

Torsional Potentials of Mono- and Fluoro-halooxopropenolates

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Abstract: Torsional potentials of mono- and fluoro-halooxopropenolates were computed using accurate quantum chemical calculations. Effects of electron correlation and basis set were studied. Most MO-based methods give similar patterns for torsional potentials. The DFT-based methods, on the other hand, yield too high barrier height for all conformations. Except for cc-pVDZ, all basis sets studied yield the similar level of accuracy for the computed torsional barriers. Steric repulsion could be used to explain the torsional potential of mono- and fluoro-halooxopropenolates. Bond conjugation also plays important roles to the stability of conformers.

Keywords: Enolates, Torsional potential, Ab initio, DFT

1 Introduction

Enol and enolate compounds have important roles in chemistry. They are used as starting materials for chemical synthesis and have many applications in various fields such as pharmaceutical, food industry, etc. The enolate compounds are the tautomeric isomers of diketones which can be applied as HIV-1 integrase (IN) inhibitor, a new class of anti-AIDS drugs. [1] It is also proposed that enolates are active forms of these diketone compounds for the integrase inhibition. [2] Knowledge about conformations of enolate compounds would be beneficial in the design of more active drugs. There are several theoretical calculations which were carried out in regarding to the binding of the inhibitor with the integrase enzyme. [3-6] However, there were very few theoretical studies that investigated the torsional potential of these compounds. Nunthaboot et. al. performed B3LYP/6-31G(d,p) for torsional potential of 5-CITEP, an HIV-1 integrase inhibitor. [7] But they aimed their investigation at the effect of substituents on conformation of 5-CITEP. In their calculations, the positions of two carbonyl groups (or keto-enol moieties) were constrained to be planar. Here, the position of the keto-enol moieties and effects of substituents on the conformations of keto-enol moieties were studied by performing very accurate quantum chemical calculations.

2 Computational Details

Geometries of various mono- and di-halo enolate compounds, Fig. 1, were optimized at MP2/cc-pVDZ. Two torsion angles, D1 and D2, were considered and varied at the optimized structures to obtain torsional potentials using varieties of methods (HF, MP2, MP4(SDTQ), CISD, CCSD(T), SVWN, BLYP, and B3LYP) and basis sets (cc-pVDZ, cc-pVTZ, cc-pVQZ, aug-cc-pVDZ, aug-cc-pVTZ, and aug-cc-pVQZ).

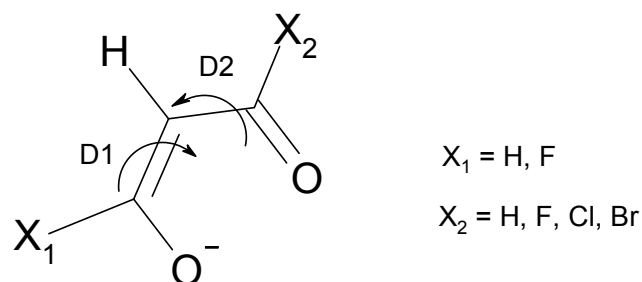


Fig. 1 Schematic display of mono-/di-halo enolate compounds at D1 and D2 torsion angles. The figure represents the (0,0) conformation.

3 Results and Discussions

3.1 Effects of electron correlation

Fig. 2 shows torsional potential of D1 at fixed D2 for 3-oxopropen-1-olate ($X_1 = \text{H}$, $X_2 = \text{H}$) computed at cc-pVDZ basis and various methods. Fig. 3 shows torsional potential of D2 at fixed D1 for 3-oxopropen-1-olate computed at cc-pVDZ and various methods.

