Bull. Chem. Soc. Jpn. Vol. 79, No. 4, 555–560 (2006)

Hyperconjugative Electron-Delocalization Mechanism Controlling the Conformational Preference of Fluoroacetaldehyde and Methyl Fluoroacetate

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We confirmed by both canonical molecular orbital analysis and the orbital deletion procedure (ODP) that a hyperconjugative electron-delocalization mechanism is the main factor controlling the conformational preference for *cis* and *trans* conformations of fluoroacetaldehyde (FAA) and methyl fluoroacetate (MFA). The quantitative analysis based on the ODP approach shows that the effects of hyperconjugation are more important in the *cis* conformation than in *trans* conformation.

In the design of molecules for applications in biological studies, the introduction of fluorine has special advantages. Indeed, fluorine-containing molecules continue to attract much attention by researchers in biochemistry, medicinal chemistry, pharmacology, and related fields. A major factor for the utility of these compounds comes from the fact that the formation of C–F bonds in general induces a relatively small change to the shape of a molecule.[1] This can permit interactions of the fluorinated analogue with enzyme active sites, transport proteins, receptors, and other macromolecules that are comparable to those of a non-fluorinated parent molecule. However, the strong electronegativity of fluorine can induce important changes to the physicochemical character of the molecule, and these changes can be exploited for a variety of purposes.

An example of this is the subject of this study. In the presence of a C=O bond, the C–F bond adopts a specific orientation, and this can influence the conformation of bio-molecules. Such orientation has been shown to be of particular interest as it affects the tuning of molecules for particular objectives.[2,3] It is thus apparent that a greater understanding of the nature of interactions between C=O and C–F bonds, and the factors that may influence this interaction would be useful, particularly for the design and synthesis of new fluorinated compounds that take advantage of controlling conformation by exploiting the orientation of the C–F bond with respect to the C=O bond. In the present theoretical study, we have chosen fluoroacetaldehyde (FAA) and methyl fluoroacetate (MFA) as prototypes. The relatively simple structures make a high level of calculations practical. In addition, since FAA has been identified as a common biosynthetic intermediate for fluoroacetic acid and 4-fluorothreonine,[4] these compounds themselves have biological relevance.

In this paper, we present a theoretical study on FAA (FCH_2CHO) and MFA (FCH_2COOCH_3) to examine the conformational effect of the F atom located at the stereogenic center of these two compounds. For FAA and MFA, previous theoretical investigations have identified only two distinct stable conformations: *cis* and *trans* conformations.[5,6] The *cis* and *trans* conformations for FAA and MFA are schematically shown in Fig. 1. So far, no explanation has been given regarding the stability of these two conformations, *cis* and *trans*, for both FAA and MFA. Using Møller/Plesset perturbation theory,[7] we show that a hyperconjugation between $\pi(CH_2F)$, the π-like orbital of a CH_2F group, and $\pi(CO)$, the π orbital of C=O (the carbon atom of which is electron deficient), is responsible for the stability of *cis* and *trans* conformations. Much attention has recently been paid to "hyperconjugation" as one of the factors, if not the only factor, that contributes to the stabilization of the preferential conformation(s).[8–12] There exist two types of molecular orbital pictures in studying the effects of hyperconjugation: One is based on the canonical orbitals of two groups that constitute FAA (MFA) and the other is based on localized bond orbitals (LBO). The essence of the hyperconjugation arises from orbital overlap in the canonical orbital picture. There exist three types of hyperconjugation: "sacrificial hyperconjugation," "negative hyperconjugation," and "isovalent hyperconjugation."[13] Our systems belong to the third category, where the interaction takes place between the σ-bonding orbitals with an adjacent empty, or partially filled p- or π-orbital. To quantitatively evaluate the hyperconjugative energy, we employed the orbital deletion procedure (ODP) approach in which certain specific atomic orbitals are forced to be vacant. The resulting ODP's wavefunction corresponds to a localized wavefunction and its corresponding energy difference with the delocalized one, i.e., the usual Hartree–Fock energy, is the hyperconjugation energy.[14–16]

Published on the web April 7, 2006; DOI: 10.1246/bcsj.79.555

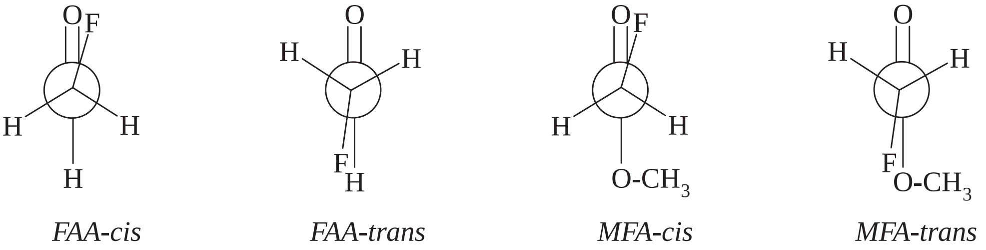


Fig. 1. Stable structures for FAA and MFA found at the MP2(fc)/6-31++G(d,p) level of theory.

