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Ab Initio Molecular Orbitals Study of the Conformational Preference in α-Cyano-α-fluorophenylacetic Acid Ester

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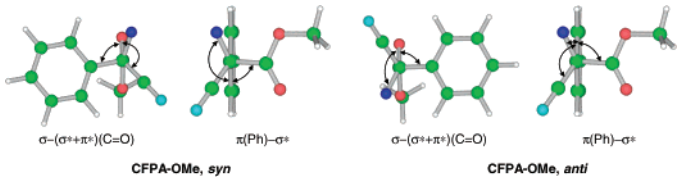

The origin of conformational preference in α-cyano-α-fluorophenylacetic acid (CFPA) methyl ester that is a model system of α-cyano-α-fluoro-*p*-tolylacetic acid (CFTA) esters was theoretically investigated by means of DFT and MP2 calculations. Two stable conformations having the C−F bond *syn* and *anti* to the C═O bond, respectively, were obtained for CFPA methyl ester. A small energy difference (0.9 kcal mol^{-1} at the MP2(fc)/6-31++G(d,p)) was found between the two conformations. From the molecular orbital analysis based on the Natural Bond Orbital analysis and supported by calculations using the Orbital Deletion Procedure technique, we found that $\sigma-(\sigma^*+\pi^*)$(C═O) and $\sigma-\sigma^*$(Ph) and π(Ph)$-\sigma^*$ hyperconjugations are the main factors responsible for the conformational preference. The role of the fluorine atom on the stereogenic center was also clarified.

Introduction

Determination of absolute configuration of chiral molecules is an indispensable process in asymmetric reactions and structural studies of complex natural products. However, there have been no practical methods generally applicable to non-crystallizable compounds and for those samples available only in very small quantities. On these grounds, there is a growing interest in using chiral derivatizing agents (CDAs) to assign the absolute configuration of chiral molecules. These CDAs are a potential tool in the NMR determination of the absolute configuration of a wide class of substrates. One of the most convenient and reliable methods is the ^{1}H NMR analysis of diastereomers formed by reactions of chiral molecules with the CDAs.[1−7] In addition to the use of ^{1}H as probe, the use of the ^{19}F nucleus is expected because the fluorine chemical shift differences between two diastereomers, produced by fluorine-containing CDAs, are much greater than those obtained by ^{1}H NMR.[8,9] Although the modified Mosher method with α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) is often employed for this purpose, many instances have arisen recently,

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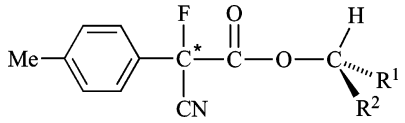

FIGURE 1. The α-cyano-α-fluoro-*p*-tolylacetic acid (CFTA). C* denotes the chiral center in CFTA, referred in the text by C_α. R^1, R^2, and Me all have been replaced by H atoms yielding the CFPA-OMe model system used in this work.

where the MTPA procedure cannot be applied probably because of the presence of multiple complex conformers observed in the MTPA ester diastereomers.[10]

α-Cyano-α-fluorophenylacetic acid (CFPA)[8,11,12] and α-cyano-α-fluoro-*p*-tolylacetic acid (CFTA)[13−17] having a unique chiral fluorine structure, developed by Takeuchi and co-workers (Figure 1), are the best among the known CDAs from the viewpoint of consistency in the $\Delta\delta$ values ($\Delta\delta = \delta_S - \delta_R$, where δ_S and δ_R are the chemical shifts of ^{1}H signals of (*S*)- and (*R*)-CFTA esters, respectively) for the derived ester diastereomers,[16,17] in addition to both the high reactivity of the agents[12] and the resolution efficiency in the NMR.[13−17] The sign of $\Delta\delta$ between diastereomeric CFTA esters can be correlated to the absolute configuration of a secondary alcohol on the basis of the model shown in Figure 2. In this model, the C−F bond is *syn* (synperiplanar) to the C═O bond, to which the carbinyl C−H bond is *syn*. This conformation was seen in the X-ray structure of the (*R*)-CFTA ester of (1*S*)-neomenthol.[16] The proton signals due to the substituents that confront the aromatic ring always shifted upfield by the magnetic anisotropy of the aromatic ring. Accordingly, the $\Delta\delta$ values for each proton in the R^1 group should be positive and those in the R^2 group should be negative. This model was supported by ab initio calculations performed at the RHF/6-31+G(d) level on the ground electronic state of diastereomeric (*R*)-CFPA esters of (1*S*)- and (1*R*)-menthols (i.e., (*R*,*S*)- and (*R*,*R*)-CFPA esters). Two predominant conformations were found for each of the (*R*,*S*)- and (*R*,*R*)-CFPA esters: one is the *syn* conformation described above and the other is the *anti* one regarding the C−F and C═O bonds. The calculations predicted a preference of the *syn* conformations by 0.94 and 0.55 kcal mol^{-1} for the (*R*,*S*)- and (*R*,*R*)-CFPA esters, respectively. However, no explanation was provided by the authors for the reasons why the *syn* and the *anti* are stable and for the conformational preference of the *syn* over the *anti*.

