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Conformational studies of (−)-epicatechin-Mosher ester

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Abstract—An in depth ab initio investigation into the factors governing the conformational behaviour of α-methoxy-α-trifluoromethyl-α-phenylacetic acid (MTPA) esters, extensively utilized to determine the absolute stereochemistry of secondary alcohols and amides, discloses the hyperconjugative interactions responsible for the important *syn*- and *anti*-periplanar conformational rigidity and the predominance of the former over the latter. The first flavonoid–Mosher ester crystal structure is reported.

During the past 30 years[1] enantiopure (*R*)- and (*S*)-α-methoxy-α-trifluoromethyl-α-phenylacetic acids (MTPA) have been the most commonly used chiral derivatizing agents (CDA) for the determination of the absolute configuration and ee of secondary alcohols and amides by ^{1}H and ^{19}F NMR spectroscopy. The origin of the conformational preference in these ester derivatives, which plays the key role in the assignment of the absolute configuration of the substrate has, however, hitherto not been accounted for. Investigation of the conformational dynamics of MTPA esters have been limited to molecular mechanics (MM) and semi-empirical (SE) calculations[1] which have proved to be inadequate, thus leading to erroneous conclusions.

The well documented Mosher protocol (Scheme 1)[1] involves the preferential shielding of protons or substituents (L^1 or L^2) by the diamagnetic effect of the aromatic ring of the MTPA derivative.

This is only conceivable for a very specific conformation of the latter. Since the configuration of, for example, (*R*)-MTPA is known, and shielding occurs only on one side of the carbinyl carbon atom, the absolute stereochemistry of the alcohol can be deduced. This is observed by NMR as the relative ((*S*)–(*R*)) chemical shift difference (ppm) between the two carbinyl substituents which is brought about by an average time weighted preferential shielding of the two groups by the π-electron cloud of the α-phenyl substituent on the MTPA ester moiety (Fig. 1).

Dale and Mosher[2] proposed a model in which the hydrogen of the carbinyl moiety is quasi-eclipsed by the carbonyl oxygen while two distinct orientations are known to exist for the trifluoromethyl group. The more dominant of the two represents a conformation with the CF_3 group aligned *syn* periplanar (sp) with the carbonyl group and the other *anti* periplanar (ap). Following extensive ab initio calculations[†] backed by IR, ^{1}H and ^{19}F NMR, we now report the predominance of the sp conformation over the ap conformation in solution and the factors which determine the stabilization of these conformations.

The energy profile of rotation about the αC–CO bond of the methyl ester of MTPA (Me-MTPA used as a model

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Keywords: Mosher ester; Flavonoid; Epicatechin; Flavonol; Hyperconjugation; MTPA; CFTA.

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[†] Computational details: all calculations were performed using the Spartan '94 and Titan '00 software packages. Initial geometry searches and optimizations were performed using semi-empirical methods with the PM3 Hamiltonian. Selected geometries, frequencies, molecular orbital, Mulliken populations and NBO calculations were performed using density functional theory, DFT/pBP/DN** and three parameter hybrid method (B3) employing the correlation functional of Lee, Yang and Parr (LYP) with the standard 6.31G** basis set which requests that a set of p function for each hydrogen atom aside from the d function on the heavy ones. In selected cases, these DFT results were verified with Hartree–Fock (HF) and Møller–Plesset perturbation theory (MP2) using the 6.31G** basis set.

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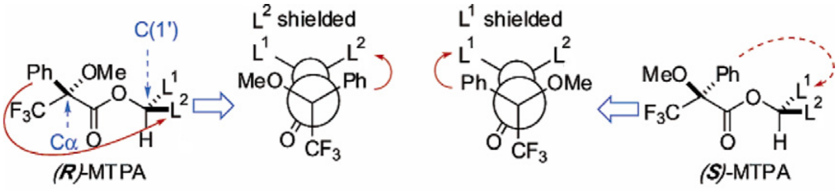
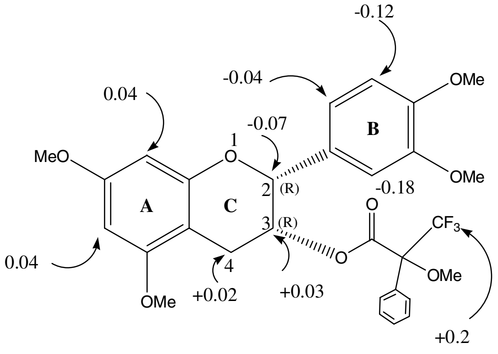


Scheme 1. Shielding effects of (*R*)-, (*S*)-MTPA esters.