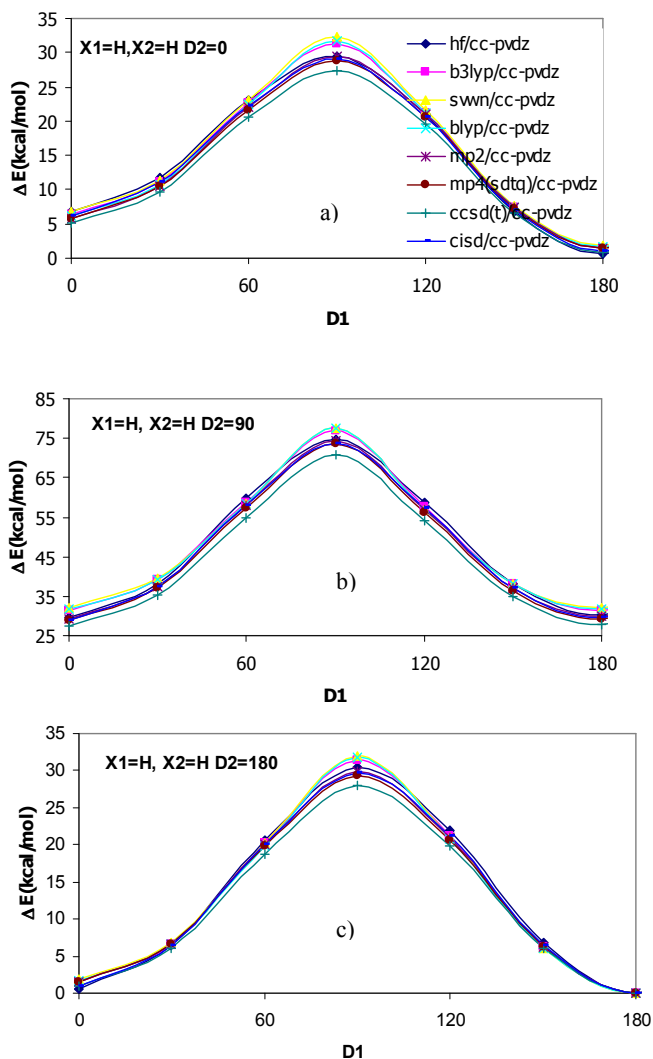


Fig. 2 Torsional potentials of D1 at fixed D2 a) $D2 = 0^\circ$, b) $D2 = 90^\circ$, c) $D2 = 180^\circ$ for 3-oxopropen-1-olate obtained using cc-pVDZ basis set and various methods.

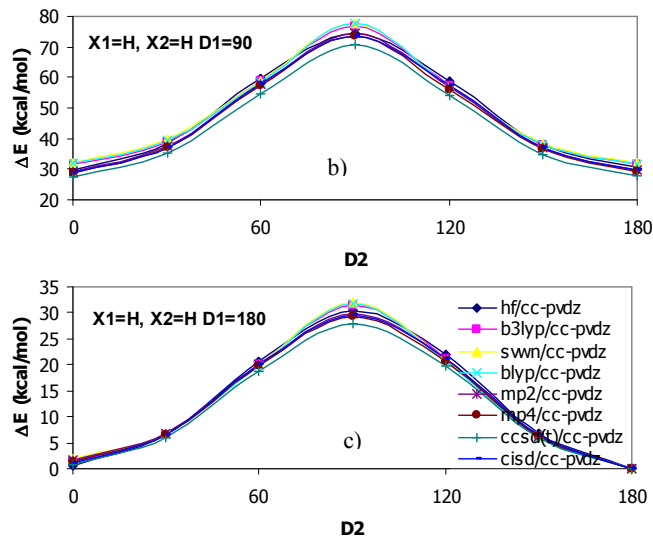
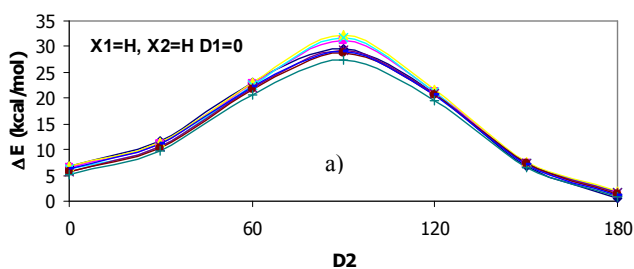


Fig. 3 Torsional potentials of D2 at fixed D1 a) $D1 = 0^\circ$, b) $D1 = 90^\circ$, c) $D1 = 180^\circ$ for 3-oxopropen-1-olate obtained using cc-pVDZ basis set and various methods.

