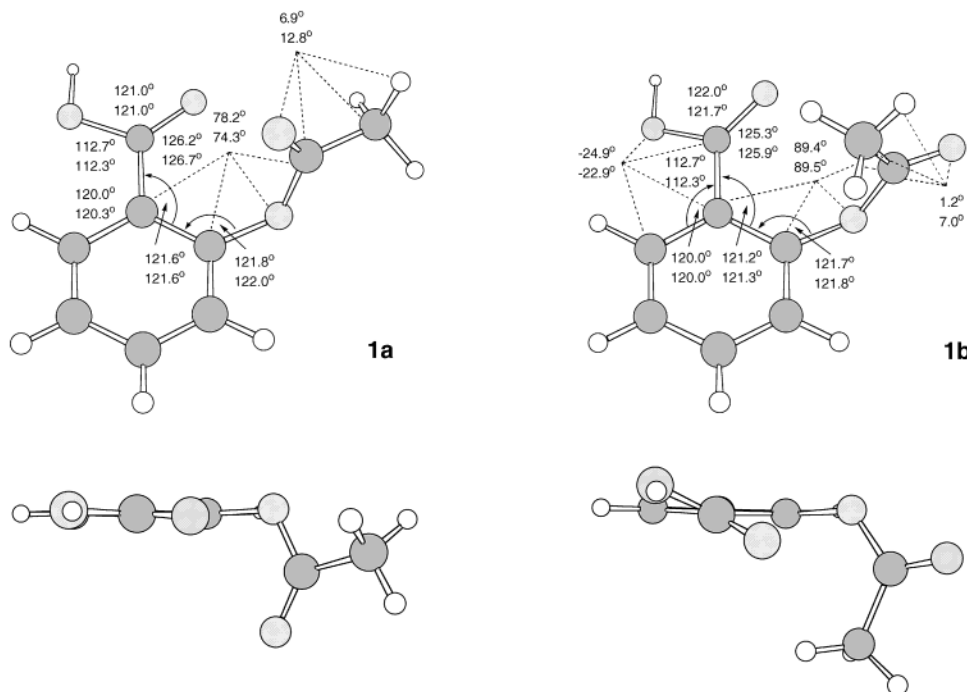
Figure 4. Conformational isomers **1a** and **1b** of aspirin with *s-trans* conformation about the acid C−O bond and *Z*-conformation about the C−COOH bond. Here and in the following figures, all molecular models are rotated by 30° about the horizontal axis and Newman projections are shown to the right. Selected structural parameters are given as determined at the levels RHF/6-31G* (top) and B3LYP/6-31G* (bottom).

Scheme 4.   Resonance Forms of Planar Phenyl Acetate
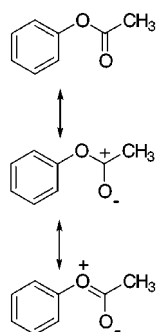
possess a plane of symmetry, the plane containing the ester group and bisecting the benzene ring.