Computational Details

Calculations at the second and fourth orders of the Møller/Plesset perturbation theory using the frozen core option, MP2(fc) and MP4(fc), were carried out using the standard 6-31++G(d,p) basis set, as implemented in the Gaussian 03 suites of program.[17] In the MP4 calculations, single, double, and quadruple excitations have been taken into account (MP4(fc)(SDQ)). The potential energy curves were calculated as a function of the F–C–C=O dihedral angle at the MP2 level. To better evaluate the energy difference and to provide the MOs required for this work, we re-optimized the geometries of the stable conformers obtained along the potential energy curves at the MP4 level as well as at the MP2 level. Energy calculations using the G2MP2[18] and G2[19] methods were then performed on the optimized MP2 and MP4 structures in order to accurately evaluate the energy difference between the *cis* and *trans* conformers.

Results and Discussion

Fluoroacetaldehyde (FAA). In agreement with previous theoretical investigations,[20] we found two distinct stable conformers of FAA: the *cis* conformation with an F–C–C=O dihedral angle equal to 0 degrees and the *trans* conformation with an F–C–C=O dihedral angle equal to 180 degrees. Figure 2a shows the FAA potential energy curve calculated at the MP2(fc)/6-31++G(d,p) level of theory.

As can be seen in Fig. 2a, the *trans* conformation is more stable than the *cis* one. Our calculations gave consistent MP2/MP4 and G2MP2/G2 energy differences between the *cis* and *trans* conformers (2.03/2.11 kcal mol^{-1} at the MP2/MP4 levels and 1.59/1.63 kcal mol^{-1} at G2MP2/G2 levels, respectively). The results are in good agreement with the CASSCF calculations done by Bataev et al. (2.21 kcal mol^{-1})[21] and with the MP2/6-31G* calculations done by Phan et al. (1.69 kcal mol^{-1}).[20]

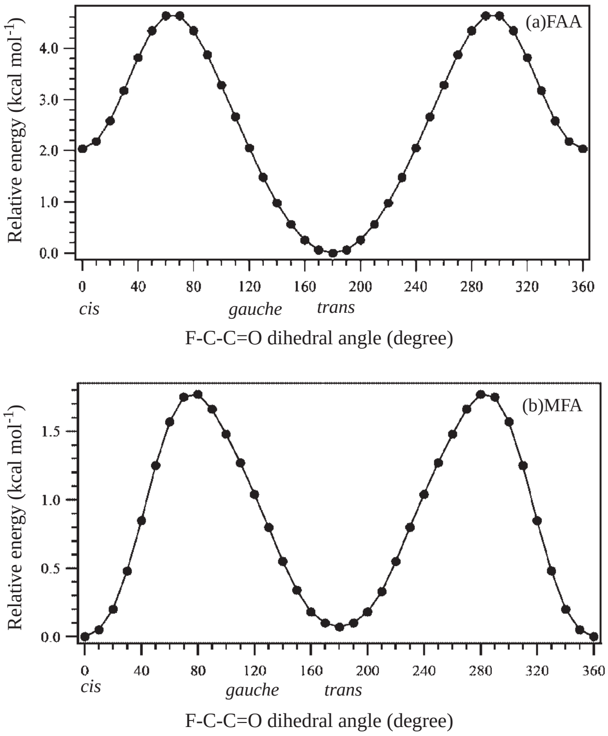
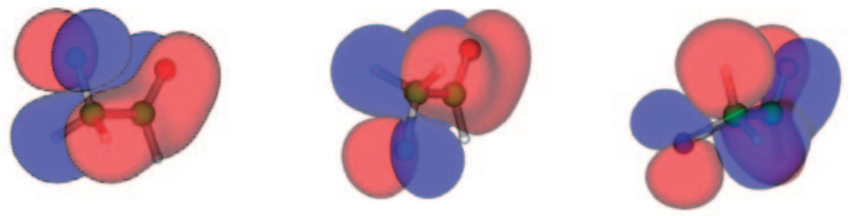
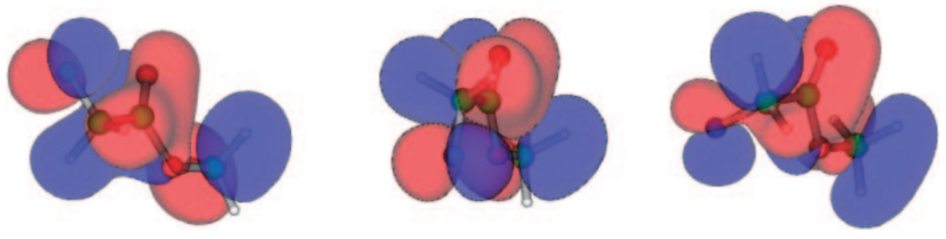