From Fig. 2 and Fig. 3, it could be observed that with cc-pVDZ basis HF, MP2, MP4(SDTQ), and CISD methods give similar torsional potential both qualitatively and quantitatively. This implies that level of electron correlation does not have an effect on the rotation potential of the enolate compounds. However, the CCSD(T) method gives the lowest barrier height as compared to other methods. Interestingly, all DFT methods employed in this work, SVWN, BLYP and B3LYP, give too high barrier height for all conformations. Thus, DFT methods may not be suitable for describing the C-C bond rotation in the enolate compounds. Considering the accuracy and cost, MP2 method is recommended for the calculations of torsional potentials for enolate compounds.

3.2 Effects of basis set

Fig. 4 shows torsional potential of D1 at fixed D2 for 3-oxopropen-1-olate computed using MP2 method and various basis sets. Fig. 5 shows torsional potential of D2 at fixed D1 for 3-hydroxypropenal computed using MP2 method and various basis sets.

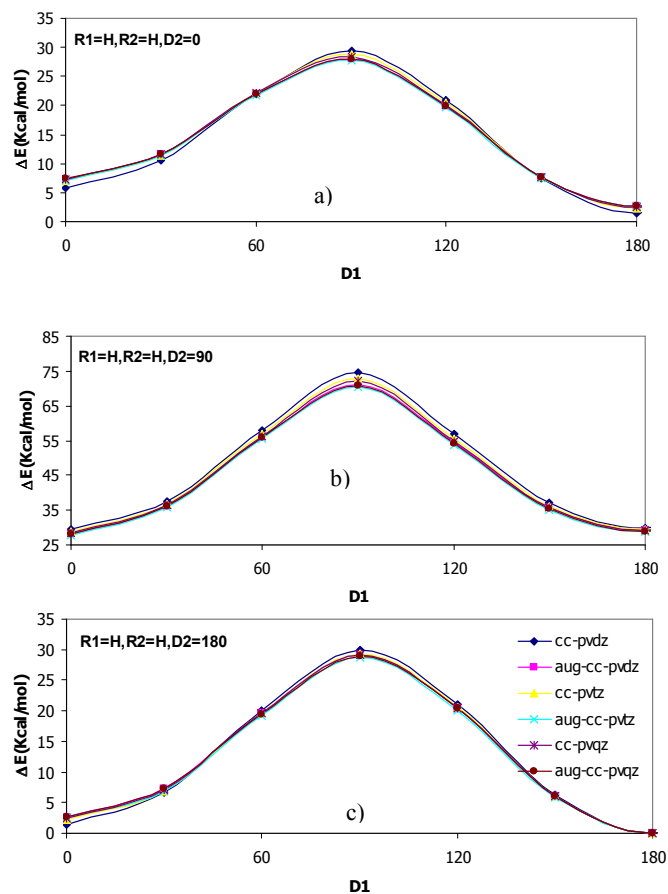


Fig. 4 Torsional potentials of D1 at fixed D2 a) $D2 = 0^\circ$, b) $D2 = 90^\circ$, c) $D2 = 180^\circ$ for 3-oxopropen-1-olate obtained using MP2 method and various basis sets.