In view of the versatility of these CDAs and the crucial importance of the preferred conformation of the chiral fluorine structure in the assignment of absolute configuration, we have undertaken a thorough investigation by means of ab initio molecular orbital calculations to identify the origin of the conformational preferences in the ester derivatives of CFTA using a simplified model system of the CFPA methyl ester.

The following section of this paper describes the methods of calculation as well as the CFTA model system used in this work. We then present our results and give our understanding of the origin of the observed conformational preference. The Molecular Orbital (MO) analysis based on the Natural Bond Orbital (NBO) approach will be used to identify the type of interactions between the different functional groups inside the CFPA model system. The Orbital Deletion Procedure (ODP) will be used to quantitatively evaluate the hyperconjugation energies. The results of localized MO analysis show that a hyperconjugative mechanism is responsible for the origin of the conformational preference. This reminds us that a hyperconjugative mechanism is the origin of the conformational preference in fluoroacetaldehyde (FAA) and methyl fluoroacetate (MFA), which have some of the same functional groups as CFPA, namely C−F and C═O.[18] We conclude this work by summarizing the validity of the different descriptions (MO based on both NBO and ODP) as applied to the model system we have used and the factors controlling the conformational preference.

CFPA Model

Since for the CFTA molecule the real substituents R^1 and R^2 of the ester group and the methyl group attached para to the aromatic ring are away from the central chiral carbon, it is expected that their effects on the conformational preference will be negligible and, therefore, they all have been replaced by H atoms, in order to reduce both computational cost and time. The resulting model system is called the CFPA methyl ester and will be labeled hereafter simply by CFPA-OMe as shown in Figure 1.

Computational Details

Two different theoretical methods have been used in this work: the density functional theory (DFT) and the Møller−Plesset second-order perturbation theory, using the frozen core option, MP2(fc).[19] In the DFT calculation, the ordinary B3LYP functional, which consists of the hybrid Becke+Hartree−Fock exchange[20] and the Lee−Yang−Parr correlation functional with nonlocal corrections,[21,22] was adopted. The DFT method has been used to generate the potential energy curve as a function of the F−C−C═O dihedral angle. To better evaluate the energy difference and to provide the molecular orbitals (MOs) required for this work, we reoptimized the geometries of the stable conformers obtained along the potential energy curves at the MP2(fc) level as well as at the B3LYP level by removing the constraint on the dihedral angles.

Natural Bond Orbitals analysis, which provides the means to analyze the atom−atom interaction in more detail than is given by MOs based on the donor−acceptor scheme, has been used.[23−25] To quantitatively evaluate the hyperconjugation energies, we

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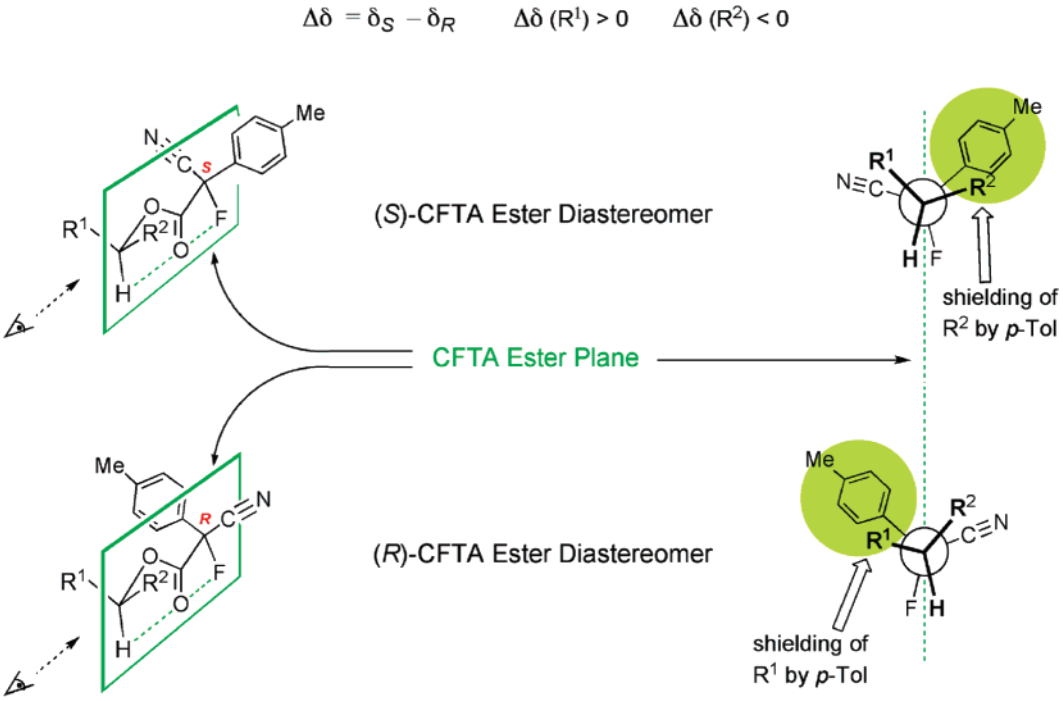

