Molecular Medicinal Chemistry
IDECEFYN
vol 12 January-April 2007, **54-57** http//:www.idecefyn.com.ar ISSN 1666-888X

Calculation of electronic properties of aromatic dienophiles for reactivity prediction in diels-alder reactions

Romina Brasca, María N. Kneeteman and Pedro M.E. Mancini

Laboratorio Fester, Departamento de Química, Facultad de Ingeniería Química. Universidad Nacional del Litoral, Santiago del Estero 2829, S3000AOM Santa Fe, Argentina. *e-mail:* pmancini@fiqus.unl.edu.ar

Introduction

Diels-Alder reaction (D-A) is one of the most widely used synthetic strategies for the synthesis of natural products due to its character of generating cyclic systems. By this reaction cyclic compounds characteristic of some families of alkaloids may be directly developed, thus being of high value in synthesis (Biolatto *et al.*, 1999; Della Rosa *et al.*, 2004a).

The use of aromatic compounds as dienes has been widely studied in D-A reactions, however, the use of them as dienophiles is a new and interesting branch that allows to state large and versatile synthetic sequences. The global electrophilicity index (ω), introduced by Maynard *et al.* (1998), and then formalized by Parr *et al.* (1999), allows to predict the trend of electron-acceptors (electrophiles) to acquire additional electronic charges from the environment. This index involves the electronegativity of the electron acceptor ($\chi = -\mu$) and its chemical hardness (η), that is to say, resistance to electron charge exchange with the environment.

Recently, some studies on Density Functional Theory applied to D-A reactions have shown that the diene/dienophile classification in a single *electrophilicity* scale is a powerful tool to predict the feasibility of a cycloaddition approach and the type of mechanism involved (Domingo, 2002; Domingo and Aurell, 2002; Domingo *et al.*, 2002 a,b).

In this work, and as a contribution to the understanding of the reactivity of heteroaromatic dienophiles in D-A reactions with normal electron demand, previously developed experimentally (Della Rosa *et al.*, 2004 a,b, 2005), the electronic properties of these dienophiles and some dienes were studied from a theoretical point of view. The dienophiles investigated are of the type of five-membered aromatic heterocycles mono-and disubstituted by electron-acceptor groups (A) (Fig. 1), while the dienes were isoprene and *trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefsky's diene) (Fig. 2).

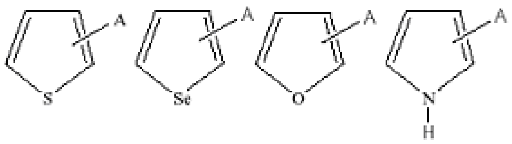

Figure 1. Studied dienophiles

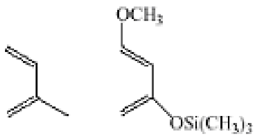

Figure 2. Studied dienes.

In all cases we calculated the chemical potential, chemical hardness and chemical electrophilicity index in order to predict the feasibility of the reaction, to evaluate the best dienophiles, and to perform mechanistic considerations. In addition, we examined the effect of dienophile substitution on the reactivity in order to select suitably the substituents leading to the most favourable reaction conditions. We have also performed an analysis of the energy levels of the reactant species with the aim of identifying the energetically more suitable reactions.

Methodology

Geometry optimizations were carried out for the mentioned series of dienes and dienophiles, using the B3LYP/6-31G (d) theory level implemented in the GAUSSIAN98 program (Frisch *et al.*, 1998).