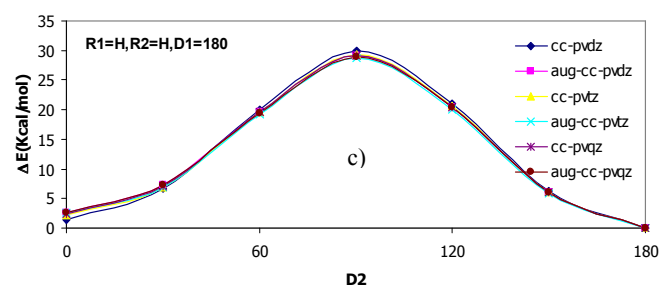
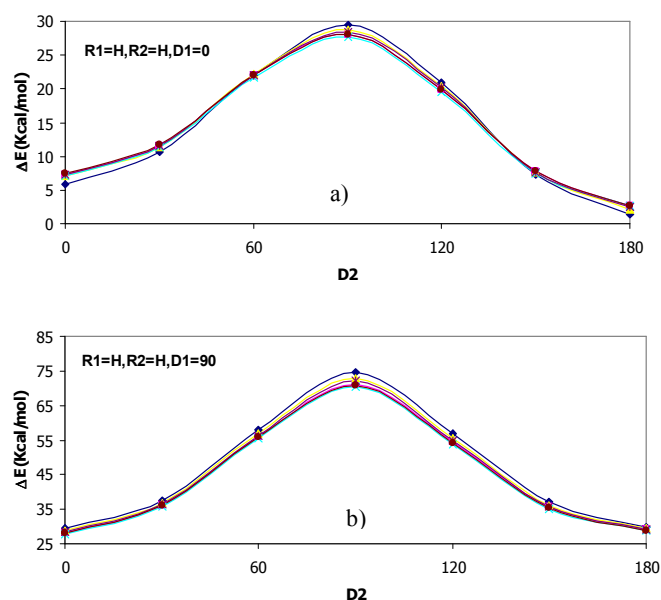
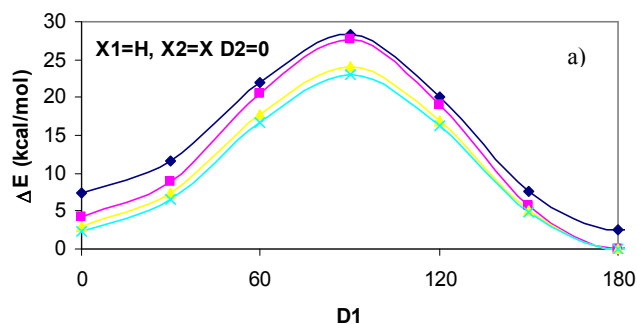


Fig. 5 Torsional potentials of D2 at fixed D1 a) $D1 = 0^\circ$, b) $D1 = 90^\circ$, c) $D1 = 180^\circ$ for 3-oxopropen-1-olate obtained using MP2 method and various basis sets.

From the preceding session, we performed MP2 calculations with various basis sets to estimate the basis set effect on the torsional barrier of enolate compounds. The cc-pVDZ basis set seems to yield too high barrier height for all conformations while other basis sets seem to give similar result. Thus, this basis set may not be suitable for calculations of rotation barriers of enolate compounds. However, the aug-cc-pVXZ basis sets seem to render similar accuracy for all conformations. The deviation of cc-pVTZ basis is observed at the conformations with torsion angle of 90° while the cc-pVQZ gives the similar accuracy to the aug-cc-pVXZ basis. Considering the accuracy and cost, the cc-pVQZ basis is recommended for the calculations of torsional potentials for enolate compounds.

3.3 Monohalo enolates

The comparison between torsional potentials of D1 at fixed D2 and of D2 at fixed D1 for monohalo enolate compounds is made in Fig. 6.



