Effects of Substitution of OH Group by F Atom for Conformational Preferences of Fluorine-Substituted Analogues of (*R*,*R*)-Tartaric Acid, Its Dimethyl Diester, Diamide, and *N*,*N*,*N*′,*N*′-Tetramethyl Diamide. Ab Initio Conformational Analysis

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Received August 17, 1998. Revised Manuscript Received December 3, 1998

Abstract: High-level ab initio methods up to MP2/6-311++G**//RHF/6-31G* have been used to characterize the conformations of isolated molecules of (2*S*,3*S*)-2,3-dideoxy-2,3-difluorotartaric acid (FTA) and its dimethyl diester (FME), diamide (FAM), and *N*,*N*,*N*′,*N*′-tetramethyldiamide (FTMA). A wide range of possible structures (84 for FTA and 63 for FME, FAM, FTMA) has been surveyed at the RHF/3-21G level. At the highest level of theory, 23 conformers were located for FTA, 15 for FME, 9 for FAM, and 11 for FTMA. Electronic correlation has been included with the relatively large basis set 6-311G, augmented with polarization and diffuse functions, to calculate MP2/6-311++G**//RHF/6-31G* single-point energies for all the conformers. Frequency analysis and thermochemical calculations have been performed at the RHF/6-31G* level and the results have been utilized to assess gas-phase populations of conformers at 298 K for the studied molecules. Moreover, SM5.4 solvation model was used to assess Gibbs free energies of conformers both in water and in chloroform. The obtained results are compared to those from previous studies of (*R*,*R*)-tartaric acid and its derivatives and analyzed in terms of effects of substitution of the hydroxyl group by the fluorine atom. It seems that substitution of the OH group by an F atom leads to greater conformational diversity of the molecules studied, mainly because the F atom cannot act as a hydrogen bond donor. From our results, it appears that if hydroxyl groups of (*R*,*R*)-tartaric acid are involved in intermolecular interactions, like in crystals or polar solvents, then the conformational preferences of these compounds are similar to the conformational preferences of isolated molecules of their dideoxydifluoro analogues.

Introduction

Fluorine-substituted analogues of naturally occurring and biologically active organic compounds have become the focus of increasing interest.[1−9] They are thought to provide insight into the interactions between enzymatic binding sites and hydroxyl groups which are replaced by fluorine.[1,2] Thus, it has already become a common practice in bioorganic chemistry to replace a hydroxyl group with fluorine to generate a fluorinated enzyme substrate or inhibitor in a given enzymatic process.[3−7] The rationale for such a strategy stems from similarities between the F atom and the OH group, with particular reference to polarity as well as to the close isosteric relationship between fluorine and oxygen.[1,5,8] Consequently, the F atom is considered to be a good substitute of the OH group because it introduces a small steric disturbance, which is especially significant in molecules where conformational recognition is important.[9] Once the F atom is introduced, the high carbon−fluorine bond energy[10] renders the substituent relatively resistant to metabolic transformation.[9] Therefore, fluorinated analogues are potentially useful in studies of metabolism[1,11] and some of them in clinical diagnostics.[12−15]

In this paper, we report the results of high-level (up to MP2/6-311++G**//RHF/6-31G*) ab initio studies[16] on the conformations of (2*S*,3*S*)-2,3-dideoxy-2,3-difluorotartaric acid and its dimethyl diester, diamide, and *N*,*N*,*N*′,*N*′-tetramethyldiamide (Figure 1). These compounds are analogues of recently extensively studied (*R*,*R*)-tartaric acid derivatives,[17−24] in which both of the OH groups were replaced by F atoms.[25] (*R*,*R*)-Tartaric

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10.1021/ja982935+ CCC: $18.00
Published on Web 02/17/1999

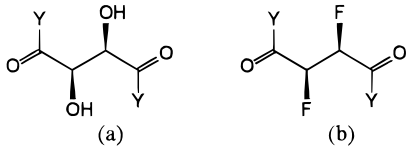

Figure 1. Zigzag formula of (a) (*R*,*R*)- and (b) (*S*,*S*)-2,3-dideoxy-2,3-difluorotartaric acid (Y = OH), dimethyl diester (Y = OMe), diamide (Y = NH2), and *N*,*N*,*N*′,*N*′-tartarmethyl diamide (Y = NMe2).

acid and its derivatives play a crucial role in the history of stereochemistry. Pasteur discovered the enantiomers[26] and Bijvoet et al.[27] assigned the absolute configuration while studying (*R*,*R*)-tartaric acid salts. Currently, (*R*,*R*)-tartaric acid and its derivatives are widely used in resolution of chiral amines[28−30] and as chiral auxiliaries in many asymmetric syntheses.[31−39] Moreover, (*R*,*R*)-tartraic amide derivatives have been successfully used in designing biodegradable polymers.[40,41]

The available data concerning (*R*,*R*)-tartaric acid derivatives made it possible to compare the conformational preferences between the derivatives of (*R*,*R*)-tartaric acid and their fluorine substituted analogues, namely the derivatives of (2*S*,3*S*)-2,3-dideoxy-2,3-difluorotartaric acid. The compared compounds are

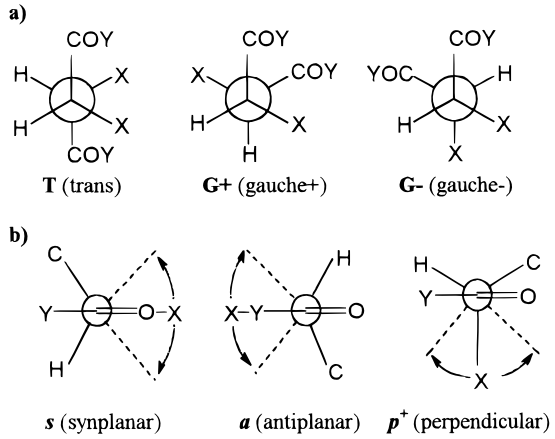

Figure 2. Rotational profiles of (*S*,*S*)-2,3-dideoxy-2,3-difluorotartaric acid and derivatives. (a) Rotation around the $C_{sp^3}-C_{sp^3}$ bond and (b) around the $C_{sp^3}-C_{sp^2}$ bond. (X = OH or F; Y = OH, OMe, NH_2, or NMe_2).

an example of conformationally labile molecules, and they focused our interest on how the substitution of the OH groups by the F atom affects the conformational preferences of these compounds. The results of this comparison appear to be very useful in studying more complex systems.

Each of the conformers of dideoxydifluorotartaric acid derivatives studied by us can be designated by a set of three characters. The first character (boldface capital letter) refers to the internal rotation about the $C_{sp^3}-C_{sp^3}$ bond (see Figure 2a) and describes the conformation of the carbon chain. The next two characters describe the mutual arrangement of the α-fluorine atom and its carboxylic, ester, or amide group (rotation about the $C_{sp^3}-C_{sp^2}$ bond, see Figure 2b). For example, **T*ss*** designates the conformer with extended conformation of the carbon chain ($C_{sp^2}-C_{sp^3}-C_{sp^3}-C_{sp^2}$ is about 180°) and the conformation about both $C_{sp^3}-C_{sp^2}$ bonds such that C═O bonds tend to or nearly eclipse (α)$C_{sp^3}-F$ bonds (rotamer syn; $F-C_{sp^3}-C_{sp^2}$═O torsion angle of about 0°).

In the case of (*R*,*R*)-tartaric acid, calculations up to the MP2/6-31G*//RHF/6-31G* level indicated that, for the isolated molecules the **T*ss*** and **T*as*** conformations were preferred.[21,23] Possessing C_2 symmetry, the **T*ss*** conformer was stabilized by two hydrogen bonds, each closing five-membered ring (S(5)-[OH→O═C] type[42]) (see Figure 3), with the OH group as a donor and the carbonyl oxygen from the same half of the molecule as an acceptor. The asymmetrical **T*as*** conformer had a relative energy of 1.27 kcal/mol and differed from the **T*ss*** only by a rotation of approximately 180° about one of the two $C_{sp^3}-C_{sp^2}$ bonds. Similarly to the **T*ss***, the **T*as*** structure gained stabilization from two hydrogen bonds, one S(5)[OH→O═C] and the other S(5)[OH→O$-C_{sp^2}$]. Both the **T*as*** and **T*ss*** conformers were also stabilized by the antiparallel local dipoles formed along H−C(*β*) and OC_{sp^2} bonds from different halves of the molecule.[18,21] Diffraction data analysis showed that, for (*R*,*R*)-tartaric acid, the **T*ss*** structure was present in crystals.[43−45] There was no intramolecular hydrogen bonding observed, but the conformation of the acid seemed to be partially stabilized

(16) We follow throughout the standard notational convention that *x*/*y*//*z*/*w* denotes a calculation with method *x* and basis *y* at geometry optimized with method *z* and basis *w*. For references for the various split-valence basis sets, explanation of basis set notation, the MP2 method of treating electron correlation in electronic structure calculation, and statistical mechanical formulas for deriving $\Delta G_{vib-rot}$, see: Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.