Fig. 2. Potential energy curves for (a) FAA and (b) MFA calculated at the MP2(fc)/6-31++G(d,p) level of theory.

In order to explain the stability of the *cis* and *trans* conformations, we examined all of the occupied MO phases and the energy lowering of both *cis* and *trans* conformers, as well as those of the *gauche* conformer. For the *gauche* conformation, the F–C–C=O dihedral angle was set equal to 120 degrees. We found that the HOMO−2 and HOMO−1 of the *cis* and *trans* conformers are the orbitals of interest. Concerning MO phases, as can be seen in Fig. 3 (top figure), there is an overlap between π(CO) and π(CH$_2$F) in both conformers for HOMO−2. We assign this overlap to the hyperconjugative electron delocalization between π(CH$_2$F) and π(CO). To better understand the origin of this overlap, we constructed the MOs correlation diagram, in which the π orbital of HCHO and the π orbital of CH$_3$F were employed for π(CO) and π(CH$_2$F), respectively. In Fig. 4 is presented the MOs correlation diagram for the FAA *cis* conformation calculated at the HF/6-31G(d,p) level of theory; that of the *trans* conformation has similar features, and therefore is not shown. Figure 4 shows that in the first-order approximation the HOMO−2 of FAA is constructed from a linear combination of occupied MO's with the same phase between the two groups, i.e., the HOMO of CH$_3$F (π(CH$_2$F)) and the HOMO−1 of CO (π(CO)). Furthermore, in Fig. 4, we note a considerable amount of energy lowering in the HOMO−1 of FAA compared with that expected from a simple MO treatment. Such an energy lowering originates from a repulsive interaction between the HOMO−1 and the LUMO of FAA. The LUMO is constructed from a linear combination of the LUMO+2 of CH$_3$F (π^*(CH$_2$F)) and the LUMO of CO(π^*(CO)). The HOMO−1 and LUMO are characterized by the same orbital phase. The energy lowering of HOMO−1 makes a dominant contribution to the stabilization of the *cis* conformation of FAA. As to the other LUMO (labeled LUMO+4 in our calculation and not shown in Fig. 4 for simplicity of the figure), its shape reflects the properties of a usual LUMO and has the feature of the LUMO+2 of CH$_3$F. However, its higher energy level makes this orbital



FAA *cis,* HOMO–2 (–0.582) FAA *trans,* HOMO–2 (–0.590) FAA *gauche,* HOMO–2 (–0.568)



MFA *cis,* HOMO–5 (–0.581) MFA *trans,* HOMO–5 (–0.584) MFA *gauche,* HOMO–4 (–0.566)

Fig. 3. Molecular orbitals of HOMO−2 for FAA conformers and HOMO−5 (HOMO−4) for MFA conformers. The blue spheres are for F, red ones are for O, green ones are for C, and gray ones are for H. In parentheses are the orbital energies in atomic unit (au).

not important, as any interaction with it will have no effect on the stability of the conformation.

It is worth correlating our results with those reported theoretically and experimentally for a similar type of hyperconjugation, although no thorough investigation on fluorine-containing compounds have been reported to the best of our knowledge. The type of interaction we have shown in Fig. 4 has been seen in several cases of compounds having methyl groups.[8–10,22–27] Nakai and Kawai have assigned this type of interaction to the hypercojugation mechanism between orbitals of the ring system and two CH bonds.[9,10] A correlation between the hypercojugation mechanism in their systems and in FAA can be easily recognized. In fact, the unoccupied MO of CO is perpendicular to the plane of the molecule. Such an eclipsed position matches very well with the two occupied orbitals of each CH bond, resulting in perfect interaction between the two orbitals. This is one evidence that the hyperconjugation plays an essential role in determining the stable *cis* conformation of FAA.