FIGURE 2. The model for correlation between Δδ in CFTA esters and absolute configuration of secondary alcohols (R^1R^2CHOH).

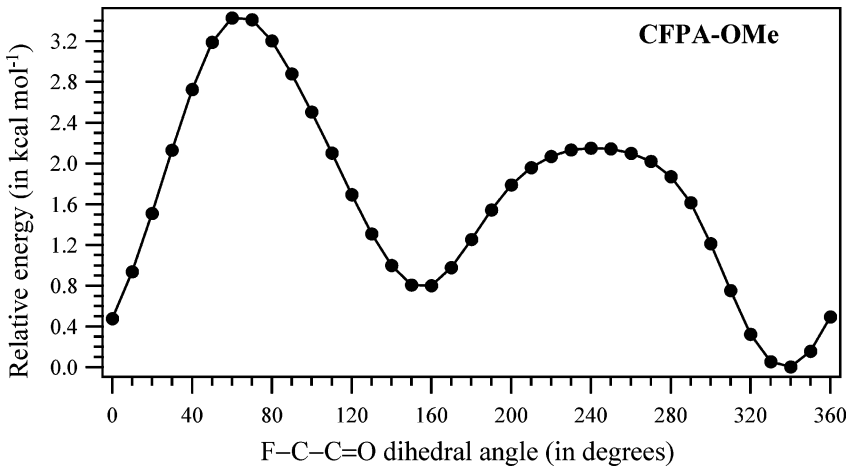

FIGURE 3. Potential energy curve for CFPA-OMe obtained at the B3LYP/6-31++G(d,p) level.

employed the ODP approach in which certain specific atomic orbitals are forced to be vacant.[26−28]

All calculations have been carried out with the Gaussian 98[29] and Gaussian 03[30] suites of programs employing the standard 6-31++G(d,p) basis set.

Results and Discussion

In Figure 3 is shown the calculated potential energy curve for the CFPA-OMe model system. The potential energy curve was generated by varying the F−C−C═O dihedral angle from 0° to 360°, using a step of 10° and smaller steps (≤5°, not displayed in Figure 3 for clarity of the curve) near each saddle point.

Geometric and Energetic. In agreement with previous calculations,[16] two distinct stable conformations were found, the *syn* and *anti* forms. The *syn* conformation corresponds to an F−C−C═O dihedral angle of the order of −20°, non-negligibly bent from a real *syn* conformation. The *anti* conformation has an F−C−C═O dihedral angle of about 153° and is also non-negligibly bent from the real *anti* conformation. It is clear that these two conformations do not belong to the *gauche* form. For the geometrical parameters, only the selected dihedral angles that are displayed in Figure 4 have been found to be of interest. All the other optimized parameters undergo slight variations when going from the *syn* conformation to the *anti* one, and this is true regardless of the method used, B3LYP or MP2(fc).