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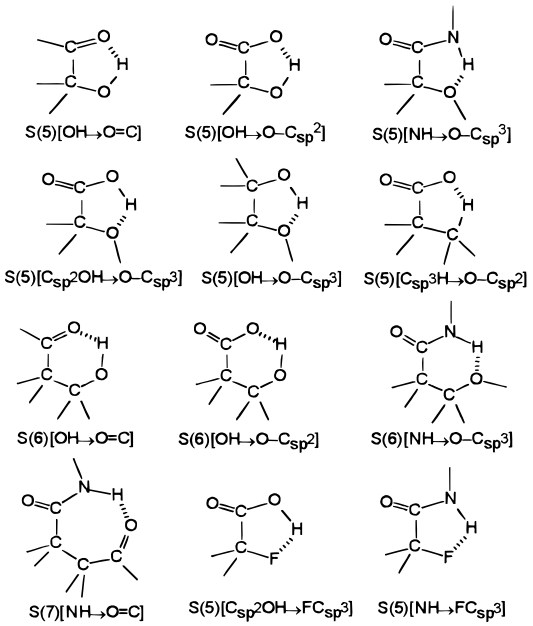

Figure 3. Hydrogen-bonding schemes of (*R*,*R*)- and (*S*,*S*)-2,3-dideoxy-2,3-difluorotartaric acid and its derivatives. S(*n*) denotes the motif of hydrogen bonds as proposed by Etter et al.[39] S means that an intramolecular hydrogen bond joins an *n* membered ring. In braces are symbols for a donor group, and after the arrow is an acceptor.

by the attraction between antiparallel local dipoles formed along H−C(β) and O−C_{sp^2} bonds, similarly to that in (*R*,*R*)-tartaric acid esters and amides.[18,22,24] The predominance of the **T** conformation was also indicated by optical rotation,[46] vibrational circular dichroism (VCD),[23] Raman optical activity (ROA),[47] and NMR studies.[18,48]

For the (*R*,*R*)-tartaric acid dimethyl diester, ab initio calculations up to MP2/6-31G*//MP2/6-31G* level showed that, for the isolated molecule, the lowest energy structure (the symmetrical **T*ss***) gained stabilization from the hydrogen bonding (two hydrogen bonds of S(5)[OH→O=C] type) and attraction of antiparallel H−C(β) and O−C_{sp^2} dipoles.[22] The second in energetical sequence was, similarly to that for (*R*,*R*)-tartaric acid, the asymmetrical **T*as*** conformer (relative energy 1.20 kcal/mol). The subsequent three **G**+ structures were very close in energetic ranking. They had relative energies of (i) 1.38, (ii) 1.49, and (iii) 1.60 kcal/mol and were stabilized by hydrogen bonds: (i) two of S(5)[OH→O=C] type, (ii) two of S(6)[OH→O=C] type, and (iii) one each of S(5)[OH→O=C] and S(6)[OH→O−C_{sp^2}] types. In the crystal structure, the **T*as*** conformer was present, and its stabilization resulted from the intramolecular hydrogen bonding of S(5)[OH→O−C_{sp^3}] type and the attraction of antiparallel dipoles H−C(β) and O=C_{sp^2} as well as H−C(β) and O−C_{sp^2}. The arrangement of atoms in H−C(β) and O−C_{sp^2} dipoles might also be considered as a hydrogen bond of S(5)-[CH→O−C_{sp^2}] type.[22] The **T** conformation of (*R*,*R*)-tartaric acid dimethyl diester was also indicated by NMR,[18,49] ROA,[50] VCD[23] methods. However, the earlier interpretations of VCD and NMR analyses pointed to the **G**+ conformer as the one which is present in chloroform solvent.[51−53]

In the case of (*R*,*R*)-tartaric acid diamide as well as (*R*,*R*)-tartaric acid *N*,*N*,*N*′,*N*′-tetramethyldiamide, MP2/6-31G*//RHF/6-31G* ab initio calculations indicated that, for isolated molecules, the conformer denoted as the **G**+***aa*** was undoubtly favored, and the second-ranked according to energy was the **G**+***ss*** form.[18,21] MP2/6-31G* relative energies of the latter conformer were 1.83 and 0.92 kcal/mol for primary and tertiary amides, respectively.[21] In the **G**+***aa*** conformation, two hydrogen bonds closing six-membered rings were formed, each involving both halves of the molecule (S(6)[OH→O=C]), while in the **G**+***ss*** one, each of the two hydrogen bonds was formed within one half of the molecule (S(5)[OH→O=C]). In the case of the primary amide, the **G**+***aa*** structure was additionally stabilized by two hydrogen bonds of S(5)[NH→O−C_{sp^3}] type. It is worth mentioning that, contrary to α-hydroxy acid and α-hydroxy ester groups, the planarity of the α-hydroxy amide group was not always conserved for the **G**+ conformers. A recent theoretical work about *N*,*N*′-dimethyl-2,3-di-*O*-methyl-(*S*,*S*)-tartaramide indicated that, for this compound, the **T*aa*** conformation was the lowest energy one and that it was stabilized by two hydrogen bonds of S(5)[NH→O−C_{sp^3}] type.[54] Crystallographic studies of (*R*,*R*)-tartaric acid diamide as well as (*R*,*R*)-tartaric acid *N*,*N*,*N*′,*N*′-tetramethyldiamide showed that the **T*aa*** and **G**−***p***+***p***+ conformations are observed in crystals of primary[18] and tertiary[19,55] amides, respectively. In the **T*aa*** conformation of (*R*,*R*)-tartaric acid diamide, the following intramolecular short contacts were observed: (i) two of S(5)[NH→O−C_{sp^3}] type and (ii) one of S(5)[OH→O−C_{sp^3}] type. The α-hydroxy amide moieties were almost ideally planar, with the O−C_{sp^3}−C_{sp^2}=O torsion angles −178.2(2)° and −179.4(2)°. On the other hand, in the **G**−***p***+***p***+ structure observed in the crystal, the two symmetrically equivalent α-hydroxy-*N*,*N*-dimethylamide moieties did not show any planarity, the O−C_{sp^3}−C_{sp^2}=O dihedral being equal to 90.5(3)°. The NMR measurements indicated that, in the polar alcohol solvent, the **T** and **G**− conformations predomiate for primary and tertiary amide, respectively. To the contrary, the NMR measurements in chloroform solvent suggested that, for the tertiary amide, there is considerable contribution of the **G**+ conformer in nonpolar solvents.[18]

Computational Methods

Ab initio molecular orbital theory up to the relatively high MP2/6-311++G**//RHF/6-31G* level of theory[16] was applied in this study. Standard values of bond lengths, valency angles, and dihedral angles needed to define the proper diastereoisomer were utilized as the initial set of parameters.[56] Typical 3-fold torsion potential with minima around 60°, 180°, and −60° was assumed for the torsion angle C_{sp^2}−C_{sp^3}−C_{sp^3}−C_{sp^2}, which determines the conformation of the main carbon chain. To examine the rotation about the C_{sp^3}−C_{sp^2} bond, six initial values of the F−C_{sp^3}−C=O torsion angles—0°, 60°, 120°, 180°, −120°, and −60°—were used. During the systematic search for stable structures, the 63 different initial structures[57] were considered for the (2*S*,3*S*)-2,3-dideoxy-2,3-difluorotartaric acid dimethyl diester, diamide, and *N*,*N*,*N*′,*N*′-tetramethyldiamide. In the case of (2*S*,3*S*)-2,3-dideoxy-2,3-difluorotartaric acid itself, we also considered, as the starting geometries, those structures where the H−O−C_{sp^2}−C_{sp^3} torsion angle was equal to

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0°, provided that the F−C_{sp^3}−C=O dihedral from the same half of the molecule was 180°. In this situation, there was a possibility of forming a hydrogen bond with the fluorine atom as an acceptor and the carboxyl hydrogen as a donor. Finally, this all gave 84 initial structures to be optimized in the case of the acid. For all cases, a complete optimization of molecular geometry was performed at the 3-21G basis set.

