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The Influence of Fluorine Substitution on Diels-Alder Reaction of 3-Vinylcoumarin and Ethylene*

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Density Functional Theory (DFT) has been applied to study the concerted mechanism of the Diels-Alder reaction between 3-vinylcoumarin and ethylene, as well as their fluorinated analogues. The main goal was to establish the fluorine influence on reactivity and structure of transition state (TS) and predict the reaction path. Computations were performed at the B3LYP/6-31G* level, which allowed to optimise the structure of reactants and products.

Key words: coumarin, Diels-Alder reaction, fluorine-substituted compounds, molecular modelling, DFT

Fluorine-substituted analogues of naturally occurring coumarins attracted increasing interest, due to their biological activity and other pronouncing properties, namely photochemical behaviour. Coumarins are used as starting material for the preparation of dyes, drugs, insecticides, enzyme inhibitors *etc.* Analogues of coumarins, containing trifluoromethyl group in C4 position in benzopyrone ring are applied as fluorescent markers [1], laser dyes [2,3,4,5] and probes for detecting enzymatic activity *in vivo.* This is mostly due to their high fluorescence [6]. Fluorine-containing analogues of Warfarin (widely used anticoagulant) have been synthesized to overcome the problem associated with drug-drug interactions [7].

Although the Diels-Alder reaction has been widely explored since the invention of this type of reaction, there is still some uncertainty of fluorine effect on these reactions. The basic goal of our work was to examine the influence of fluorine, assuming substitution of the hydrogen atom by fluorine in diene, as well as in the dienophile in the Diels-Alder reaction of 3-vinylcoumarin with ethylene, using computational methodology.

A few 3,4-fused 6-membered rings are formed *via* Diels-Alder reaction between 3-vinylcoumarins with various dienophiles [8]. Moreover, many chemists have studied the [4+2] cycloaddition (called also Diels-Alder reaction) with fluorinated reactants. On the base of these experimental data, reviewed by Hudlicky [9], the effect of fluorine on the reactivity of dienes and dienophiles in the cycloaddition reactions was explained. Numerous examples have been given to prove the relative lack of re-

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*Dedicated to Prof. M. Szafran on the occasion of his 70th birthday.

activity in Diels-Alder cycloaddition, exhibited by fluorinated ethylenes. On the other hand, fluorine-substituted heterodienes eagerly undergo [4+2] cycloaddition with electron-rich dienophiles.

It is well known that electron donors rises the reaction rate in the Diels-Alder reaction by increasing the HOMO (the Highest Occupied Molecular Orbital) energy level. The same effect reveal the electron withdrawing substituents in the dienophile molecule by lowering the LUMO (the Lowest Unoccupied Molecular Orbital) energy level. The interaction is least efficient and the reaction is slowest, if the electron-withdrawing group is attached to the diene or electron donors are present in the dienophile [10].

COMPUTATIONAL OUTLINE

The Density Functional Theory (DFT) is a useful tool for the study of the mechanism of pericyclic reactions. It was shown that the B3LYP functional [11] taking into consideration effects of dynamic correlation of electrons reproduces excellently geometries [12] and also the computed energies are in a good agreement with the experimental data for the concerted reaction path [13].

Geometry optimization and vibrational analyses were performed at the B3LYP/6-31g* level using Gaussian 98 program [14]. The Gibbs Free Energies (ΔG^0) and other single-point energies were computed to estimate the effect of introduction of electron withdrawing substituents (fluorine atoms) into diene or/and dienophile molecule in Diels-Alder reaction of 3-vinylcoumarin with ethylene.