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 substitutent. 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 ∠(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 ∠(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[27] (vide supra). The carboxylic acid group and the benzene ring also are not coplanar in the other isomer **4a** but the torsion angle of ∠(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.
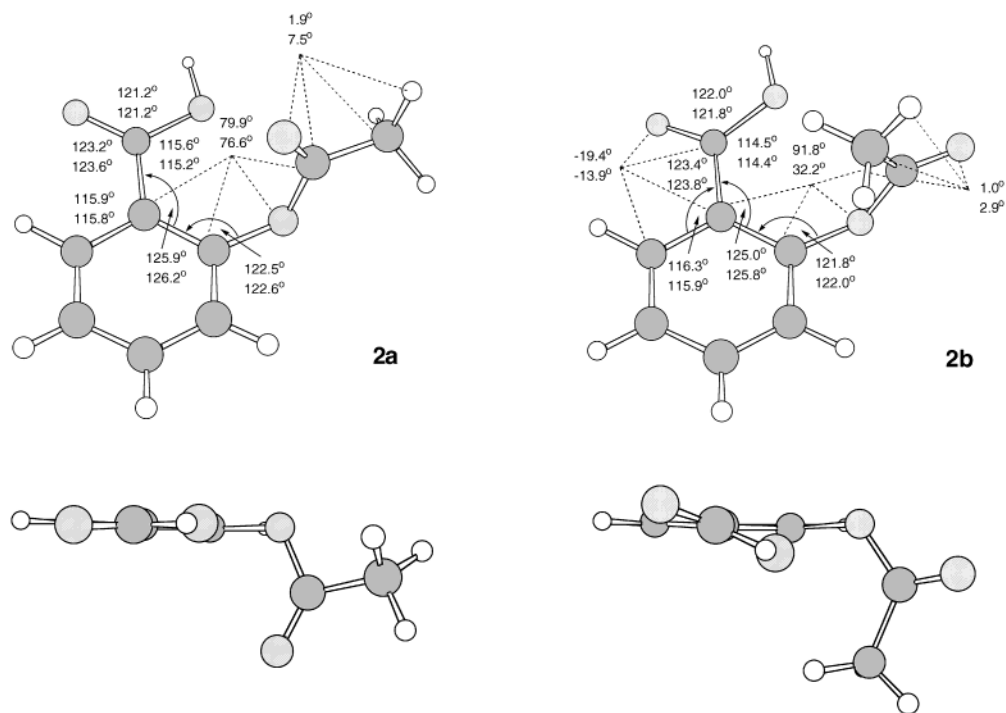
Figure 5. Conformational isomers **2a** and **2b** of aspirin with *s-trans* conformation about the acid C—O bond and *E*-conformation about the C—COOH bond.
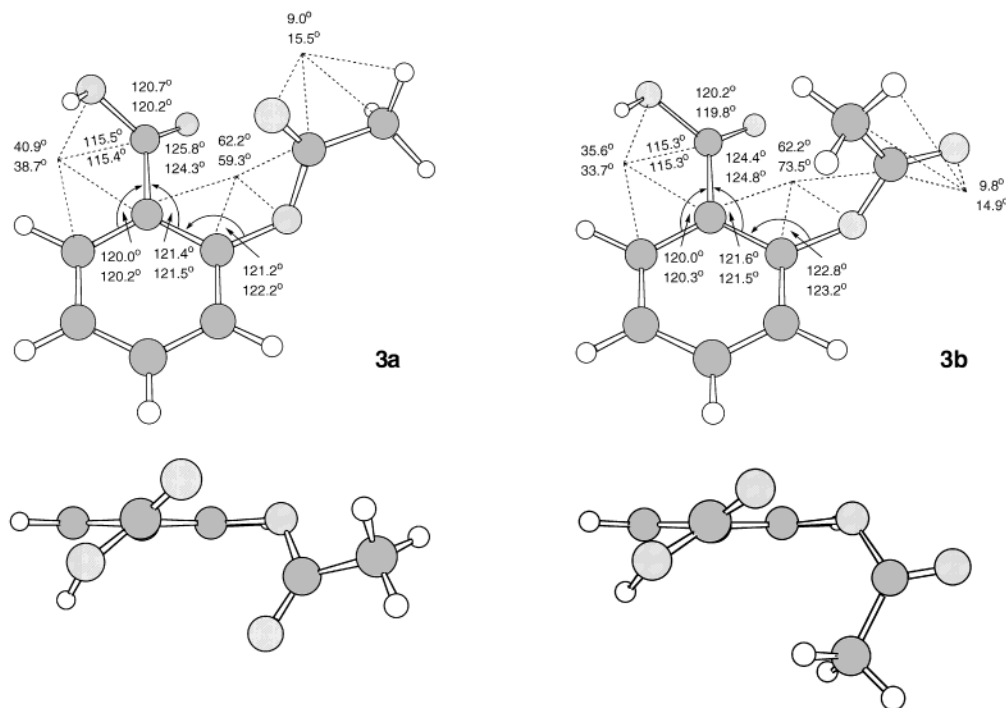

Figure 6. Conformational isomers **3a** and **3b** of aspirin with *s-cis* conformation about the acid C—O bond and *Z*-conformation about the C—COOH bond.