The shape of the hyperconjugative MO found in the *trans* conformation is similar to the *cis* one. Comparing the energy of the HOMO−2 levels of both *cis* and *trans* conformations, which have almost the same energy as the HOMO−2 level in *gauche* conformation, we found an upward shift of the energy level by about 0.02 au.

For the *gauche* conformation, π(CO) partially overlaps with π(CH_2F) because of the "unfavorable" geometrical position of one of the two C–H bonds that lies in an eclipsed arrangement with C=O. In addition, the out-of-phase of the F-orbital is not fitted to overlap with π(CO). These two factors result in a non-rigid interaction and therefore contribute to the instability of the *gauche* conformation.

In order to clarify how the hyperconjugation mechanism occurs, one should look at the donor–acceptor scheme given by the natural bond orbital (NBO) analysis.[28–30] Inspection of the NBOs shows that there exist two types of charge transfers between the two fragments, CH_2F and CO. A charge transfer from the two localized donor CH σ-bonds, assigned in this paper by π(CH_2F), to the localized vacant acceptor orbitals σ^*(CO) and π^*(CO) for the *cis* conformation and only to π^*(CO) for the *trans* conformation has been noticed. The π(CH_2F) to σ^*(CO) energy contribution in the stability of the *cis* conformation represents almost 33% of that of the π(CH_2F) to π^*(CO) one. The second type is a charge transfer from π(CO) to π^*(CH_2F). When numerically comparing the two types of contributions to the stability of either the *cis* or *trans* conformation, we found that the contribution of the π(CO) to π^*(CH_2F) charge transfer represents approximately 19–24% of that of the π(CH_2F) to π^*(CO) one. This result clearly indicates that the latter interaction, π(CH_2F) to π^*(CO), is the dominant factor in the stability of both the *cis* and *trans* conformations.[31] As one can easily conclude, the coupling hypothesis between the two fragments, CH_2F and CO, discussed above is in line with the analysis of the NBOs.

To confirm the hyperconjugative mechanism, we used the ODP approach based on the NBO analysis. Deletion of selected donor–acceptor interactions in the NBO description of FAA conformers by using the ODP approach quantitatively demonstrates the non-negligible contribution of the hyperconjugation effect in the stability of the *cis* and *trans* conformers (Fig. 5). It is also clear from Fig. 5 that the effect of the hyperconjugation on the stability of *cis* is more important than that on *trans* and *gauche*, which follows the order *cis* > *trans* > *gauche*. This finding provides additional clear evidence that the stability of the *cis* conformer is largely maintained by hyperconjugation, while that of *trans* is attributed to a combination of hyperconjugation and other effects such as electrostatic ones. The electrostatic effects involve repulsive interactions between the charge of the F atom and that of the O atom, and the dipole–dipole interactions between the CF group and the CO group, both of which favor the *trans* conformation of FAA.