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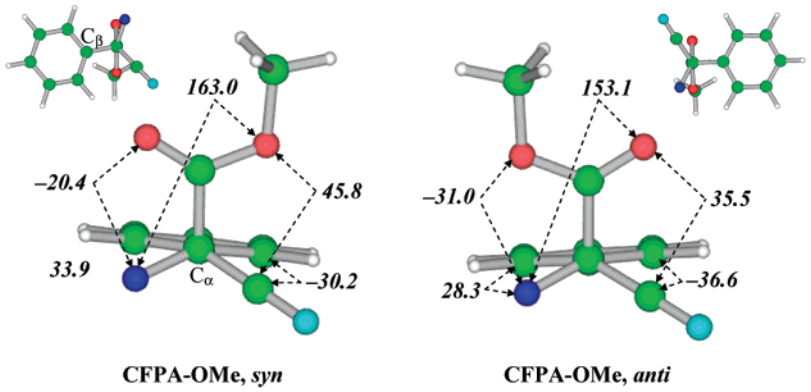

FIGURE 4. MP2(fc)/6-31++G(d,p) optimized structures for CFPA-OMe. In the top-left (top-right) corner picture of the *syn* (*anti*) conformation is the side view with respect to the F−C−C=O dihedral angle, which shows the fluoroester fragment model while the actual structure is shown in the fluorotoluene fragment model. Only the most important dihedral angles are given. Bond distances, bond angles, and dihedral angles undergo small variation on going from the *syn* conformation to the *anti* one and therefore are not shown. The blue spheres stand for F atoms, red ones for O atoms, blue-sky ones for N atoms, green ones for C atoms, and gray ones for H atoms.

Overall, there is a good agreement between the two methods in predicting the energy difference between the *syn* and *anti* conformations. The energy difference ($\Delta E_{anti-syn}$) between the *anti* and *syn* conformations of the fully optimized structures with use of B3LYP and MP2(fc) levels of theory gives 0.79 and 0.89 kcal mol^{-1}, respectively, i.e., the *syn* conformation is more stable than the *anti* one. These values are in good agreement with that calculated at the HF/6-31+G(d) for the (*R*,*S*)-CFPA (0.94 kcal mol^{-1}) by Takahashi et al.[16] A relatively small energy difference between the two conformations reflects the rotamer character for CFPA-OMe since the difference in their structures is mainly attributed to a rotation around the C−C single bond of the F−C−C=O group.

NBO Analysis. The *syn* and *anti* terminology was chosen based on the geometrical position of C_α−F with respect to C_{ester}=O (where C_{ester} refers to the carbonyl carbon atom of the $-CO_2CH_3$ group), which is thought to be crucial, as pointed out in the introduction. However, the CFPA-OMe model system can also be regarded as "C_α-substituted fluorotoluene fragment" type, referred to thereafter by the term "fluorotoluene fragment". In that case, the position of C_α−F with respect to the plane of the aromatic ring is also important and should receive careful attention when elucidating the factors controlling the conformational preference.

A systematic comparison of the MO orbitals of *syn* and *anti* conformations did reveal the existence of hyperconjugative molecular orbitals in both conformations. Depending on how the CFPA-OMe system is looked at, the hyperconjugative MOs can be between the π-orbital of the C=O bond and each of the C_α−F, C_α−C_N, and C_α−$C_{\beta Ph}$ σ-bonds in the fluoroester fragment and between the π-orbital of the aromatic ring (Ph) and each of the C_α−F, C_α−CO_2CH_3, and C_α−C_N σ-bonds in the fluorotoluene fragment. However, the presence of substituents such as cyano (−CN), phenyl ($-C_6H_5$), and ester ($-CO_2CH_3$) renders the orbital overlap more complicated. While substitution of cyano and phenyl in the fluoroester fragment and cyano and ester in the fluorotoluene fragment by simpler substituents is highly appreciated to show the hyperconjugative MOs in the delocalized canonical orbitals, the substitutions may even lead to more complicated systems. On the other hand, investigation of the donor−acceptor scheme provided by the NBO analysis may greatly clarify the hyperconjugative issue.