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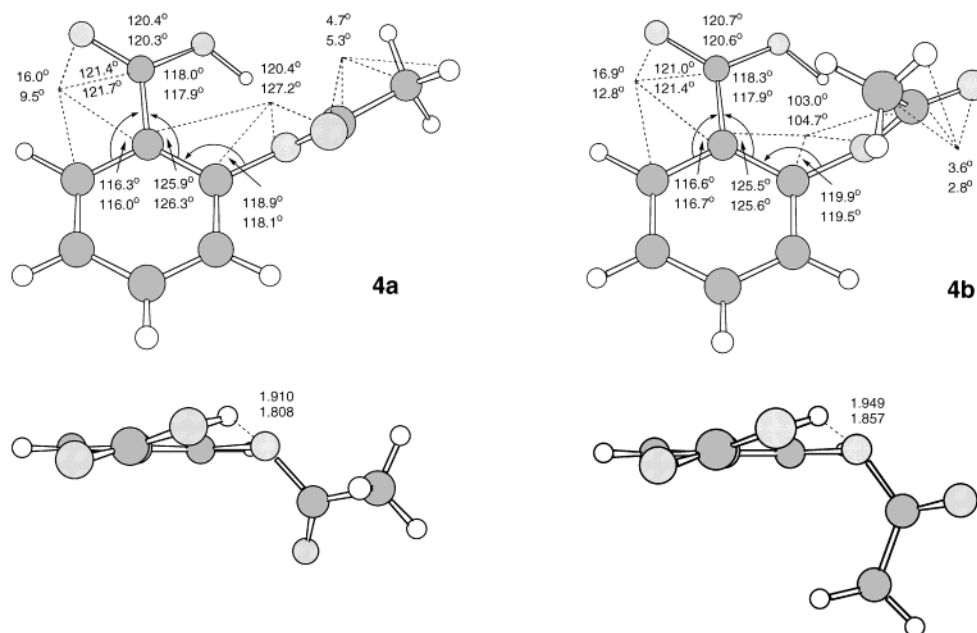
Figure 7. Conformational isomers **4a** and **4b** of aspirin with *s-cis* conformation about the acid C−O bond and *E*-conformation about the C−COOH bond. Intramolecular H-bonding forms a six-membered ring.
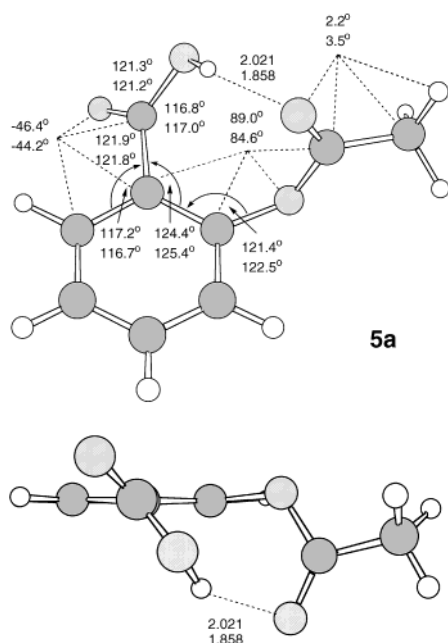

Figure 8. Conformational isomers **5a** of aspirin with *s-cis* conformation about the acid C−O bond and *E*-conformation about the C−COOH bond. Intramolecular H-bonding forms an eight-membered ring.

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.[28] 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°, $\alpha =$

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 ϕ, and this angle $\phi = 122.0°$ 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 ($\epsilon = 126.2°$) and of the ester ($\phi = 122.6°$) 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° 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 carbonyl-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 minimiation of the O,O-repulsion at the same time (α, γ, ϕ 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

(28) For related studies of neighboring group interactions involving a carboxyl group, see: (a) Glaser, R.; Horan, C. J. *Can. J. Chem.* **1996**, *74*, 1200−1214. (b) Horan, C. J.; Barnes, C. L.; Glaser, R. *Chem. Ber.* **1993**, *126*, 243−249. (c) Horan, C. J.; Haney, P. E.; Barnes, C. L.; Glaser, R *Acta Crystallogr.* **1993**, *C49*, 1525−1528. (d) Horan, C. J.; Barnes, C. L.; Glaser, R. *Acta Crystallogr.* **1993**, *C49*, 507−509. (e) Glaser, R.; Horan, C. J.; Nelson, E.; Hall, M. K. *J. Org. Chem.* **1992**, *57*, 215−228.

to many because the intramoleculer 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 neigboring group interaction. The β- and ϵ-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 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 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 isoenergetic. 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 *Z*-**1a** over *E*-**2a**. 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.[18] computed a structure of type **2b**. Our results suggest that **2b** is 5.54 kcal/mol less stable than **1a**. Binev et al. mentioned an H-bonded structure that was still 13.3 kcal/mol higher in energy, and this relative energy seems much too high. The *Molecule of the Month* featuring aspirin also displays an ester *s-cis* structure.[3]

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**. Binov et al. reported previously that the *ortho* repulsion is more effective than the H-bond formation.[18]

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[29] 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 carbonyl-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.

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

JO001241S

(29) (a) Ponomarev, D. A.; Takhistov, V. V. *J. Chem. Educ.* **1997**, *74*, 201−203. (b) Hehre, W. J.; Ditchfield, R.; Radom, L.; Pople, J. A. *J. Am. Chem. Soc.* **1970**, *92*, 4796−4801.