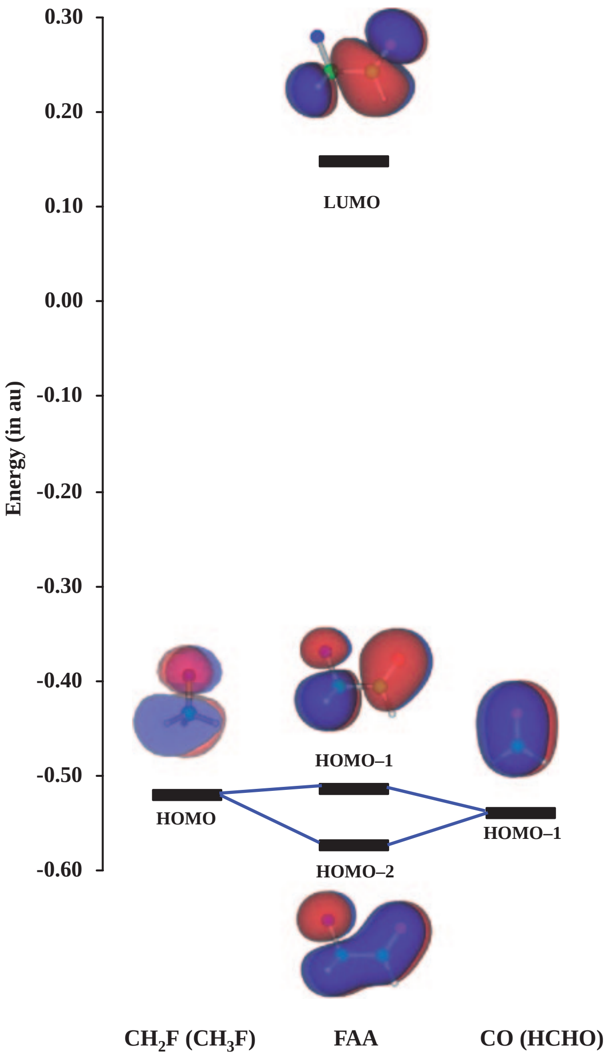


Fig. 4. Molecular orbital correlation diagram for FAA *cis* conformer calculated at the HF/6-31G(d,p) level of theory. Blue spheres are for F, red ones are for O, green ones are for C, and gray ones are for H.

Methyl Fluoroacetate (MFA). Again, the *cis* and the *trans* conformations of MFA are the only stable ones, as shown in Fig. 2b. In contrast to FAA, the energy difference between the *cis* and the *trans* conformers in MFA is insignificant (0.07/0.20 and 0.10/0.09 kcal mol^{-1} at MP2/MP4 and G2MP2/G2, respectively). These results are also consistent with Abraham's DFT calculations.[6] Hyperconjugation was found in the HOMO−5 molecular orbital for both *cis* and *trans*, at almost the same energy level (−0.584 and −0.581 au for *trans* and *cis*, respectively, see bottom of Fig. 3). For the *gauche* conformation, a unique molecular orbital where hyperconjugation occurs, the HOMO−4 orbital, lies at a higher energy level than those in *cis* and *trans* ones. The calculated deviation is 0.02 au, the same as that found for the FAA *gauche* conformer. The HOMO−5 molecular orbital, which lies at −0.566 au in the *gauche* conformer, is mainly π(CO) with no interaction with either of the F or H atoms away from the CO by 120 degrees.

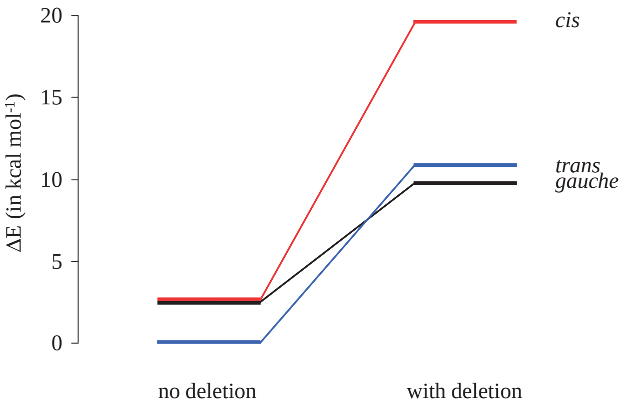


Fig. 5. Effect of deletion on the stability of *cis*, *trans*, and *gauche* conformations for FAA calculated at HF/6-31++G(d,p) level. Optimized geometries at MP2(fc)/6-31++G(d,p) level are used. ΔE denotes energies of FAA relative to energy without deletion in the *trans* conformation.

The NBO analysis shows three types of charge transfers between the two fragments, CH_2F and CO, in MFA *cis* and *trans* conformations. The first two charge-transfer types are those found in the case of FAA, namely $\pi(CH_2F)$ to (σ^*(CO) + π^*(CO)) and π(CO) to $\pi^*(CH_2F)$, while the third one is a charge transfer from π^*(CO) to $\pi^*(CH_2F)$ that occurs at higher energy levels. It should be noted that the π^*(CO) to $\pi^*(CH_2F)$ charge transfer is relatively important compared with the π(CO) to $\pi^*(CH_2F)$ contribution, and this is true for all MFA conformations. Indeed, our calculations give 13.3 and 16.3% with respect to the energy contribution of $\pi(CH_2F)$ to π^*(CO), which is the most important contribution, for *cis* and *trans* conformations, respectively. This type of interaction, which has been identified as hyperconjugation, has already been pointed out by Nakai and Kawai for the internal rotation of the methyl group in the substituted toluene,[9,10] and also by other groups.[23,25–27] Overall, the contribution of both π(CO) to $\pi^*(CH_2F)$ and π^*(CO) to $\pi^*(CH_2F)$ represents 26.7–32.8% of the $\pi(CH_2F)$ to π^*(CO) one, confirming once again the dominant effect of $\pi(CH_2F)$ to π^*(CO) in the stability of both *cis* and *trans* conformations.