To confirm the hyperconjugation we performed NBO analysis on each conformation of the CFPA-OMe. The results are summarized in Table 1. On the basis of the NBO analysis, the orbital interaction occurs between the double bond C=O and each of the σ-bonds C_α−F, C_α−C_N, and C_α−$C_{\beta Ph}$ for the fluoroester fragment. The dominant donor−acceptor interactions are the $\sigma-\sigma^*$(C=O) and $\sigma-\pi^*$(C=O), as clearly shown in Table 1, for both *syn* and *anti* conformers. In the $\sigma-\sigma^*$(C=O) and $\sigma-\pi^*$(C=O) interactions, charge transfers, featuring the hyperconjugative mechanism, take place mainly from the two localized donor orbitals $\sigma(C_\alpha-C_N) + \sigma(C_\alpha-C_{\beta Ph})$, denoted simply as σ in Table 1, to the two unoccupied acceptor orbitals σ^*(C=O) and π^*(C=O) for *syn* conformation, while for the *anti* conformation the hyperconjugation mainly occurs between $\sigma(C_\alpha-F) + \sigma(C_\alpha-C_{\beta Ph})$ and σ^*(C=O) + π^*(C=O). Indeed, the geometrical arrangement of C_α−F with C=O in *syn-like* and *anti-like* positions favors such hyperconjugation, particularly in the *syn* conformation. The staggered position of $\sigma(C_\alpha-C_N) + \sigma(C_\alpha-C_{\beta Ph})$ with π^*(C=O) leads to a favorable overlap between them and hence facilitates the hyperconjugative mechanism. The results presented in Table 1 clearly show that the electron-withdrawing effect exerted by the CN group reduces the effect of the hyperconjugation in both conformations. It should be pointed out here that the charge transfer from $\sigma(C_\alpha-F)$ to either σ^*(C=O) or π^*(C=O) is only present in the *anti* conformation and non-negligibly contributes to its stability. For the *syn* conformation, the interaction of $\sigma(C_\alpha-F)$ takes place with σ^*(C−O), instead. As can be deduced from Table 1, the $\sigma-\sigma^*$(C=O) and $\sigma-\pi^*$(C=O) types of interaction are more important in the *syn* conformation than those in the *anti* conformation. The common isovalent hyperconjugation,[31] featured by $\sigma-\pi^*$(C=O), was found to have the most significant hyperconjugative effect in both conformations, followed by $\sigma-\sigma^*$(C=O) [$\sigma(C_\alpha-C_N) + \sigma(C_\alpha-C_{\beta Ph})$ to σ^*(C=O) in *syn* and $\sigma(C_\alpha-F) + \sigma(C_\alpha-C_{\beta Ph})$ to σ^*(C=O) in *anti*]. However, one should not neglect other types of interaction, particularly π-(C=O)−σ^* [$\sigma^*(C_\alpha-C_N) + \sigma^*(C_\alpha-C_{\beta Ph})$ for *syn* and $\sigma^*(C_\alpha-F) + \sigma^*(C_\alpha-C_{\beta Ph})$ for *anti*], which is defined as negative hyperconjugation,[31] and to a lesser extent, π^*(C=O)−σ^* [$\sigma^*(C_\alpha-C_N) + \sigma^*(C_\alpha-C_{\beta Ph})$ for *syn* and $\sigma^*(C_\alpha-F) + \sigma^*(C_\alpha-C_{\beta Ph})$ for *anti*].

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TABLE 1. Calculated NBO and ODP Hyperconjugation Energies (HCE, in kcal mol^{-1}) Resulting from the Different Types of Interaction in the Fluoroester Fragment and in the Fluorotoluene Fragment for the *Syn* and *Anti* Conformations[a] of the CFPA-OMe Obtained at the HFF/6-31++G(d,p) Level of Theory

	NBO		ODP	
type of interaction	HCE (*syn*)	HCE (*anti*)	HCE (*syn*)	HCE (*anti*)
fluoroester fragment				
$[\sigma(C_\alpha-F)+\sigma(C_\alpha-C_N)+\sigma(C_\alpha-C_{\beta Ph})]-\sigma^*(C=O)$	4.25	3.38	3.78	3.08
$[\sigma(C_\alpha-F)+\sigma(C_\alpha-C_N)+\sigma(C_\alpha-C_{\beta Ph})-\pi^*(C=O)$	5.22	4.63	4.42	3.98
$\pi(C=O)-[\sigma^*(C_\alpha-F)+\sigma^*(C_\alpha-C_N)+\sigma^*(C_\alpha-C_{\beta Ph})]$	2.22	2.17	1.89	1.78
$\pi^*(C=O)-[\sigma^*(C_\alpha-F)+\sigma^*(C_\alpha-C_N)+\sigma^*(C_\alpha-C_{\beta Ph})]$	1.53	2.49	0.53	0.60
total (fluoroester fragment)	13.22	12.67	10.62	9.44
del $(C_\alpha FC_NC_{\beta Ph})/(O-C=O)$[b]			32.64	32.86
del $(C_\alpha F)/(O-C=O)$[b]			17.24	17.82
fluorotoluene fragment				
$[\sigma(C_\alpha-F)+\sigma(C_\alpha-CO_2CH_3)+\sigma(C_\alpha-C_N)]-\sigma^*(Ph)$	5.42	5.68	5.05	5.20
$[\sigma(C_\alpha-F)+\sigma(C_\alpha-CO_2CH_3)+\sigma(C_\alpha-C_N)]-\pi^*(Ph)$	2.89	3.57	2.25	2.93
$\sigma(Ph)-[\sigma^*(C_\alpha-F)+\sigma^*(C_\alpha-CO_2CH_3)+\sigma^*(C_\alpha-C_N)]$	2.93	2.98	2.66	2.67
$\pi(Ph)-[\sigma^*(C_\alpha-F)+\sigma^*(C_\alpha-CO_2CH_3)+\sigma^*(C_\alpha-C_N)]$	8.76	8.36	5.98	5.75
$\pi^*(Ph)-[\sigma^*(C_\alpha-F)+\sigma^*(C_\alpha-CO_2CH_3)+\sigma^*(C_\alpha-C_N)]$	4.60	4.11	1.57	1.35
total (fluorotoluene fragment)	24.60	24.70	17.51	18.37
del $(C_\alpha FC_NC_{ester})/(C_{Ph}C_{\beta Ph}C_{Ph})$[b]			35.75	35.15
del $(C_\alpha F)/(C_{Ph}C_\beta PhC_{Ph})$[b]			18.83	17.79
total (fluoroester fragment + fluorotoluene fragment)			28.13	27.81
total fluorine-HC in[c]				
fluoroester fragment		6.16		4.16
fluorotoluene fragment	8.24	7.38	5.76	5.44
F/O_{ester}[d]	5.25		4.56	