Δδ$^{(SR)}$ Epicatechin-MTPA ester

Figure 1. Preferential shielding in the ^{1}H, ^{19}F NMR of diastereomeric (*R*)- and (*S*)-MTPA esters.

structure), calculated by the SE/PM3 method, confirms the sp and ap conformations as low energy states with the ap conformer as the preferred conformer, analogous to that established earlier.[1] Higher-level re-optimizations (DFT/pBP/DN** and B3LYP/6.31G**) of the Me-MTPA ap/sp conformations, however, show the sp conformer to be favoured by 1.5 kcal/mol. Similar behaviour (by 1.4 kcal/mol) is observed for the permethylated epicatechin ester of MTPA (MeEC-MTPA), indicating for both derivatives greater electronic stabilization of the sp conformer relative to the ap conformer. Subsequent frequency analyses of these optimized conformers show no imaginary frequencies reminiscent of real energy minima.

The calculated carbonyl IR stretching frequencies for Me-MTPA and MeEC-MTPA correspond well with the experimental IR data in CHCl$_3$ confirming the lower frequency component of the deconvoluted carbonyl peak as the energetically preferred isomer in solution (Table 1). The deconvoluted frequencies occur in an approximate ratio of 7:3[3] in favour of the sp conformer. These calculations are in line with the previously postulated predominance of the sp conformer as the energetically preferred rotational isomer.[4]

Much attention is currently focused on hyperconjugation as a major factor responsible for establishing a conformational preference in molecules[5] and to the definition of the molecular orbital(s) involved in the stabilization of these conformers. In general three types of hyperconjugation (HC) are defined, viz. sacrificial (cations),[6] isovalent (neutral)[7] and negative (anionic)[8] hyperconjugation. The MTPA-system belongs to the neutral hyperconjugation category, apparently resulting from overlap between the nearly vacant σ^*-(anti-bonding) orbitals on the α-carbon and the filled π-(bonding) orbitals of the carbonyl group (Fig. 2).

Table 1. Ab initio calculation results for the sp and ap conformations of Me-MTPA and MeEC-MTPA[a]

B3LYP\6.31G**	Me-MTPA		MeEC-MTPA	
	sp	ap	sp	ap
ΔE (kcal/mol)	−1.47	0	−1.42	0
ϕCF$_3$–C–CO	−33.7°	125.3°	−31.7°	153.8°
θF$_3\underline{C}$–$\underline{C}$–$\underline{CO}$	108.4°	107.4°	108.8°	112.2°
C=O Freq calcd cm^{-1}	1819	1834	1793	1823
C=O Freq obs. cm^{-1}	n/a	n/a	1742	1765
Mulliken population				
C=$\underline{O}$	−0.474	−0.465	−0.498	−0.484
$\underline{C}$=O	0.629	0.599	0.656	0.644
α–C	0.112	0.106	0.122	0.115
$\underline{C}$–F$_3$	0.843	0.832	0.841	0.846
C–$\underline{F_3}$	−0.262	−0.258	−0.259	−0.257
Bond length (Å)				
C–O	1.340	1.345	1.337	1.279
C=O	1.210	1.208	1.214	1.209
α–$\underline{C}$–$\underline{CO}$	1.550	1.558	1.552	1.557
α–$\underline{C}$–$\underline{CF_3}$	1.5612	1.561	1.561	1.557
$\underline{C}$–$\underline{F_3}$	1.347	1.345	1.348	1.350
α–C–Ph	1.541	1.537	1.541	1.540
α–$\underline{C}$–$\underline{O}$Me	1.405	1.411	1.401	1.406
MO with ΔE > 0.2 eV (ap–sp)				
HOMO−5	0.27	0	0.18	0
LUMO+2	−0.20	0	0.15	0

[a] DFT/pBP/DN** data not included, because the same conclusions are made.