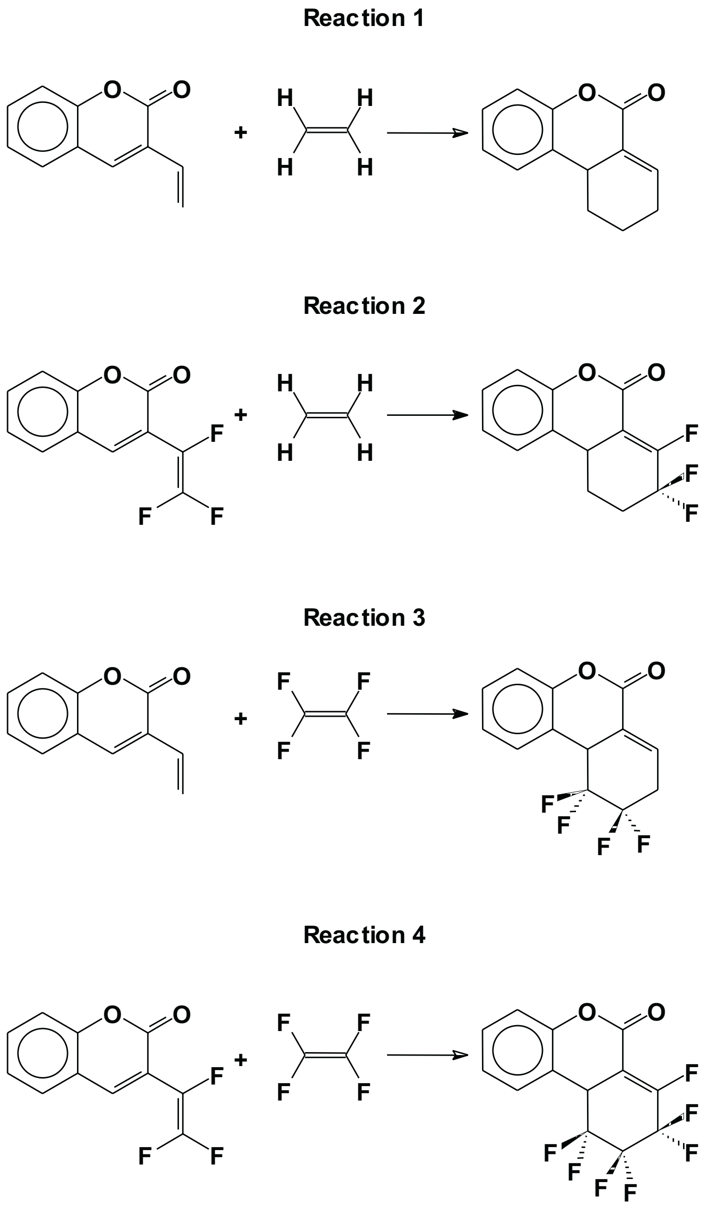
Gibbs free energies were computed as the sum of total energy E and thermal corrections, *i.e*
$E = E_{electronic} + E_{Zero\,Point} + E_{vibrational} + E_{rotational} + E_{translational}$; $H = E + RT$; $G = H - TS$; where H – entalphy, S – entropy, T – temperature, R – gas constant.

RESULTS AND DISCUSSION

Four Diels-Alder reactions of 3-vinylcoumarin and ethylene and their fluorinated analogues (Scheme 1) have been examined with B3LYP functional in a 6-31G* basic set. All structures were optimised, using AM1 method and then reoptimised using B3LYP/6-31G*. We have computed the transition states (TS) for above mentioned reactions to verify if the Diels-Alder reaction of 3-vinylcoumarin and ethylene is concerted (synchronous) or not (Scheme 1).

The results of the DFT computations show that all studied Diels-Alder reactions of 3-vinylcoumarin with ethylene (Reaction 1 in Scheme 1) and their fluorinated analogues (Reactions 2, 3 and 4) are spontaneous ($\Delta G^0 > 0$). The effect of substitution of hydrogen atom by fluorine results in higher ΔG^0 of the transition state (ΔG_1^0 for discussed reactions) comparing with non-substituted reactants (Table 1).