In a way similar to that used for FAA, the ODP approach gave evidence of the effect of hyperconjugation on the stability of both the *cis* and *trans* conformations for MFA. Figure 6 shows the hyperconjugative energy for each the *cis*, *trans*, and *gauche* conformations for MFA. One can easily notice from Fig. 6 that, while the energy difference between the *cis* and *trans* conformations with no deletion of hyperconjugative MOs is almost zero, deletion of those MOs enhances the energy difference between them up to 6.4 kcal mol^{-1}. Once more, the effect of hyperconjugation is more important in the *cis* conformation than that in *trans* and *gauche*, and follows the order *cis* > *trans* > *gauche*, as is the case for FAA, suggesting that the stability of *cis* is mainly attributed to hyperconjugative effects.

The hyperconjugation in the two systems studied in the present work, FAA and MFA, is schematically shown in Fig. 7. As a result of the electron-withdrawing effect exerted by the carbonyl oxygen atom, the partially empty 2p orbital of the carbon facilitates electron delocalization with $\pi(CH_2F)$. For the *gauche* conformation, the orbital overlap takes place

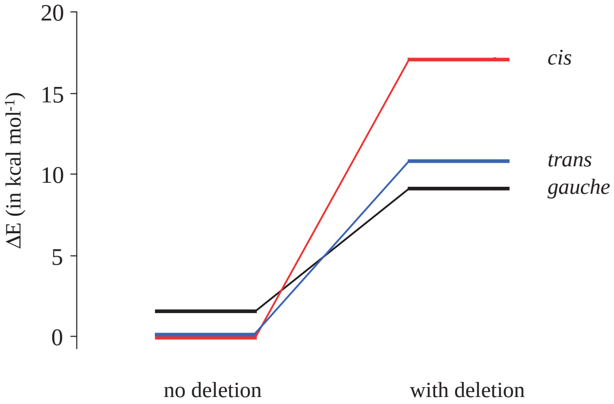


Fig. 6. Effect of deletion on the stability of *cis*, *trans*, and *gauche* conformations for MFA calculated at HF/6-31++G(d,p) level. Optimized geometries at MP2(fc)/6-31++G(d,p) level are used. ΔE denotes energies of MFA relative to energy without deletion in the *trans* conformation.

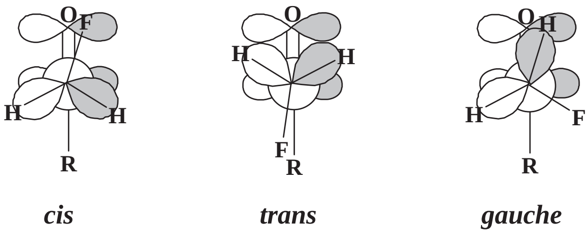


Fig. 7. Schematic representation of hyperconjugation between $\pi(CH_2F)$ and $\pi(CO)$ in FAA (R = H) and MFA (R = OCH_3) conformers.

between CO and only one of the two CH in FCH_2, yielding a non-stable conformation. It should be mentioned here that the hyperconjugative model type proposed by Nakai and Kawai,[9,10] and questioned by Suzuki et al.,[25] has been confirmed and supported by the NBO analysis. Nevertheless, both NBO and ODP have advantages in identifying which of the existent interactions is the most dominant. More examples with substituted methyl groups are needed to check the validity of Nakai's model.

Conclusion

The stabilities of the *cis* and *trans* conformations of fluoroacetaldehyde and methyl fluoroacetate have been theoretically investigated by means of MP2 and MP4 levels of theory. By analyzing the MOs based on the Hartree–Fock wave function of both FAA and MFA, we have demonstrated that the stabilities of the *cis* and *trans* conformations originate from hyperconjugation effects. Using the NBO analysis and the ODP approaches, we have confirmed that hyperconjugative interactions non-negligibly reduce the energy difference between *cis* and *trans* conformations, and is the main factor for the stability of the *cis* conformation. An important issue from this study is that the geometrical position of the F atom in the same plane with the carbonyl is crucial for maximizing the effect of hyperconjugation. Finally, the results obtained by MP2 calculations should be useful for further investigations of larger molecules that contain fundamental functions, i.e. C–F and C=O, such as in α-cyano-α-fluoro-p-tolylacetic acid.[32,33]

R. S. acknowledges the receipt of a JSPS grant (P02353). This work was partially supported by grant of the 21st Century COE Program "Giant Molecules and Complex Systems." Part of the computational results in this research were obtained using the supercomputing resources at Information Synergy Center, Tohoku University.

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