In an attempt to rationalize the predominant stabilization displayed by the sp rotamer, a systematic comparison between the MOs of the sp and ap conformers in both Me-MTPA and MeEC-MTPA, disclosed a few MOs with a meaningful energy difference (approximately 0.2 eV). Two MOs (Table 1) were selected on the grounds of their stability (lower relative energy) while retaining the necessary π-orbital symmetry across

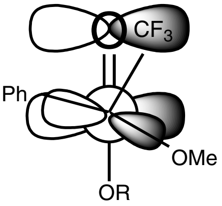


Figure 2a. Orbital overlap.

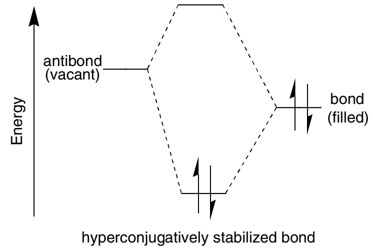


Figure 2b. Orbital interaction.

the αC–CO bond, indicative of hyperconjugative orbital overlap. The HOMO−5 (Fig. 3) with an energy decrease of 0.266 eV for the sp isomer clearly displays π-overlap from the $\pi_{C=O}$ over the αC–CO and αC–CF$_3$ bonds, resulting in the slight shortening calculated for the αC–CO bond, distinctive of hyperconjugative stabilization (for the sp isomer). LUMO+2 (Fig. 4) similarly shows a high degree of π-delocalization over the αC–CO bond together with a 0.2 eV lower relative energy in the ap isomer, thus contributing to the stabilization of this isomer. Hyperconjugative stabilization is then mainly prevalent in the HOMO−5 and LUMO+2, which contains the bonding and anti-bonding combination of atomic orbitals shown in Figure 2.

Three molecular parameters (one geometrical and two electronic) obtained via our higher level re-optimizations of the relevant conformers were applied to evaluate the hyperconjugative effects: (1) the four bond lengths: O=C, αC–CO, O–CO and αC–CF$_3$; (2) the Mulliken atomic populations of these atoms; and (3) natural bond orbital (NBO)[9] analysis.

For the sp isomer, the data (Table 1) disclosed lengthening of the typical C=O bond length due to the loss of π-character, the αC–CO bond is shorter due to an increase in 'π-character' and the αC–CF$_3$ bond is slightly longer probably due to $\sigma_{C\text{–}O}$-donation (α-ester bond) into the $\sigma^*_{\alpha C\text{–}CF3}$ orbital (Fig. 5) (located mainly on the α-carbon) which is an excellent electron acceptor due to the high electronegativity of the CF$_3$ group.[10] These observations support the proposed HC model and are underscored by Mulliken population analysis. The latter shows the carbonyl and α-carbon to be less populated with a greater positive charge in the sp isomer and an increased negative charge on the fluorine atoms due to the delocalization of electron density from the $\pi_{C=O}$ orbitals to the electronegative CF$_3$ group on the α-carbon, reminiscent of hyperconjugative vicinal charge transfer. The αC–CO bond polarization coefficient shifts to the α-carbon.

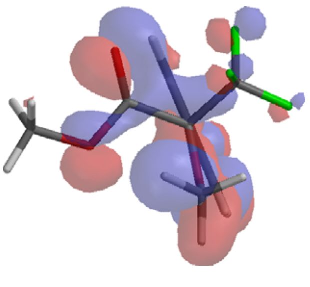


Figure 3. HOMO−5.

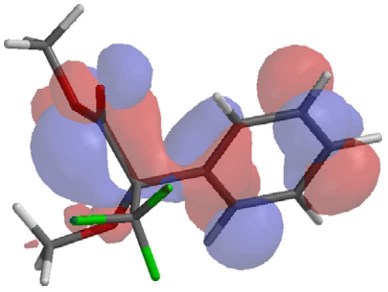


Figure 4. LUMO+2.

Natural bond orbitals (NBO's) provide a means to analyze hyperconjugative interactions with greater detail than is possible by molecular orbitals. Our DFT/pBP/DN** and B3LYP/6.31G** natural bond orbital (NBO) calculations show a highly delocalized electronic configuration. These orbitals are nearly doubly occupied, localized bonding orbitals (bonds) and nearly vacant localized anti-bonding orbitals (anti-bonds). A hyperconjugative interaction is expressed as a charge (electron) transfer between selected bonds and anti-bonds, allowing specific hyperconjugative interactions that influence structural preference, to be pinpointed (Fig. 2b). Our NBO calculations show a strongly delocalized structure with total core, lone pair and bond occupancy of 97.57% and a total Rydberg and anti-bond occupancy of 2.43% for both isomers.