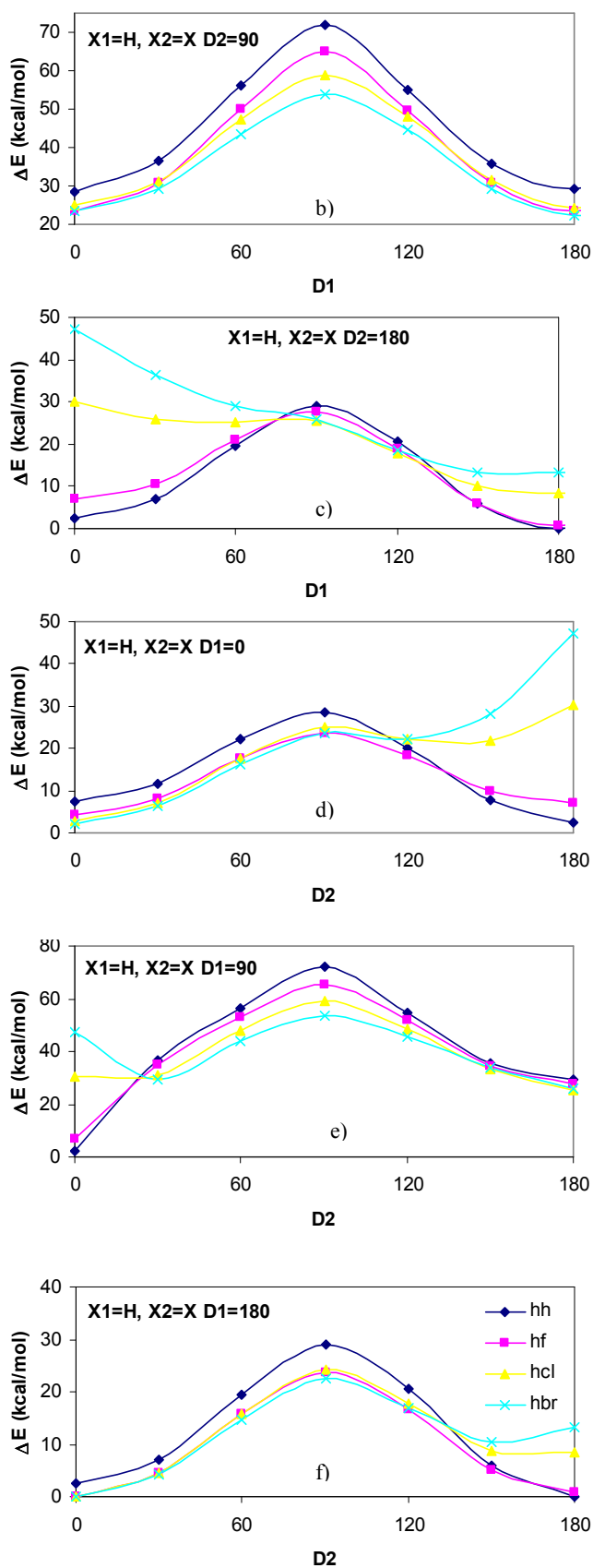


Fig. 6 a) – c) torsional potentials of D1 at fixed D2 (0° , 90° , and 180° , respectively) and d) – f) of D2 at fixed D1 (0° , 90° , and 180° , respectively) for monohalo enolate compounds obtained using MP2/cc-pVQZ

Steric repulsion seems to dominate the interaction between moieties on the enolate compounds. The most stable conformer for HH (refers to X_1X_2) enolate compound is (180, 180), the number in the parenthesis representing torsion angle (D1, D2), which is unlike other HX enolate compounds where the minimum was found at (180, 0). For HH enolate compound, the interaction between H-H moieties, (180, 180) conformation, is the weakest while those between H-O and O-H, (0, 180) and (180, 0) conformations, are slightly stronger (2.43 kcal/mol above) and that between O-O, (0, 0) conformation, is the strongest (7.34 kcal/mol). The O-H and H-O conformation have the same energy implies that conjugation is established in this molecule. For HF enolate compound, the strongest interaction (6.98 kcal/mol) is between F-O, (0, 180) conformer, which has higher energy than between O-O moieties (4.15 kcal/mol), (0, 0) conformer. The O-H interaction, (180, 0) conformer, is the weakest while H-F interaction, (180, 180) is slightly higher (0.81 kcal/mol). This implies that the size of F atom is very similar to H atom. The HCl and HBr enolate compounds have similar interaction patterns with (180, 0) conformation, O-H interaction, is the most stable. The O-O interaction (2.90 and 2.22 kcal/mol for HCl and HBr, respectively) has energy lower than H-X (8.34 and 13.30 kcal/mol) and the X-O interaction is the strongest (30.20 and 47.25 kcal/mol). The maximum of the torsional potentials are observed at D1 or D2 = 90° since at this conformation the enolate compound loses conjugation and the compound becomes unstable.