The results of calculations at this basis set showed that 29, 18, 13, and 23 structures were stable at this level for the acid, ester, amide, and *N*,*N*,*N*′,*N*′-tetramethylamide, respectively. However, for *N*,*N*,*N*′,*N*′-tetramethylamide, only 12 structures (of 23) possessed the skeleton of (2*S*,3*S*)-2,3-dideoxy-2,3-difluorotartaric acid *N*,*N*,*N*′,*N*′-tetramethylamide and were subjected to further studies. These stable structures at the RHF/3-21G level were subsequently optimized at the 6-31G* basis set. At this level, there were 23, 15, 9, and 11 unique conformers for the acid, ester, amide, and *N*,*N*,*N*′,*N*′-tetramethylamide, respectively. For these conformers, frequency and thermochemical analyses at the RHF/6-31G* level were performed. Furthermore, single-point energies at the MP2/6-311++G** level for all these unique structures were calculated. These energies were converted to relative gas-phase Gibbs energies employing standard statistical formulas[16] using unscaled and scaled (with scaling factor suggested for thermochemical calculations at the HF/6-31G* level[67] equal to 0.9135) vibrational frequencies and moments of inertia calculated at the HF/6-31G* level. This level was also used to verify all structures as local minima. Finally, each conformer had a contribution to its gas-phase free energy of $-RT \ln \omega$, where ω is the structural degeneracy of the conformation.[58] Thus, the composite G^0_{298K} is given by the formula

$$G^0_{298K} = E(\text{MP2/6-311++G**//HF/6-31G*}) + \Delta G_{vib-rot}(T) - RT \ln \omega \quad (1)$$

where E(MP2/6-311++G**//HF/6-31G*) is the single-point energy at the MP2 level computed at the 6-311++G** basis set for geometry optimized at the HF level at the 6-31G* basis set, and $\Delta G_{vib-rot}(T)$ is the thermal correction to the Gibbs free energy.

Equilibrium populations of conformers were calculated using a standard Boltzmann formalism. The percentage of a conformer X is given as

$$\%(X) = \frac{\exp(-G^0_X/RT)}{\sum_i \exp(-G^0_i/RT)} \times 100\% \quad (2)$$

where G^0_X is the composite G^0_{298K} as calculated from eq 1 and i runs over all conformers.

To assess free energies of solvation in water and chloroform, a semiempirical quantum chemistry program, AMSOL6.5.3,[59] was utilized with AM1-SM5.4 and PM3-SM5.4 models, which use AM1[60] and PM3[61] Hamiltonians. In the SM5.4 method,[62−65] solvation effects are included via two terms. The first accounts self-consistently for polarization of the solvent based on a distributed monopole representation of solute charges with dielectric screening. The second term is proportional to the solvent-accessible surface area, with a set of proportionality constants which depend on the local nature of the solute for each atom's or group's interface with the solvent. To calculate the percentage of a conformer X in a solution, eq 2 was utilized, but the Gibbs free energy of solvation was added to the composite Gibbs free energy of the isolated molecule.

All ab initio calculations were carried out with the Gaussian94 program suite[66] on Cray J-916 and Cary T3E supercomputers at the Poznan Supercomputing and Networking Center. Semiempirical SM5.4 calculations were performed with the AMSOL6.5.3 program[59] on a Cray J-916.

Results and Discussion

In Tables 1−4, we present the following relative energies and selected properties of conformers: the relative energy at MP2/6-311++G** (MP2) in kcal/mol, the relative value of the first perturbation to the Hartree−Fock energy, the correlation effect (Cor) in kcal/mol, the torsion angle $C_{sp^2}-C_{sp^3}-C_{sp^3}-C_{sp^2}$ (CCCC) in degrees, the structural degeneracy of the conformer (ω), the relative composite Gibbs free energy as calculated from eq 1 (G^0_{298K}) in kcal/mol, the percentage of the contribution of the conformer to the equilibrium gas-phase population of conformers, the relative composite Gibbs free energy calculated with scaled frequencies (G^{0S}_{298K}) in kcal/mol, and the percentage of the contribution of the conformer (%^{S}) calculated with scaled frequencies. The scaling factor 0.9135 was used in thermochemical calculations, as suggested for such calculations at the 6-31G* basis set.[67] In Tables 1−4 are also given solvation free energies calculated with the AM1-SM5.4 method both in water (ASM-w) and in chloroform (ASM-c) and corresponding percentages of the contribution of the conformer.

Scaling of the frequencies did not affect values of relative composite Gibbs free energies of conformers and did not change equilibrium gas-phase populations. The conformers of (*S*,*S*)-2,3-dideoxy-2,3-difluorotartaric acid (FTA) (Table 1), its dimethyl diester (FME) (Table 2), the diamide (FAM) (Table 3), and the *N*,*N*,*N*′,*N*′-tetramethyldiamide (FTMA) (Table 4) are ranked according to their relative energy at the MP2 level. In the Supporting Information, more information about each conformer is presented.

It is well known that small split-valence, like 3-21G, or medium-size split-valence plus polarization, like 6-31G*, basis sets perform adequately in SCF geometry optimizations of closed-shell organic compounds, but extended sets with flexible valence spaces and several sets of polarization as well as diffuse functions are needed for more accurate calculations of energy.[68] It is also generally accepted that a correct theoretical description of weak interactions, such as hydrogen bonding, depends strongly on the accuracy of the method used in calculations, and such error sources as neglecting electronic correlation, finite basis set expansions, etc. can strongly affect subtle energy differences between conformers resulting from RHF calculations.[68] Therefore, we expect that including electronic correlation via Møller−Plesset second-order perturbation theory[69,70] can improve the results considerably.

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Table 1. Selected Energetic and Geometric Parameters for Conformers of (*S*,*S*)-2,3-Dideoxy-2,3-difluorotartaric Acid (FTA)[a]

conformer	MP2	Cor	CCCC	ω	G^0_{298K}	%	$G^{0S\,b}_{298}$	%$^{S\,b}$	ASM-w	%^{W}	ASM-c	%^{C}
T*ss*	0.00	0.00	169.5	1	0.00	18.3	0.00	18.1	−8.79	44.4	−7.00	30.9
T*as*	0.07	0.54	175.8	2	−0.40	35.7	−0.40	35.7	−8.17	30.4	−6.65	33.4
T*aa*	0.14	1.09	−178.0	1	0.05	16.9	0.03	17.1	−7.63	5.8	−6.32	9.1
T*as**	0.76	−0.33	176.2	2	0.42	9.0	0.41	9.0	−8.42	11.7	−6.95	14.0
T*aa**	0.91	0.23	−178.0	2	0.55	7.3	0.53	7.3	−8.02	4.8	−6.71	7.5
G−*as*	1.60	−0.76	−54.9	2	0.81	4.7	0.80	4.7	−6.69	0.3	−5.72	0.9
G−*aa*	1.73	−0.42	−51.8	1	1.17	2.5	1.16	2.5	−6.75	0.2	−5.79	0.6
G−*ss*	1.81	−0.97	−57.0	1	1.65	1.1	1.65	1.1	−6.92	0.1	−5.91	0.3
G−*p*+*p*+	1.88	0.88	−68.5	1	1.43	1.6	1.41	1.7	−6.85	0.1	−5.69	0.3
T*aa***	2.03	−0.63	−178.6	1	2.29	0.4	2.27	0.4	−8.82	1.0	−7.39	1.3
G−*ap*−	2.44	0.22	−60.2	2	1.84	0.8	1.84	0.8	−6.90	0.1	−5.80	0.2
G+*ss*	2.53	−0.73	52.4	1	2.36	0.3	2.35	0.3	−8.08	0.2	−6.75	0.4
G+*aa*	2.78	0.34	45.1	1	2.76	0.2	2.76	0.2	−8.31	0.2	−6.89	0.2
G+*as*	3.01	−0.61	58.3	2	2.38	0.3	2.38	0.3	−7.50	0.1	−6.38	0.2
G+*p*+*s*	3.02	−0.11	42.2	2	2.68	0.2	2.68	0.2	−8.05	0.1	−6.69	0.2
G+*ss*	3.03	−0.65	36.9	1	2.95	0.1	2.96	0.1	−7.24	0.0	−6.24	0.1
G−*ap*+*	3.21	−0.75	−69.1	2	2.87	0.1	2.86	0.1	−8.30	0.2	−6.91	0.2
G−*ap*−*	3.47	−0.82	−60.1	2	3.12	0.1	3.11	0.1	−8.16	0.1	−6.85	0.1
G+*aa*	3.67	−0.47	62.2	1	3.50	0.0	3.49	0.1	−7.20	0.0	−6.25	0.0
G−*p*−*p*−	3.76	−0.57	−55.6	1	2.93	0.1	2.92	0.1	−6.24	0.0	−5.39	0.0
G+*aa**	3.87	−0.49	43.5	2	3.54	0.0	3.54	0.0	−8.73	0.1	−7.28	0.1
G+*as**	4.40	−1.07	35.0	2	4.11	0.0	4.11	0.0	−8.85	0.0	−7.34	0.1
G+*aa***	5.26	−1.31	38.5	1	5.33	0.0	5.33	0.0	−9.62	0.0	−8.07	0.0