It is commonly understood that in terms of thermodynamic stability, the fluorine atom prefers to be attached to sp^3 rather than sp^2 hybridised carbon atom. In comparison to the first reaction, where 3-vinylcoumarin reacts with ethylene, electron withdrawing substituents (3 fluorine atoms) in the diene yield an energy profit of about 6.9 kcal/mole (ΔG_3^0 in Table 1 for the first two reactions, namely fluorine non-substituted reactants and 3-trifluorovinylcoumarin with ethylene). One can expect the third


Reaction 1

Reaction 2

Reaction 3

Reaction 4

Scheme 1. Diels-Alder reactions of fluorine-substituted analogues of 3-vinylcoumarin and ethylene.

reaction, it is 3-vinylcoumarin reacts with tetrafluoroethylene, should go smoothly, because of the presence of electron withdrawing substituents in the dienophile. Our results show that the ΔG^0 of the transition state (ΔG_1^0) for the second reaction is lower than that for the third one. It confirms that fluorine-containing reactants are prone to react in "the inverse-electron Diels-Alder reaction".

Table 1. Relative free energies (ΔG^0) for the concerted mechanism of the Diels-Alder reaction of 3-vinylcoumarin and ethylene and their fluorinated analogues, kJ/mole (in brackets in kcal/mole).

	Reaction 1	Reaction 2	Reaction 3	Reaction 4
ΔG_1^0	149.5 (35.7)	141.5 (33.8)	154.1 (36.8)	157.4 (37.6)
ΔG_2^0	–204.3 (–48.8)	–224.8 (–53.7)	–302.7 (–72.3)	–284.7 (–68.0)
ΔG_3^0	–54.4 (–13.0)	–83.3 (–19.9)	–148.6 (–35.5)	–127.3 (–30.4)

ΔG_1^0 – the Free Energy gap between transition state and reactants.
ΔG_2^0 – the Free Energy gap between transition state and product.
ΔG_3^0 – the Free Energy gap between product and reactants.

The Diels-Alder product of 3-trifluorovinylcoumarin with tetrafluoroethylene (Reaction 4) has the highest activation energy and the product is less stable in comparison to reaction of 3-vinylcoumarin and tetrafluoro substituted ethylene (Reaction 3). The differences in this case can be explained as the overlapping of two opposite effects: (1) thermodynamic stabilization – six of seven fluorine atoms are attached to sp^3 carbon instead of sp^2 and (2) steric hindrance – the new-formed 6-membered ring is "overcrowded" by fluorine atoms.

Analysis of the structures of calculated transition states shows, that all computed transition states (TS) are asymmetrical. For example, the transition state for the Diels-Alder reaction between 3-trifluorovinylcoumarin with ethylene (Reaction 2) is shown below (Figure 1):

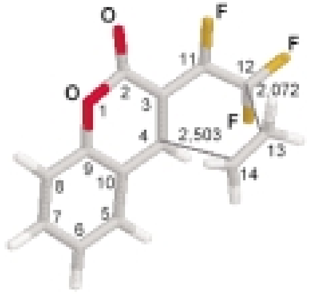


Figure 1. Transition state of the Reaction 2. Lengths of bonds being formed in Å.

The lengths of the new-formed bonds (Table 2) are not equal in the TS, thus the Diels-Alder reaction on these reactants seems to be a bit asynchronous, but still should be considered as a concerted reaction. The bond between C4 in coumarin and carbon atom in dienophile (C4–C14 in Table 2) is about 0.3–0.4 Å longer than the second new-formed bond for all TS structures containing F atoms, while in the product both of them have almost the same length. The smallest difference between those two bonds is in the transition state for non-fluorinated reactants (Reaction 1).

Table 2. Lengths of new-formed bonds in transition states. Atom numbering shown in Figure 1.