[a] Optimized structures at the MP2(fc)/6-31++G(d,p) level have been used for *syn* and *anti* conformations of the CFPA-OMe. [b] del means deletion of all types of interaction between the two fragments shown in parentheses. [c] Fluorine-HC means fluorine hyperconjugation (HC). [d] The other oxygen atom of the $-CO_2CH_3$ group.

We note here that $\sigma-(\sigma^* + \pi^*)(C=O)$ hyperconjugation favors the *syn* conformation over the *anti* one, while $\pi^*(C=O)-\sigma^*$ favors the *anti* conformation over the *syn* one and $\pi(C=O)-\sigma^*$ has seemingly no major effect on the conformational preference. As can be seen in Table 1, the effect of all hyperconjugations is slightly more important in the *syn* conformation, suggesting that the stability of this conformation is attributed to hyperconjugative effects.

In the second model type, which is referred to as the fluorotoluene fragment, the plane of the aromatic ring is located in a staggered position away from the $C_\alpha-CO_2CH_3$ and $C_\alpha-F$ bonds, respectively, while it is almost eclipsed with the $C_\alpha-C_N$ bond (see Figure 4). From the NBO analysis, the hyperconjugative interaction takes place between the π-orbital of the aromatic ring and each of the $C_\alpha-F$, $C_\alpha-CO_2CH_3$, and $C_\alpha-C_N$ σ-bonds. Two prominent hyperconjugative mechanisms can be identified in Table 1, the $\pi(Ph)-\sigma^*$ and the $\sigma-\sigma^*(Ph)$. While the $\pi(Ph)-\sigma^*$ hyperconjugative interaction is mainly attributed to $\pi(Ph)-\sigma(C_\alpha-C_{ester})$ orbital interaction in both conformations, the $\pi(Ph)-\sigma^*(C_\alpha-F)$ was also found to be important particularly for the *syn* conformation. Indeed, the $\pi(Ph)-\sigma^*(C_\alpha-F)$ hyperconjugative interaction represents ~40% of the total $\pi(Ph)-\sigma^*$ in the *syn* conformation and ~23% of that in the *anti* one. The second most important hyperconjugation in this series is $\sigma-\sigma^*(Ph)$. In this interaction, hyperconjugation takes place mainly between $\sigma(C_\alpha-C_N) + \sigma(C_\alpha-F)$ and $\sigma^*(Ph)$ in both conformations. The $\sigma(C_\alpha-C_N)-\sigma^*(Ph)$ hyperconjugation represents ~52% of the total $\sigma-\sigma^*(Ph)$ in the *syn* conformation and ~48% in the *anti* one, clearly indicating that it is the dominant hyperconjugation in both conformations. As for $\sigma-\pi^*(Ph)$, $\pi^*(Ph)-\sigma^*$, and $\sigma(Ph)-\sigma^*$ hyperconjugations, the calculations show that they non-negligibly contribute to the stabilization of the two conformations (see Table 1).