[a] Absolute energies (in hartrees): MP2, −654.0888036479; Cor, −1.743218076. *T*, 298.15 K; *p*, 1 atm. [b] Superscript S means calculated with scaled frequencies.

Table 2. Selected Energetic and Geometric Parameters for Conformers of (*S*,*S*)-2,3-Dideoxy-2,3-difluorotartaric Acid Dimethyl Diester (FME)[a]

conformer	MP2	Cor	CCCC	ω	G^0_{298K}	%	$G^{0S\,b}_{298}$	%$^{S\,b}$	ASM-w	%^{W}	ASM-c	%^{C}
T*as*	0.00	0.00	175.2	2	−0.41	30.9	−0.41	30.9	−2.52	28.7	−6.38	35.7
T*ss*	0.02	−0.44	168.8	1	0.09	13.2	0.10	13.1	−3.39	53.1	−6.95	39.8
T*aa*	0.02	0.41	−178.5	1	−0.05	16.7	−0.05	16.8	−1.85	5.0	−5.91	8.8
G−*ss*	0.50	−2.37	−57.1	1	0.60	5.6	0.60	5.6	−1.75	1.4	−5.50	1.5
G−*as*	0.52	−1.90	−54.7	2	−0.07	17.3	−0.06	17.2	−1.44	2.6	−5.41	3.9
G−*aa*	0.90	−1.28	−50.8	1	0.48	6.9	0.47	6.9	−1.29	0.8	−5.42	1.6
G−*p*+*p*+	1.36	0.10	−67.4	1	0.91	3.3	0.90	3.4	−1.36	0.4	−5.56	1.0
G+*ss*	1.59	−1.68	50.0	1	1.51	1.2	1.51	1.2	−3.23	3.7	−6.83	3.0
G+*ss*	1.92	−1.78	36.1	1	1.96	0.6	1.97	0.6	−2.47	0.5	−6.39	0.7
G−*ap*−	1.93	−0.61	−59.9	2	1.35	1.6	1.36	1.6	−1.59	0.3	−5.72	0.6
G+*as*	2.10	−1.75	57.8	2	1.56	1.1	1.56	1.1	−2.78	1.6	−6.49	1.5
G−*p*−*p*−	2.26	−1.70	−54.4	1	1.64	1.0	1.64	1.0	−1.11	0.1	−5.48	0.2
G+*aa*	2.57	−0.53	44.3	1	2.54	0.2	2.55	0.2	−3.24	0.7	−6.95	0.6
G+*p*+*s*	2.61	−1.08	41.9	2	2.30	0.3	2.31	0.3	−3.20	0.9	−6.96	1.0
G+*aa*	2.65	−1.86	61.4	1	2.66	0.2	2.66	0.2	−2.48	0.1	−6.22	0.2

[a] Absolute energies (in hartrees): MP2, −732.4458156367; Cor, −2.036069166. *T*, 298.15 K; *p*, 1 atm. [b] Superscript S means calculated with scaled frequencies.

Table 3. Selected Energetic and Geometric Parameters for Conformers of (*S*,*S*)-2,3-Dideoxy-2,3-difluorotartaric Acid Diamide (FAM)[a]

conformer	MP2	Cor	CCCC	ω	G^0_{298K}	%	$G^{0S\,b}_{298}$	%$^{S\,b}$	ASM-w	%^{W}	ASM-c	%^{C}
T*aa*	0.00	0.00	−176.8	1	0.00	99.3	0.00	99.3	−11.02	99.1	−8.54	99.1
G+*aa*	2.40	−1.43	36.9	1	2.97	0.7	2.96	0.7	−10.81	0.5	−8.61	0.7
G−*ap*+	5.45	−1.62	−73.7	2	5.25	0.0	5.23	0.0	−11.13	0.0	−8.78	0.0
T*as*	5.66	−1.38	−179.9	2	5.08	0.0	5.09	0.0	−12.84	0.4	−9.84	0.2
G+*ss*	7.50	−0.85	−85.6	1	7.13	0.0	7.13	0.0	−11.24	0.0	−8.86	0.0
G−*p*+*p*+	6.42	−3.16	45.2	1	6.81	0.0	6.80	0.0	−9.70	90.0	−7.78	0.0
G+*as*	9.28	−2.30	44.5	2	8.61	0.0	8.63	0.0	−11.77	0.0	−9.04	0.0
G+*p*+*p*−	9.10	−2.60	90.1	2	8.62	0.0	8.60	0.0	−11.41	0.0	−8.94	0.0
G+*as*	9.01	−2.64	55.7	2	8.16	0.0	8.18	0.0	−11.64	0.0	−8.97	0.0

[a] Absolute energies (in hartrees): MP2, −614.3912072817; Cor, −1.705713508. *T*, 298.15 K; *p*, 1 atm. [b] Superscript S means calculated with scaled frequencies.

As far as the accurate assessment of the relative energies between the conformers is concerned, it was concluded by Gronert and O'Hair[71] that the MP2/6-31+G*//RHF/6-31G* level appears to be sufficient for the amino acids studied by them. Similarly, it was reported that the MP2/6-31G*//RHF/6-31G* level seems to be adequate for studying (*R*,*R*)-tartaric acid and its derivatives.[21] Those compounds were comparable in size and complexity to the systems considered in this study. It therefore

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Table 4. Selected Energetic and Geometric Parameters for Conformers of (*S,S*)-2,3-Dideoxy-2,3-difluorotartaric Acid *N,N,N′,N′*-Tetramethyldiamide (FTMA)[a]

conformer	MP2	Cor	CCCC	ω	G^0_{298K}	%	G^{0S}_{298} [b]	%^{S} [b]	ASM-w	%^{W}	ASM-c	%^{C}
G−***aa***	0.00	0.00	−28.9	1	0.00	28.5	0.00	28.7	−8.69	7.7	−4.73	18.0
G−***p***+***p***+	0.54	3.57	−70.3	1	−0.46	62.4	−0.46	62.3	−9.65	84.9	−5.06	68.7
T*aa*	1.96	3.10	−171.4	1	1.29	3.2	1.30	3.2	−9.06	1.6	−4.93	2.8
G+***ss***	2.13	−1.10	24.2	1	2.12	0.8	2.13	0.8	−9.33	0.6	−5.94	3.8
T*aa*	2.63	3.69	−171.6	2	1.28	3.3	1.29	3.3	−9.33	2.6	−4.99	3.2
T*aa*	3.15	4.31	−170.4	1	1.98	1.0	2.00	1.0	−9.64	1.3	−5.23	1.5
T*as*	3.48	2.40	−177.1	2	2.18	0.7	2.18	0.7	−9.57	0.9	−5.43	1.5
G+***p***+***a***	4.50	2.31	45.4	2	3.40	0.1	3.42	0.1	−10.04	0.2	−5.50	70.2
G+***aa***	5.36	2.62	48.5	1	4.35	0.0	4.38	0.0	−10.78	0.2	−6.40	0.2
G−***p***+***p***−	7.15	1.99	−61.3	2	5.69	0.0	5.71	0.0	−9.21	0.0	−4.75	0.0
G+***p***+***s***	8.22	1.11	17.8	2	6.66	0.0	6.68	0.0	−9.83	0.0	−5.96	0.0

[a] Absolute energies (in hartrees): MP2, −771.1273652898; Cor, −2.323859681. *T*, 298.15 K; *p*, 1 atm. [b] Superscript S means calculated with scaled frequencies.