The $\pi^*_{C=O}$ shows a significant increase in bond population in the sp isomer which can be attributed to donation from $\sigma_{\text{–}C\text{–}Ph}$ with a corresponding bond population and bond length decrease (Fig. 2).

The $\pi_{C=O}$ orbital also shows a significant decrease in population and the bond polarization coefficient shifting to oxygen. This π-bond/anti-bond population changes result in a lower bond order for the carbonyl bond, which is reflected in the lower experimental and calculated IR frequencies found for the sp isomer. $\sigma^*_{C\text{–}CF3}$ Display a large increase in population, due to overlap with the $\sigma_{C\text{–}O}$ ester bond leading to the slight lengthening of these bonds in the sp isomer.

$\sigma_{C\text{–}CF3}$ Is more populated in the sp isomer but the bond polarization is shifted towards the CF$_3$-group, leaving

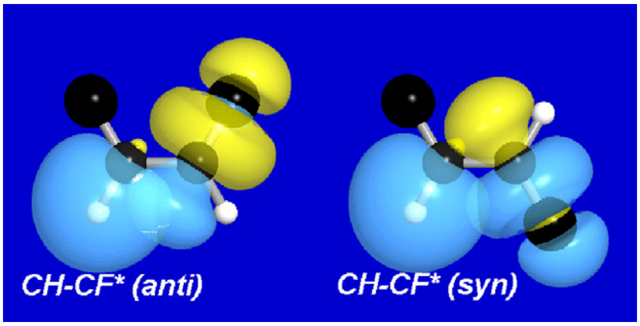


Figure 5. Example of fluorine negative hyperconjugation.

the $\sigma^*_{C–CF3}$ orbital concentrated on the α-carbon. The $\sigma_{C–O}$ ester bond orbital overlap with the $\sigma^*_{C–CF3}$ is analogous to the orbital configuration found for 1,2-difluoroethene, which is responsible for its well-known cis effect. Here the greater overlap of CH–CF* (*anti*) relative to the *syn* configuration greatly stabilizes the cis conformation[11] (Fig. 5). This is reflected in the longer calculated bond lengths of the $\sigma_{C–O}$ ester and αC–CF_3 bonds in the sp isomer of the MTPA derivatives. This interaction between the $\sigma^*_{C–CF3}$ and $\sigma_{C–O}$ orbitals is a classical example of fluorine negative hyperconjugation,[12] a special class of hyperconjugation, and is in line with NBO analysis and the slightly longer bond lengths of these interacting bonds in the sp isomer.

Although the αC–CO bond also, is only slightly shorter in the sp isomer, it remains in line with hyperconjugation because it is now proven that central C–C bond lengthening is crucial in eliminating vicinal repulsive interactions in rotational isomers.[5] It is demonstrated that the well-known staggered conformation of ethane is brought about by hyperconjugation and vicinal steric effects are nullified by the central C–C bond lengthening, thus eliminating an energy increase due to steric effects. Consequently, the αC–CO bond length and the magnitude of the bond length difference is not a reliable indication of the magnitude of hyperconjugation between vicinal interacting bonds.

An additional factor that may play a role in stabilization of the sp and ap conformers may be aided by the electrostatic interaction between the ester (ap) or carbonyl (sp) oxygen and $^{\delta+}CF_3$ group, resulting from the substantial van der Waals radii[13] overlap of 0.357 Å and 0.387 Å for the sp and ap conformations, respectively. H-bonding between the OMe carbon and the carbonyl oxygen lone pair with a van der Waals radii overlap of ca. 0.395 Å will contribute similarly to the stability of the ap conformer.

Flavonoids are notoriously noncrystalline and very few flavonoid crystal structures are known.[14,15] To our knowledge, permethylated epicatechin-(*R*)-α-methoxy-α-trifluoromethyl-α-phenyl acetate (MeEC-MTPA), is the only known flavonoid-MTPA ester derivative in a crystalline state (Fig. 6). It is noteworthy that MeEC-MTPA crystallized as the ap conformer, which also displays a large van der Waals interaction between the CF_3 group and the ester oxygen. These interaction distances measure 2.721 Å corresponding to a 0.499 Å van der Waals overlap between the ester oxygen and the CF_3 carbon and a 2.668 Å distance between this oxygen and closest fluorine on the CF_3 group. The latter corresponds to a 0.322 Å van der Waals overlap. Crystal packing and π–π interactions were probably responsible for the ap conformation which is not the preferred conformation found experimentally in solution[1,2] and in our calculations.