3.4 Fluorohalo enolates

The comparison between torsional potentials of D1 at fixed D2 and of D2 at fixed D1 of fluorohalo enolate compounds is shown in Fig. 7.

The minimum conformer for all fluorohalo enolate compounds is (0, 0) implying interaction between O-O as the weakest interaction among all moieties. The O-F interaction as described by (180, 0) conformer is the second lowest. The (0, 180) conformer is the same as (180, 0) conformer for the FF compound. For FCl and FBr compounds, the O-X interaction becomes very large as the size of X increases from Cl to Br. The (180, 180) conformation which described by F-X interaction possesses the strongest interaction. This interaction is very large for F-Br. It is even larger than the instability causing by breaking conjugation, conformation with torsion angle of 90° . Again, the

steric repulsion dominates the interaction between all moieties.

4 Conclusion

Torsional potentials of mono- and fluoro-halo oxopropenolate compounds could be mainly described by steric repulsion between moieties on the enolate compounds. For HH compound, the minimum conformer is found at torsion angle D1 and D2 of 180° and 180° or $(180, 180)$ representing H-H interaction while the strongest interaction is at $(0, 0)$ representing O-O interaction. For HX, the most stable conformer is observed at $(180, 0)$ representing H-O interaction, while the conformation $(0, 180)$ representing O-X interaction. For FX, the minimum is at $(0, 0)$ representing O-O interaction. For FF, the conformation $(0, 180)$ representing O-F interaction has the strongest interaction while it is F-X interaction, conformation $(180, 180)$, which possesses the strongest interaction when X=Br and Cl. Strong conjugation between double bonds is observed for oxopropenolate, losing this interaction would cause instability for the compounds.