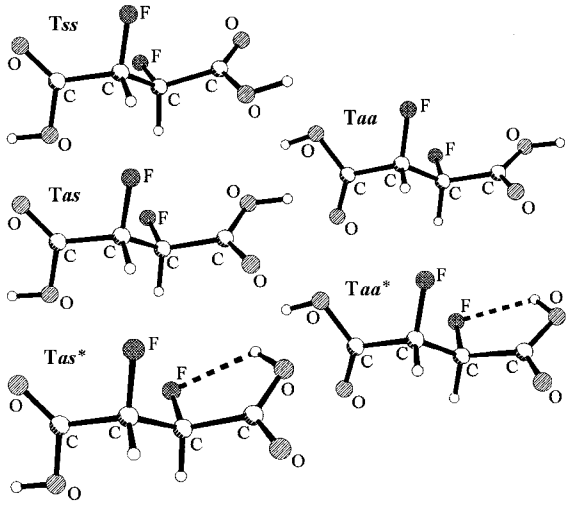

Figure 4. Lowest energy conformers of (*S,S*)-2,3-dideoxy-2,3-difluorotartaric acid (FTA).

seemed that a further increase in the basis set size would put a much larger demand on the computer resources without significantly changing the results.

(S,S)*-2,3-Dideoxy-2,3-difluorotartaric Acid (FTA).** The first five conformers, ranked according to their relative energy at the MP2 level, presented in Figure 4, have the extended carbon chains and planar arrangements of the α-fluorocarboxylic moieties. The energy differences between them are small, less than 1 kcal/mol. All are stabilized by the attraction of antiparallel local dipoles formed along the H−C(β) and C_{sp^2}−O bonds. The lowest energy conformation at MP2 level is the **T*ss one. It is easy to notice that this conformation gains more stabilization from correlation effects than the **T*as*** and **T*aa*** conformers. Moreover, in general, almost all ***s*** rotamers are by about 0.5 kcal/mol more stable due to correlation effects than the corresponding ***a*** rotamers. This was the reason the lowest energy **T*ss*** structure, when the electron correlation was not taken into account, was the third in energetic sequence with relative energy 1.16 and 0.95 kcal/mol at the 6-31G* and 6-311++G** basis sets, respectively.

The two conformers closest energetically to the **T*ss*** one are the **T*as*** and **T*aa***. They differ from the **T*ss*** by a rotation of about 180° around one (**T*as***) or two (**T*aa***) C_{sp^3}−C_{sp^2} bonds, and their relative energies at the MP2 level are only 0.07 and 0.14 kcal/mol for the **T*as*** and **T*aa*** structures, respectively. The next two low-energy conformers, the fourth **T*as*** and the fifth **T*aa***, each have one hydrogen bond of S(5)[C_{sp^2}OH→FC] type, with the carboxyl hydrogen as a donor and the fluorine as an acceptor. It is not surprising that the carboxyl proton tends to be syn with respect to the carbonyl oxygen (like in **T*ss***, **T*as***, and **T*aa***), not anti (like in **T*as*** and **T*aa***). A similar situation was also observed in the cases of serine[71] and α-hydroxyacetic acid.[21] In these cases, the conformations with hydrogen bonds formed by the carboxyl hydrogen (anti) acting as a donor and the α-hydroxy group as an acceptor were not favored. Also in crystals of both monofluoroacetic acid and fluoromalonic acid,[72] syn, rather than anti, arrangement of the carboxyl hydrogen was observed, despite the fact that, in fluoromalonic acid, both the carboxylic OH groups were eclipsing the fluorine atom, creating perfect conditions for hydrogen bond formation. Moreover, it has already been pointed out[5,73] that the fluorine atom is not as good at accepting hydrogen bonds as oxygen. A hydrogen bond energy with the F($-C_{sp^3}$) as an acceptor is about half that of the case when the oxygen atom is accepting a hydrogen bond.[5] Some authors even suggest that the pronounced tendency of the carboxyl hydrogen to adopt the syn arrangement with respect to carbonyl oxygen may be considered as a hydrogen bond[71] which closes a four-membered ring with the carboxyl OH group as a donor and the carbonyl oxygen as an acceptor (S(4)[OH→O=C] type).

The population analysis of gas-phase conformations at 298 K, performed both with scaled and unscaled frequencies, indicates that the asymmetrical **T*as*** conformer contributes the most to the total population of conformers. Its contribution is almost 36%, which is twice as high as the contribution of the symmetrical **T*ss*** (18%) and **T*aa*** (17%) conformers, despite the fact that the relative energies of these conformers are very similar. This is because any asymmetrical conformation is favored over a symmetrical one by $-RT \ln \omega$, where ω is the structural degeneracy of the isomer ($\omega = 1$ for conformers with C_2 symmetry, whereas $\omega = 2$ for asymmetrical ones). The subsequent **T*as*** and **T*aa*** conformers, each with a hydrogen bond with F atom as an acceptor, were also asymmetrical. Their contributions to the population of conformers were 9% and 7% for **T*as*** and **T*aa***, respectively. Thus, the ratio of all **T**:**G**−:**G**+ conformers is 80:10:1. Having considered solvation effects utilizing solvation free energies calculated with AM1-SM5.4 and PM3-SM5.4 models for water and chloroform allowed us to state that the energy of solvation of the **T*ss*** conformer is greater than those of **T*as*** and **T*aa*** ones. Therefore, the population of **T*ss*** conformers has increased (31% in chloroform and 44% in water as calculated with the AM1-SM5.4 method), whereas the population of **T*aa*** conformers has decreased (9% in chloroform, 6% in water).

All in all, the results for (*S,S*)-2,3-dideoxy-2,3-difluorotartaric

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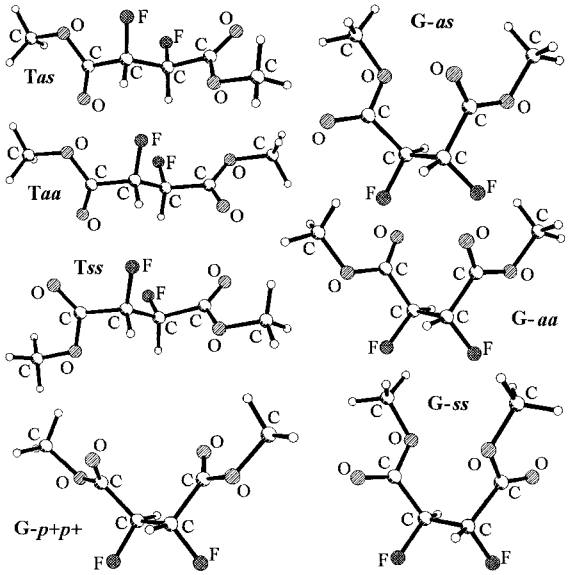

Figure 5. Lowest energy conformers of (*S*,*S*)-2,3-dideoxy-2,3-difluorotartaric acid dimethyl diester (FME).

acid, when compared with the results for (*R*,*R*)-tartaric acid,[21,23] indicate that the dideoxydifluoro analogue of (*R*,*R*)-tartaric acid possesses more conformational freedom than the (*R*,*R*)-tartaric acid itself. This is the result of the absence of the intramolecular hydrogen bonds found in the case of (*R*,*R*)-tartaric acid. Very small energy differences between the lowest energy **T** conformers of (*S*,*S*)-2,3-dideoxy-2,3-difluorotartaric acid indicate that, although for this molecule the structure with the extended carbon chain and both the α-fluorocarboxylic moieties planar is certainly favored, there are almost no preferences for the syn or anti planar arrangement of (α)C_{sp^3}−F and C═O bonds. This is different from the case of the (*R*,*R*)-tartaric acid, for which the energy differences between conformers were much greater.[21] Our results compare favorably with the findings concerning fluoromalonic and hydroxymalonic acids.[72] The crystal structure of fluoromalonic acid showed temperature-dependent disorder, which was explained by the fact that, at room temperature, fluoromalonic acid was present as a mixture of conformers with syn and anti planar arrangement of (α)C_{sp^3}−F and C═O bonds. At the temperature of liquid nitrogen, only the anti planar conformation predominated. For hydroxymalonic acid both at room temperature and at the temperature of liquid nitrogen, the syn planar conformation was observed.