	Bond lengths in transition state, Å		Bond lengths in product, Å	
	C4–C14	C12–C13	C4–C14	C12–C13
Reaction 1	2.304	2.155	1.541	1.536
Reaction 2	2.503	2.072	1.554	1.527
Reaction 3	2.414	2.158	1.532	1.517
Reaction 4	2.501	2.135	1.553	1.542

CONCLUSIONS

Thermodynamic stability of Diels-Alder products is as expected: the fluorine stabilizes the product, no matter if it is the diene or dienophile fluorine-substituted. The lowest energy barrier required to achieve the transition state is observed for the reaction of fluorine-substituted diene and non-substituted dienophile (Reaction 2). That can be explained as electron-inverse effect caused by fluorine. The best product stability is achieved for the reaction of 3-vinylcoumarin with tetrafluoroethylene (electron-deficient dienophile).

Summarizing, fluorine-substitution in dienophile (Reaction 3) stabilizes better the product of Diels-Alder reaction between 3-vinylcoumarin and ethylene than fluorine-substitution in diene (Reaction 2) although in the second case the TS is reached with the smallest amount of energy in comparison to the others mentioned reactions.

Supplementary material. Full data for reactants, products and TS geometry are available on request.

REFERENCES

1. Bissell E.R., Mitchell A.R. and Smith R.E., *J. Org. Chem.*, **45**, 2283 (1980).
2. Work presented at the National Meeting of the ACS ('97) by C.A. Roney.
3. Schimitschek E.J., Trias J.A., Hammond P.R. and Atkins R.L., *Optics Commun.*, **11**, 352 (1974).
4. Mühlpfordt A., Schanz R., Ernsting N.P., Farztdinov V. and Grimme S., *Phys. Chem. Chem. Phys.*, **1**, 3209 (1999).
5. Fletcher A.N., Pietrak M.E. and Bliss D.E., *Appl. Phys. B*, **42**, 79 (1987).
6. Gee K.R., Haugland R.P. and Sun W., Pat. US 5, 830, 912.
7. Li H.Y. and Boswell G.A., *Tetrahedron Lett.*, **37** (10), 1551 (1996).
8. Minami T., Matsumoto Y., Nakamura S., Koyanagi S. and Yamaguchi M., *J. Org. Chem.*, **57**, 167 (1992).
9. Hudlicky M. and Pavlath A.E., Organic Fluorine Compounds II, A Critical Review, ACS Monograph, American Chemical Society, Washington, DC 1995.
10. Houk K.N., *Acc. Chem. Res.*, **8**, 361 (1975).
11. Becke A.D., *J. Chem. Phys.*, **98**, 5648 (1993).
12. Houk K.N., Li Y. and Evanseck J.D., *Angew. Chem. Int. Ed. Engl.*, **31**, 682 (1992).
13. Goldstein E., Beno B. and Houk K.N., *J. Am. Chem. Soc.*, **118**, 6036 (1996).

14. Frisch M.J., Trucks G.W., Schlegel H.B., Scuseria G.E., Robb M.A., Cheeseman J.R., Zakrzewski V.G., Montgomery J.A., Stratmann R.E., Burant J.C., Dapprich S., Millam J.M., Daniels A.D., Kudin K.N., Strain M.C., Farkas O., Tomasi J., Barone V., Cossi M., Cammi R., Mennucci B., Pomelli C., Adamo C., Clifford S., Ochterski J., Petersson G.A., Ayala P.Y., Cui Q, Morokuma K., Malick D.K., RabuckA.D., Raghavachari K., Foresman J.B., Cioslowski J., Ortiz J.V., Stefanov B.B., Liu G., Liashenko A., Piskorz P., Komaromi I., Gomperts R., Martin R.L., Fox D.J., Keith T., Al-Laham M.A., Peng C.J., Nanayakkara A., Gonzalez C., Challacombe M., Gill P.M.W., Johnson B.G., Chen W., Wong M.W., Andres J.L., Head-Gordon M., Replogle E.S. and Pople J.A., Gaussian 98 (*Revision A.1*), Gaussian, Inc., Pittsburgh PA, 1998.