The fluorotoluene fragment model that we have considered is a very well-known system for which ample investigations have been reported.[32−38] However, unlike simple substituents such as CH that have been used in the previous works,[32−33,35−38] or even CH_3,[39] with the actual substituents, namely CN and CO_2CH_3, the interpretation and manifestation of the hyperconjugation is more difficult and more complicated if we restrict the analysis to only the MO pictures. On the basis of the NBO analysis, it is easier to identify the mechanism of the hyperconjugation between the different substituents and the π-network of the aromatic ring. Compared with only one π-orbital of C=O, the π-network of the aromatic ring significantly enhances the effect of the hyperconjugation. This is well observed in Table 1, where the hyperconjugation energies in the fluorotoluene fragment are larger than those of the fluoroester fragment. This may be attributed to an easiness of the electron transfer between the aromatic ring and each of the $C_\alpha-F$, $C_\alpha-C_{ester}$, and $C_\alpha-C_N$ σ-bonds. While $\sigma-\pi^*(Ph)$ slightly favors the *anti* conformation, $\pi(Ph)-\sigma^*$ barely favors the *syn*. Furthermore, in contrast with the fluoroester fragment, all the hyperconjugation energies found in the fluorotoluene fragment scarcely show significant variation between the two conformations. This is well reflected

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also in the overall total hyperconjugation energy in each conformation where the overall hyperconjugative effects cancel each other.

Orbital Deletion Procedure (ODP). To quantify the energies of each type of hyperconjugation and assess their importance, we have calculated their acquired stabilization energies using the orbital deletion procedure technique (ODP). In this calculation, we used the structures optimized at the MP2(fc)/6-31++G-(d,p) level and performed single point energy calculations at the HF level within the same based set, namely, the 6-31++G-(d,p) one. Deletion of selected donor−acceptor interactions was based on the NBO description presented above and shown in Table 1. Since our attention is particularly addressed to the hyperconjugative effects, the deletion was made on selected bond−antibond, lone pair−antibond, and antibond−antibond interactions, that is, the off-diagonal elements of the Fock matrix in the NBO representation. The results of the ODP are presented in Table 1 together with the NBO ones for comparative purposes. In addition, deletion of all types of interaction between the units C═O and $C_\alpha FC_NC_{\beta Ph}$ in the fluoroester fragment model and between the units $C_{Ph}C_{\beta PhCPh}$ and $C_\alpha FC_NC_{ester}$ in the fluorotoluene fragment model were carried out to assess quantitatively their hyperconjugative effects.

All the acquired stabilizing energies of the different hyperconjugative mechanisms that have been obtained from the NBO analysis are fairly reproduced with the present ODP calculations. In agreement with NBO analysis, the ODP results confirm that *syn* conformation is more stabilized by hyperconjugations in the fluoroester fragment than the *anti* one. However, the energy differences are less important than those obtained from NBO.

Inasmuch as the tendencies in the stabilizing energy differences between the two conformations were conserved, the calculated energies of the hyperconjugations occurring at higher energy levels, particularly π^*(C═O)−σ^*, π(Ph)−σ^*, and π^*-(Ph)−σ^*, are visibly underestimated compared with those obtained from the NBO analysis.

From the NBO analysis, the calculated π^*(C═O)−σ^* hyperconjugation energy is less important compared with the $\sigma-\sigma^*$(C═O) and $\sigma-\pi^*$(C═O) ones, suggesting that π^*(C═O)−σ^* acts in such a way to compensate for the difference of the first two effects. Unfortunately, the ODP calculation largely underestimates the energy of the latter hyperconjugation, yielding comparable hyperconjugation energies in both conformations. Although π^*(C═O) and $\sigma^*(C_\alpha-F) + \sigma^*(C_\alpha-C_N) + \sigma^*(C_\alpha-C_{\beta Ph})$ are basically vacant, their interaction is thought to be promoted by the relatively small energy difference between the two orbitals in the MOs description. This type of hyperconjugation that has recently been proposed[32−33,35−36,40] needs to be further investigated since the present ODP calculations did not reveal any particular effect on the conformational preference and have not supported the NBO findings.

On the other hand, the results of the deletion of all types of interactions between the two units C═O and $C_\alpha FC_NC_{\beta Ph}$ in the fluoroester fragment show that the *anti* conformation is slightly more stabilized by hyperconjugation than the *syn* one. In the fluorotoluene fragment, the reverse tendency was found where the *syn* is more stabilized by hyperconjugation than the *anti*. By summing up the hyperconjugation energies of the fluoroester fragment to those of the fluorotoluene fragment one can easily find the right tendency of the conformational preference, with less accentuation in the energy difference between the two conformations. It should be noted here that, in this deletion procedure, all types of orbital interactions between the two units, including those involving the Rydberg orbitals, are taken into consideration, unlike the deletion of specific donor−acceptor interaction.