(*S*,*S*)-2,3-Dideoxy-2,3-Difluorotartaric Acid Dimethyl Diester (FME). The first three lowest energy structures of FME (like for FTA) have the extended carbon chain and planar α-fluoroester moieties. The energy differences between them are negligibly small, within 0.02 kcal/mol. These structures are stabilized by the attraction of antiparallel dipoles formed along the H−C(*β*) and C_{sp^2}−O bonds. Similarly to the case for the FTA, almost all ***s*** rotamers are about 0.5 kcal/mol more stable due to electron correlation than the corresponding ***a*** rotamers. The lowest energy structure at the MP2 level is the asymmetrical **T*as*** one, which was the second in energetic sequence at the HF level. The other low-energy ***T*** conformers differ from the **T*as*** structure by rotation around one of the C_{sp^3}−C_{sp^2} bonds of about 180°. The subsequent four conformers are the **G**− ones, and their conformations about the C_{sp^3}−C_{sp^2} bond correspond to "staggered" rotamers. These **T** and **G**− conformers are presented in Figure 5.

The population analysis of gas-phase conformations at 298 K, performed both with scaled and unscaled frequencies, shows

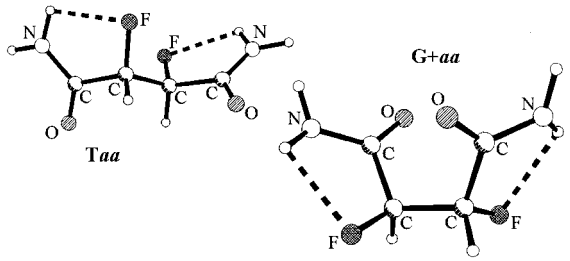

Figure 6. Lowest energy conformers of (*S*,*S*)-2,3-dideoxy-2,3-difluorotartaric acid diamide (FAM).

that, at the lowest energy, the asymmetrical **T*as*** conformer with contribution slightly less than 31% contributes most to the population of conformers. The fractions of the symmetrical **T*aa*** and **T*ss*** conformers are 16.7 and 13.2%, respectively, whereas the asymmetrical **G**−***as*** conformer is found to constitute 17.4% of the total gas-phase population. The total fraction of all **T** conformers is 60.8%, all **G**− 35.6%, and all **G**+ 3.6%, so the ratio of **T**:**G**−:**G**+ is roughly equal to 17:10:1. Similarly to the case for FTA, the **T*ss*** conformation gained more stabilization from solvation than **T*as*** and **T*aa*** conformers, as calculated with AM1-SM5.4 and PM3-SM5.4 methods for water and chloroform. Moreover, the stabilization of **T** conformers was generally higher than the stabilization of **G**− ones. Therefore, **T** conformers constituted about 90% when solvation effects were taken into account.

The comparison of the results for dimethyl (*R*,*R*)-tartrate[22] and dimethyl (*S*,*S*)-2,3-dideoxy-2,3-difluorotartrate shows that the dideoxydifluoro analogue of (*R*,*R*)-tartaric acid dimethyl diester (FME), like the FTA, has again more conformational diversity than the dimethyl (*R*,*R*)-tartrate. It is worth mentionning that, for the FTA, the predominant conformers are the **T** ones, whereas for FME the **T** and **G**− conformers contribute almost equally to the total population of conformers. Interestingly, the subsequent, other than **T**, conformers of (*R*,*R*)-tartaric acid dimethyl diester were the **G**+, not the **G**− ones. Moreover, in contradiction to dimethyl (*R*,*R*)-tartrate, the planar arrangement of α-X−C_{sp^3}−COOMe (X = OH or F) moieties for conformers of dimethyl (*S*,*S*)-2,3-dideoxy-2,3-difluorotartrate (FME), other than the **T** ones, was not conserved.

(S,S)*-2,3-Dideoxy-2,3-difluorotartaric Acid Diamide (FAM).** Unlike FTA and FME, there is a pronounced tendency of the diamide FAM to adopt only one, the **T*aa conformation, with extended carbon chain and planar α-fluoroamide moieties. This lowest energy conformation is stabilized by the attraction of antiparallel local dipoles formed along H−C(*β*) and C═O atoms as well as hydrogen bonds of the S(5)[NH→FC] type. Similarly, for fluoroacetamide, a hydrogen bond of this type was found in the crystal structure and was pointed out by ab initio calculations.[74] The second conformation in energetic ranking of FAM is the **G**+***aa*** conformer. Its carbon chain is bent, and the structure is also stabilized by hydrogen bonds of the S(5)-[NH→FC] type. These two conformers are presented in Figure 6.

The population analysis of gas-phase conformers at 298 K, carried out both with scaled and unscaled frequencies, indicates that the lowest energy form is found to constitute almost 99.3% of the total gas-phase population and the **G**+***aa*** structure slightly less than 0.7%. The ratio of all **T**:**G**−:**G**+ conformers for FAM is 151:0.02:1. Taking into account solvation free energies did not much change the relative ratio of conformers. The **T*aa*** conformation constituted more than 99% of conformers.

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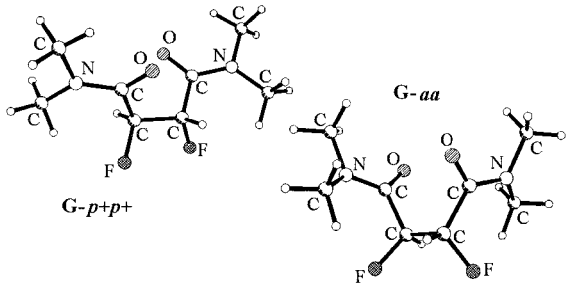

Figure 7. Lowest energy conformers of (*S*,*S*)-2,3-dideoxy-2,3-difluorotartaric acid *N*,*N*,*N*′,*N*′-tetramethyldiamide (FTMA).

For the (*R*,*R*)-tartaric acid diamide, the calculations at the MP2/6-31G*//RHF/6-31G* level indicated that, for the isolated molecules, the **G**+***aa*** conformation is certainly favored due to formation of hydrogen bonds: two of S(6)[OH→O═C] type and two of S(5)[NH→O−C_{sp^3}] type.[18,21] On the other hand, in the crystal structure of (*R*,*R*)-tartaric acid diamide, the **T*aa*** conformation was observed.[18] The results of our calculations for (*S*,*S*)-2,3-dideoxy-2,3-difluorotartaric acid diamide seem to compare favorably with these findings. For an isolated molecule of (*R*,*R*)-tartaric acid diamide, the **G**+***aa*** conformation is preferred because of the formation of intramolecular hydrogen bonds, where the OH groups act as proton donors. If the OH groups are involved in intermolecular hydrogen bonds, like in crystals, or are replaced by fluorine atoms, like for FAM, or are substituted by OCH_3 moieties, like for *N*,*N*′-dimethyl-2,3-di-*O*-methyl-(*S*,*S*)-tartaramide[54] so that they cannot act as intramolecular hydrogen bond donors, then the conformational preferences takes precedence and the **T*aa*** conformer is favored for the primary or secondary amide. The same is true in the case of the crystal structure of (*R*,*R*)-tartaric acid diamide,[18] for isolated molecules of (*S*,*S*)-2,3-dideoxy-2,3-difluorotartaric acid diamide, and for isolated molecules of *N*,*N*′-dimethyl-2,3-di-*O*-methyl-(*S*,*S*)-tartaramide.[54]

(*S*,*S*)-2,3-Dideoxy-2,3-difluorotartaric Acid *N*,*N*,*N*′,*N*′-Tetramethyldiamide (FTAM). The first two lowest energy structures of *N*,*N*,*N*′,*N*′-tetramethyldiamide of (*S*,*S*)-2,3-dideoxy-2,3-difluorotartaric acid are the **G**− ones. The lowest energy structure is the **G**−***aa***; however, the value of $C_{sp^2}-C_{sp^3}-C_{sp^3}-C_{sp^2}$ torsion angle converged after optimization at the 6-31G* basis set to −28.9°, which is almost exactly halfway between the ideal **G**− (−60°) and eclipsed (0°) conformers. Moreover, this structure gains much more stabilization due to electron correlation (3.57 kcal/mol more) than the second in energy sequence, the **G**−***p***+***p***+ conformer, for which the relative energy is 0.54 kcal/mol. These conformers are presented in Figure 7.