Our calculations on a recently developed α-fluoroacetate chiral derivatizing agent, CFTA,[16] which has an α-fluorine atom, also show noteworthy fluorine–oxygen van der Waals interactions in the energetically favoured sp and ap conformations. This suggests that, in the MTPA case, the peculiar oxygen–fluorine van der Waals overlap in the sp and ap conformers is not necessarily only the result of the electrostatic oxygen and $^{\delta+}CF_3$ carbon interaction.

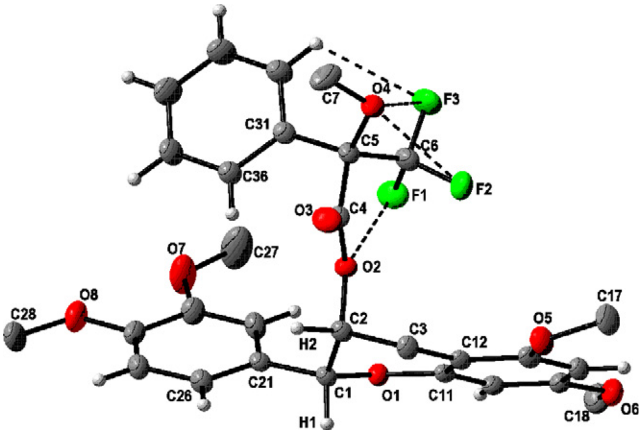


Figure 6. Diamond software drawing of epicatechin-(*R*)-α-methoxy-α-trifluoromethyl-α-phenyl acetate; ellipsoids at 20% probability, methyl protons omitted for phenyl rings, first digit (1–3) refers to ring number, second digit (1–6) to atom in ring. Interaction of fluorine atoms ca. 2.5–2.7 Å.

In conclusion, our results disclose the anti-bonding interactions and the molecular orbitals involved in the hyperconjugative stabilization of the sp and ap conformer pair and the predominance of the former. The conclusions are substantiated by the calculated (DFT/pBP/DN** and B3LYP/6.31G**) bond length changes, Mulliken populations and NBO analysis.

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References and notes

1. Seco, J. M.; Quinoa, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17–117.
2. Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519.
3. Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.
4. Merckx, E. M.; Vanhoeck, L.; Lepoivre, J. A.; Alderweireldt, F. C. *Spectrosc. Int. J.* **1983**, 30–42.
5. Pophristic, V.; Goodman, L. *Nature* **2001**, *411*, 565–568.
6. Laube, T. *Acc. Chem. Res.* **1995**, *28*, 399–405.
7. Lambert, J. B.; Robert, A. S. *J. Am. Chem. Soc.* **1992**, *114*, 10246–10248.
8. Koppel, I. A.; Pohl, V.; Koppel, I. A.; Anvia, F. *J. Am. Chem. Soc.* **1994**, *116*, 8654–8657.

9. Weinhold, F. In *The Encyclopedia of Computational Chemistry*; Schleyer, P. v. R., Ed.; John Wiley & Sons: Chichester, 1998; pp 1792–1811.
10. Apeloig, Y. *J. Chem. Soc., Chem. Commun.* **1981**, 396–398.
11. Craig, N. C.; Entemann, E. A. *J. Am. Chem. Soc.* **1961**, *83*, 3047–3050.
12. Schleyer, P. v. R.; Kos, A. J. *Tetrahedron* **1983**, *39*, 1141–1150.
13. Bondi, A. *J. Phys. Chem.* **1964**, *68*, 441–451.
14. Cantrell, J. S. *Plant Flavonoids in Biology and Medicine: Biochemical, Pharmacological and Structure–Activity Relationships* **1986**, 391–394.
15. Jiang, R.; Ye, W.; Woo, K.; Du, J.; Che, C.; But, P. P.; Mak, T. C. W. *J. Mol. Struct.* **2002**, *642*, 77–84.
16. Takeuchi, Y.; Fujisawa, H.; Noyori, R. *Org. Lett.* **2004**, *6*, 4607–4610.