Finally, it is worth mentioning the role played by the F atom. From both NBO and ODP calculations, the F atom is significantly involved in the hyperconjugative mechanisms in both fluoroester fragment and fluorotoluene fragment. From ODP calculations (see Table 1), the total stabilizing energy acquired by deletion of all interactions between C═O and $C_\alpha-F$ represents the third of the total hyperconjugation energies in the fluoroester fragment in both conformations, whereas the deletion of all interactions between $C_{Ph}C_{\beta Ph}C_{Ph}$ and $C_\alpha-F$ in the fluorotoluene fragment gives an order of more than half of the total hyperconjugation energy and also for both conformations. Of course, for a proper evaluation of the $C_\alpha-F$ contributing stabilizing energy, hyperconjugation with C−O (the other oxygen atom of the $-CO_2CH_3$ group) should be considered in the fluoroester fragment, so that the calculated energy difference is well reproduced. In the fluorotoluene fragment, the $\sigma^*(C_\alpha-F)$ exhibits a good acceptor character when the position of $C_\alpha-F$ bond is out of the plane of (i.e., not eclipsed with) the π-network of the aromatic ring, which may explain the large hyperconjugation energy originating from interaction with $C_\alpha-F$.

Furthermore, when C═O and $C_\alpha-F$ are eclipsed (or nearly eclipsed), the *anti* conformation is more stabilized by π(C═O)−$\sigma^*(C_\alpha-F)$ and $\sigma(C_\alpha-F)-\pi^*$(C═O) hyperconjugations, following the Pauli repulsion expectations. In the fluorotoluene fragment, it was shown that an out-of-plane arrangement of $C_\alpha-F$ with the aromatic ring enhances the hyperconjugative mechanisms, which contradicts the trends of the electrostatic interactions but is in line with the tendency of the steric effects (see the Supporting Information for more details). In all cases, the *syn* conformation is the preferred conformation due to a π(Ph)−$\sigma^*(C_\alpha-F)$ hyperconjugation, which is more important than that in the *anti* conformation.

Concluding Remarks

A theoretical investigation of the origin of the conformational preference in the CFTA model system has been presented. The calculations have been performed at a reasonable and affordable level of theory, namely the MP2(fc) level, on a simplified CFPA-OMe model system that possesses all the features of the parent CFTA functional groups. By assimilating the CFPA-OMe model system into the fluoroester fragment (recently proposed by us[18]) on one hand and into the usual fluorotoluene fragment on the other hand, the origin of the conformational preference could be identified and the role of the fluorine atom could be clarified. Both fluoroester fragment and fluorotoluene fragment models evidenced that the stability of *syn* and *anti* conformations is attributed to hyperconjugative mechanisms, particularly $\sigma-(\sigma^* + \pi^*)$(C═O) in the fluoroester fragment and $\sigma-\sigma^*$-(Ph) and π(Ph)−σ^* in the fluorotoluene fragment. Upon comparison of the effects of the different types of hyperconjugation we found that $\sigma-(\sigma^* + \pi^*)$(C═O) hyperconjugation has the main effect for the stability of the *syn* conformation, while $\sigma-\pi^*$(Ph) and π^*(C═O)−σ^* hyperconjugations slightly stabilize the *anti* conformation. The importance of this latter effect was not confirmed by ODP calculations and further

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investigations are required to clarify this issue. It is also concluded from the calculations that the fluorine atom, and more precisely the $C_\alpha-F$ bond, non-negligibly contributes in the hyperconjugative mechanisms in both fluoroester fragment and fluorotoluene fragment models. Both NBO analysis and ODP calculations prove that the *anti* conformation is more stabilized by $\pi(C{=}O)-\sigma^*(C_\alpha-F)$ and $\sigma(C_\alpha-F)-\pi^*(C{=}O)$ hyperconjugations, whereas $\pi(Ph)-\sigma^*(C_\alpha-F)$ hyperconjugation non-negligibly stabilizes the *syn* conformation.

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Supporting Information Available: Details of donor−acceptor interactions for CFPA-OMe *syn* and *anti* conformations; hyperconjugation energies resulting from deletion of interaction between CFCC and O−C═O in the fluoroester fragment and between CFCC and $C_{Ph}C_{Ph}C_{Ph}$ in the fluorotoluene fragment; Mulliken and Natural Population Analysis (MPA and NPA) together with discussion; and complete refs 29 and 30. This material is available free of charge via the Internet at http://pubs.acs.org.

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