The population analysis, carried out both with scaled and unscaled frequencies, shows that the **G**− conformers constitute almost 90%, the **T** structures 8.2%, and the **G**+ ones 0.9%, so that the **T**:**G**−:**G**+ ratio is about 9:100:1. The conformer which contributes most to the gas-phase population is the **G**−***p***+***p***+ one, and its fraction is 62.3%, whereas the fraction of the lowest energy form, the **G**−***aa*** structure, is 28.7%. These differences result from the greater stabilization of the **G**−***p***+***p***+ structure due to the thermal correction to the Gibbs free energy, which is caused by the greater entropy of this conformer. Free energies of solvation indicated that solvation effects favored the **G**−***p***+***p***+ structure even more in chloroform (85% according to AM1-SM5.4) than in water solution (69% according to AM1-SM5.4).

The comparison of the results for (*R*,*R*)-tartaric acid *N*,*N*,*N*′,*N*′-tetramethyldiamide[18,21] and (*S*,*S*)-2,3-dideoxy-2,3-difluorotartaric acid *N*,*N*,*N*′,*N*′-tetramethyldiamide indicates that conformational preferences of the isolated molecules of these compounds are different. For isolated molecules of (*R*,*R*)-tartaric acid *N*,*N*,*N*′,*N*′-tetramethyldiamide, the favored conformation was the **G**+***aa*** one, as indicated by ab inito calculations.[18,21] Moreover, NMR studies in chloroform solvent indicated that the **G**+ conformer was present in nonpolar solutions.[18] To the contrary, the NMR measurements in polar alcohol solvent showed that the **G**− conformer of (*R*,*R*)-tartaric acid *N*,*N*,*N*′,*N*′-tetramethyldiamide is favored in polar solutions.[18] Similarly, the **G**−***p***+***p***+ conformation was observed in the crystal structure.[19,55] It is very interesting that the **G**−***p***+***p***+ conformer observed in the crystal structure of the (*R*,*R*)-tartaric acid *N*,*N*,*N*′,*N*′-tetramethyldiamide[19,55] corresponds to the most prevalent conformer present in the gas-phase population of conformers of (*S*,*S*)-2,3-dideoxy-2,3-difluorotartaric acid *N*,*N*,*N*′,*N*′-tetramethyldiamide.

Fluorine as a Hydrogen Bond Acceptor. The geometrical parameters of hydrogen bonds as well as electron densities between protons and acceptors calculated according to the Mulliken scheme are presented in Table 5. In this table, the results for the lowest energy **T*aa*** and **G**+***aa*** conformers of the FAM and for the **T*as*** and **T*aa*** conformers of FTA are presented. For comparison, the data for the lowest energy structure of glycolic acid (α-hydroxyacetic acid)[21] with a hydrogen bond S(5)[OH→O═C] is also displayed in Table 5. For all these compounds, the geometries were optimized at the HF/6-31G* level, and the electron densities between atoms presented in Table 5 were calculated at this level, too.

From these results, we conclude that the fluorine atom may accept hydrogen bonds effectively. The electron densities between proton and fluorine indicate that hydrogen bonds with a fluorine as an acceptor do exist. The Mulliken population analysis at the 6-31G* basis set shows that electron densities between hydrogen and fluorine are about 0.017 e^- when the hydrogen bond donor is a carboxyl hydrogen and about 0.011 e^- when an amide hydrogen is the donor. In the case of the intramolecular hydrogen bond formed in glycolic acid (α-hydroxyacetic acid), with the α-hydroxyl group as a donor and the carbonyl oxygen as an acceptor, the electron density is about 0.022 e^-. It has already been shown that the energy of an intermolecular hydrogen bond with a carbonyl oxygen as an acceptor is twice the energy of a hydrogen bond with an organofluorine atom.[5] Thus, our answer to a question that has arisen lately, whether covalently bonded fluorine is capable of accepting hydrogen bonds,[5,73,75] is positive, but its accepting ability is roughly 2 times lower than that of the carbonyl oxygen. Our results are in line with the results of ab initio calculations for systems with intermolecular hydrogen bonds, which indicated that, although oxygen is a better acceptor, fluorine may accept hydrogen bonds.[5,76] The experimental evidence as to whether a fluorine atom acts as an acceptor of hydrogen bonds is limited. Statistical analyses of the Cambridge Structural Database showed that short CF···H−X contacts are extremely rare.[5,73] On the other hand, some studies provide support for F···H bonding.[12,77−82] For example, it was suggested that a hydrogen bond with fluorine as an acceptor controls an

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Table 5. Hydrogen Bonding Parameters for Some Conformers of (*S,S*)-2,3-Dideoxy-2,3-difluorotartaric Acid (FTA) and Its Diamide (FAM) as Well as Glycolic Acid

compound	conformer	bonding type	D···A	H···A	AHD	population
FTA	**T*as*** *	S(5)[C_{sp^2}OH→FC_{sp^3}]	2.572	2.019	115.2	0.0173
FTA	**T*aa*** *	S(5)[C_{sp^2}OH→FC_{sp^3}]	2.568	2.012	115.5	0.0177
FAM	**T*aa***	S(5)[NH→FC_{sp^3}]	2.594	2.196	102.2	0.0114
FAM	**G+*aa***	S(5)[NH→FC_{sp^3}]	2.612	2.213	102.3	0.0103
glycolic acid	***s***	S(5)[OH→O=C]	2.690	2.151	114.6	0.0216

Table 6. Values of Torsion Angles (deg) for Lowest Energy Conformers of (*R,R*)-Tartaric Acid Derivatives as Well as Its Dideoxydifluoro Analogues

molecule	method	$C_{sp^2}C_{sp^3}C_{sp^3}C_{sp^2}$	$XC_{sp^3}C_{sp^2}$=O	$XC_{sp^3}C_{sp^2}$=O
FTA	ab initio	169.5	−2.0	−2.0
OHA[a]	ab initio	174.1	3.5	3.5
OHA[a]	X-ray	−175.4(2)	4.4(2)	4.9(2)
FME	ab initio	175.2	−179.9	−2.4
OHE[b]	ab initio	172.7	3.2	3.2
OHE[b]	X-ray	−169.2(1)	−176.8(2)	0.2(2)
FAM	ab initio	−176.8	175.6	175.6
OH1°AM[c]	ab initio	62.6	160.0	160.0
OH1°AM[c]	X-ray	−167.0(2)	−178.2(2)	−179.4(2)
FTMA	ab initio	−70.3	107.7	107.7
OH3°AM[d]	ab initio	65.5	140.0	140.0
OH3°AM[d]	X-ray	−52.4(2)	90.5(3)	90.5(3)

[a] OHA, (*R,R*)-tartaric acid. [b] OHE, dimethyl (*R,R*)-tartrate. [c] OH1°AM, (*R,R*)-tartaric acid diamide. [d] OH3°AM, (*R,R*)-tartaric acid *N,N,N′,N′*-tatramethyldiamide, X = OH or F.

enzymatic transformation of UDP-deoxyfluoroglucose by UDP glucose dehydrogenase[1] and that the fluorine atom of 2-deoxy-2-fluoro-D-myoinositol-1,4,5-triphosphate accepts the hydrogen bond from the cellular receptor.[2]

Conformations of (*S,S*)-2,3-Dideoxy-2,3-difluorotartaric Acid and Its Derivatives versus (*R,R*)-Tartaric Acid and Its Derivatives. Table 6 shows torsion angles crucial for determining the conformations of (*R,R*)-tartaric acid, its derivatives, and its dideoxydifluoro analogues. Interestingly, in the cases of FTA, FME, and FAM, the lowest energy structures correspond to the conformers of (*R,R*)-tartaric acid, its dimethyl diester, and its diamide found in the crystal structure. For the FTAM, the **G−*p*+*p*+** conformer for which the composite free energy is the lowest, is very similar to the **G−*p*+*p*+** conformer observed in the crystal structure of the *N,N,N′,N′*-tetramethyldiamide of (*R,R*)-tartaric acid.