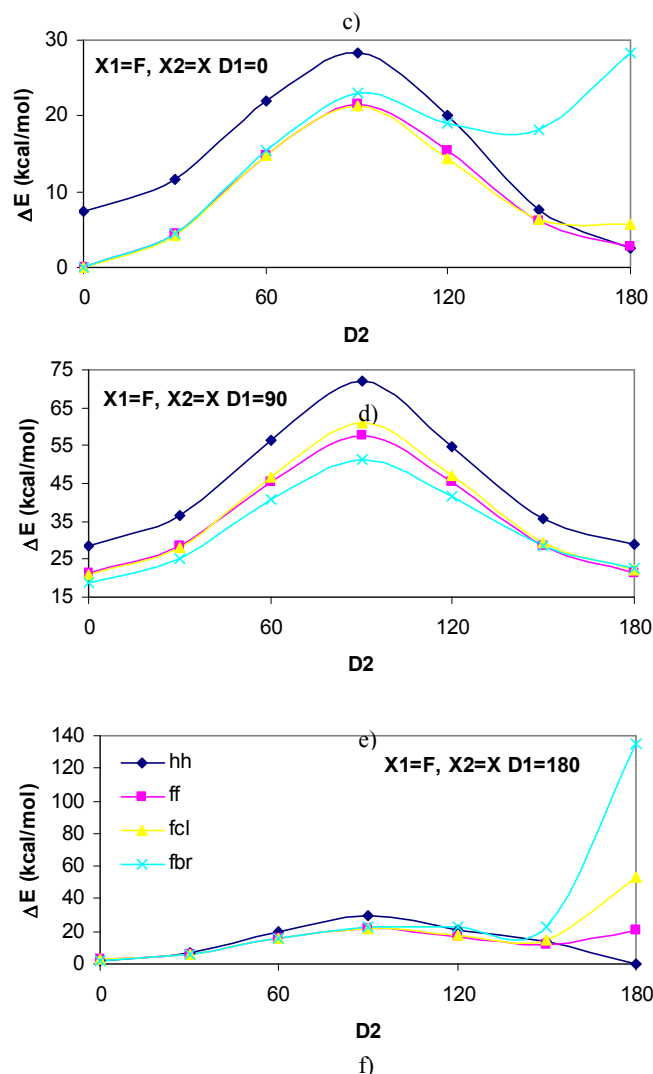
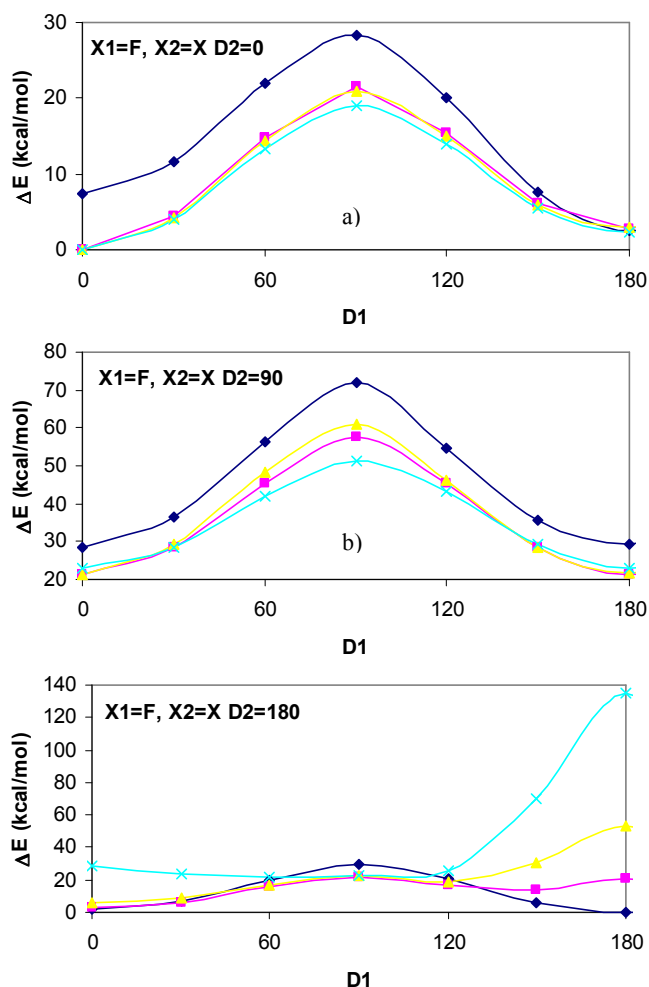


Fig. 7 a) – c) torsional potentials of D1 at fixed D2 (0° , 90° , and 180° , respectively) and d) – f) of D2 at fixed D1 (0° , 90° , and 180° , respectively) for fluorohalo enolate compounds obtained using MP2/cc-pVQZ

The maximum of the rotation barrier is observed at conformation with torsion angle of 90° for all compounds.

5 Acknowledgement

The author would like to thank the Rajchada Pisek Sompjoj endowment fund of Chulalongkorn University, the TRF senior research scholar of the Thailand Research Fund, National Science and Technology Development Agency for the financial support. Thanks are also given to the Computational Chemistry Unit Cell (CCUC), department of chemistry, faculty of science, Chulalongkorn University for computing facilities throughout this work.

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