The comparison of ab initio results for (*R,R*)-tartaric acid and its derivaties with the results for their dideoxydifluoro analogues enables us to state that, for the diamide and the *N,N,N′,N′*-tetramethyldiamide, the lowest energy conformations of the isolated molecules are different. For both amides of (*R,R*)-tartaric acid, the preferred conformer is the symmetrical **G+*aa*** one stabilized by the hydrogen bonds of S(6)[OH→O=C] type (and additionally S(5)[NH→O−C_{sp^3}] for the primary amide). The conformational preferences of the dideoxydifluoro analogues of these amides are altered. For the primary amide FAM, the lowest energy structure is the **T*aa***, with hydrogen bonds of S(5)-[NH→F−C_{sp^3}] type, and for the tertiary amide, FTAM, the lowest energy structures are the **G−*aa*** and **G−*p*+*p*+**.

In the case of FME, the energy differences between **T*as***, **T*aa***, and **T*ss*** conformers are negligible, and for FTA they are very small. This indicates that these molecules have more conformational freedom than the analogous derivatives of (*R,R*)-tartaric acid due to hydrogen bonds present in the latter. This is in line with the findings concerning the crystal structure of fluoro- and hydroxymalonic acids. The temperature-dependent disorder in the crystal structure of fluoromalonic acid was the result of the presence of ***s*** and ***a*** conformers in its crystals at room temperature.[72]

It was suggested that conformational preferences of isolated molecules of (*R,R*)-tartaric acid ester and amide derivatives are mostly affected by the intramolecular hydrogen bonds.[18] From our results, it seems that, if hydroxyl groups of (*R,R*)-tartaric acid are involved in intermolecular interactions, like in crystals, then the conformational preferences of these compounds are similar to the conformational preferences of their dideoxydifluoro analogues in vacuo. Whether such a hypothesis is true for other molecules must be tested during analysis of a number of compounds with the OH group replaced by an F atom.

Conclusions

Our studies showed that, for conformationally labile (*R,R*)-tartaric acid and its derivatives, the substitution of the OH group by an F atom leads to profound changes in conformational preferences of isolated molecules.

Although among 2,3-dideoxy-2,3-difluoro analogues of (*R,R*)-tartaric acid and its ester and amide derivatives, similarly as for (*R,R*)-tartaric acid derivatives, there is a tendency toward adopting **T** conformations with an extended carbon chain and the α-fluorocarboxylic, ester, or amide moieties forming a plane, (*S,S*)-2,3-dideoxy-2,3-difluorotartaric acid might exist in the gas phase as a mixture of several **T** conformers, which differ from one another by rotation of approximately 180° around C_{sp^3}−C_{sp^2} bonds and/or by the position of the carboxyl hydrogen. This carboxyl hydrogen can be either syn or anti with respect to the carbonyl oxygen. In the latter case, it forms a hydrogen bond with its α-fluorine atom.

For both the (*S,S*)-2,3-dideoxy-2,3-difluorotartaric acid and its dimethyl diester, the ***s*** structures are usually more stabilized by solvation effects than the ***a*** structures. Therefore, when solvation is taken into account, the **T*ss*** conformers contribute most to the populations of the acid and the ester.

The dimethyl diester of (*S,S*)-2,3-dideoxy-2,3-difluorotartaric acid might exist in gas-phase equilibrium as a mixture of not

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only **T** conformers but also **G**− ones. Although the **T*as*** conformer has the lowest energy, the energy differences between it and the subsequent **T** conformers are negligible. What is more, the **G**− conformers have very small relative energies and comprise up to 36% of the population of conformers at 298 K.

Only (*S*,*S*)-2,3-dideoxy-2,3-difluorotartaric acid diamide has a pronounced preference, both in an isolated state and in solution, toward only one conformation, namely the **T*aa***, with an extended carbon chain and planar arrangements of α-fluorine amide moieties, stabilized by hydrogen bonds with amide hydrogen as a donor and α-fluorine as an acceptor.

It is worth mentioning that all the **T** structures of all the compounds studied are stabilized by the attraction of antiparallel dipoles formed along the H−C_{sp^3}(*β*) and O−C_{sp^2} bonds. This seems to be the main factor that affects the conformation of (*S*,*S*)-2,3-dideoxy-2,3-difluorotartaric acid and its derivatives.

In the case of the *N*,*N*,*N*′,*N*′-tetramethyldiamide of (*S*,*S*)-2,3-dideoxy-2,3-difluorotartaric acid, the **G**− conformers are favored in the isolated state and in solution, probably because of the destabilization of the **T** conformers by steric repulsion between relatively larger methyl groups of tertiary amide moieties and the *β* hydrogen atom.

Our results suggest that, for conformationally labile molecules, the deoxyfluoro analogues would probably have different conformations from their parental compounds and would be present as a mixture of conformers. Therefore, they would probably not be suitable substrates or inhibitors for a given enzymatic process. However, the lowest energy structures for all the studied 2,3-dideoxy-2,3-difluoro analogues closely resemble the structures observed in crystals of their parental compounds. Moreover, in polar solvents, conformational preferences of (*R*,*R*)-tartaric acid and its derivatives were similar to these in the crystal structure. The rationale for this is that, in crystals of the parental compounds, hydroxyl groups are involved as donors in intermolecular hydrogen bonds, so their potential to act as proton donors in intramolecular hydrogen bonds is very limited, while their accepting ability remains unchanged. In this context, it is understandable that the behavior of deoxyfluoro analogues in the isolated state is so much like that of their parent compounds in the crystal structure and, presumably, also in condensed media. This also explains why the conformational preferences of dideoxydifluorotartaric acid amides are similar to the preferences of di-*O*-methyl-substituted tartaric acid amides.[54] Both of them cannot act as hydrogen bond donors.

Encouraging for bio-organic chemists is the fact, that for molecules which do not have much conformational freedom (such as cyclic molecules), the substitution of an OH group by an F atom should not much change the shape and the electrostatic properties of these molecules. This seems to compare favorably with the finding that fluorine is most successful in replacing hydroxyl group for cyclic compounds such as fluoro deoxysugars,[77] UDP-4-deoxy-4-fluoroglucose,[1] fluorodeoxymuscarine,[12] and 2-deoxy-2-fluoro-D-myoinositol-1,4,5-triphosphate.[2]

Acknowledgment. The authors thank Professor D. G. Truhlar and Professor C. J. Cramer for providing a free academic license for AMSOL-6.5.3. The authors gratefully acknowledge financial support from the Polish Committee for Scientific Research (KBN), Grants 8 T11F 007 12 and 8 T11F 028 15, and thank Poznan Supercomputing and Networking Center for the access to computer resources therein.

Supporting Information Available: Tables S1−S8, presenting relative energies and selected properties of conformers of studied molecules (relative energy at MP2/6-311++G** relative value of the first perturbation to Hartree−Fock energy, relative energies at HF/6-311++G** and HF/6-31G* (6-31), dipole momentum calculated at MP2 level (*μ*), torsion angles $C_{sp^2}-C_{sp^3}-C_{sp^3}-C_{sp^2}$, both F−$C_{sp^3}$−$C_{sp^2}$═O (in the case of the acid, both H−O−C_{sp^2}−C_{sp^3}), structural degeneracy of the conformer (*ω*), relative zero-point correction, relative thermal correction to Gibbs free energy, relative composite Gibbs free energy as calculated from eq 1, and the percentage of the contribution of the conformer to the equilibrium gas-phase population of conformers; zero-point energies, thermal corrections to the Gibbs free energy, and the percentage of the conformer calculated both with scaled and unscaled frequencies; and solvation free energies calculated with AM1-SM5.4 and PM3-SM5.4 methods both in water and in chloroform) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA982935+