The global electrophilicity index was evaluated using eq. (1) (Parr *et al.*, 1999). Chemical potential and chemical hardness were calculated from the energies of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) in the ground state of the molecule, using eqs. (2) and (3), respectively (Parr and Yang, 1989).

$$\omega = \frac{\mu^2}{2\eta} \qquad \text{Eq. (1)}$$

$$\mu \approx \frac{\epsilon_{HOMO} + \epsilon_{LUMO}}{2} \qquad \text{Eq. (2)}$$

$$\eta \approx \epsilon_{LUMO} - \epsilon_{HOMO} \qquad \text{Eq. (3)}$$

Results

Dienes and dienophiles classified in decreasing order of electrophilicity power (ω) are shown in Table 1. Some global properties are also included, such as the values of chemical potential (μ) and chemical hardness (η). It is assumed that high nucleophilicity and high electrophilicity are in opposite ends of this scale and, therefore, a molecule that shows a low electrophilicity power can be considered as a nucleophile (Parr *et al.*, 1999). Therefore, the larger the difference between ω index of both diene and dienophile, a higher reactivity is expected.

Table 1. Global properties of some reagents involved in D-A reactions.

Molecule	Global properties			Δω	Δω'
	μ (u.a.)	η (u.a.)	ω (eV)		
3-Ethoxycarbonyl-5-nitroselenophene	-0.1889	0.1714	2.83	1.82	2.17
3-Ethoxycarbonyl-5-nitrothiophene	-0.1911	0.1764	2.82	1.81	2.16
2-Nitroselenophene	-0.1829	0.1695	2.68	1.67	2.02
3-Ethoxycarbonyl-5-nitrofuran	-0.1886	0.1810	2.67	1.66	2.01
2-Nitrothiophene	-0.1845	0.1738	2.66	1.65	2.00
2-Nitrofuran	-0.1810	0.1775	2.51	1.50	1.85
3-Ethoxycarbonyl-5-nitropyrrole	-0.1754	0.1723	2.43	1.42	1.77
2-Nitropyrrole	-0.1654	0.1692	2.20	1.19	1.54
Thiophene	-0.1545	0.1566	2.07		
Isoprene	-0.1209	0.1962	1.01		
Selenophene	-0.1220	0.2195	0.92		
Danishefsky's diene	-0.0945	0.1851	0.66		
Furan	-0.1024	0.2441	0.58		
Pyrrole	-0.0753	0.2525	0.31		

$$\Delta\omega = (\omega_{\text{Dienophile}} - \omega_{\text{Isoprene}}) \quad \text{and} \quad \Delta\omega' = (\omega_{\text{Dienophile}} - \omega_{\text{Danishefsky's diene}})$$

It can be appreciated that the structural and electronic characteristics induced by chemical substitution are reflected as different responses of the global electrophilicity power.

For pyrrole, furan, thiophene and selenophene, the substitution of a hydrogen atom by a strong electroattractor group, such as nitro, gives rise to an increase of the electrophilic character. Likewise, upon substitution of two hydrogen atoms by two different electroattractor groups (-NO_2 and -CO_2CH_3) the electrophilicity power further increases, thus indicating an increase of reactivity towards a nucleophile. On the other hand, when increasing the chemical substitution in the diene groups by electrodonor groups, global electrophilic character decreases from

Molecular Medicinal Chemistry
IDECEFYN
vol 12 January-April 2007, **54-57** http//:www.idecefyn.com.ar ISSN 1666-888X

1.01 eV in isoprene to 0.66 eV in the Danishefsky's diene, thus supporting that electrodonor substituents in diene would accelerate the reaction (Fleming, 1999). It is therefore demonstrated that this scale of global electrophilicity is a useful tool for explaining the effect of substituents on reactant species.

The reactivity of the D-A process depends on the energy separation between frontier molecular orbitals (FMO) of reagents, HOMO of the diene, and LUMO of dienophile (Fukui, 1982). A small energy difference between interacting FMO will contribute to a higher stabilization of the transition state, therefore, all factors that decrease HOMO-LUMO distance will increase reaction rate. Then, from the energy point of view, the most favourable HOMO-LUMO interaction will be that of less ΔE.

The following schema show FMO energies for isoprene and the studied dienophiles. In each scheme the effect of mono- and disubstitution of the dienophile with electroattractor groups is analysed. It can be clearly observed that electron-attractor substituents decrease LUMO energy, which would result in an acceleration of the reaction rate. These results are in agreement with those obtained by analysing the global electrophilicity index.

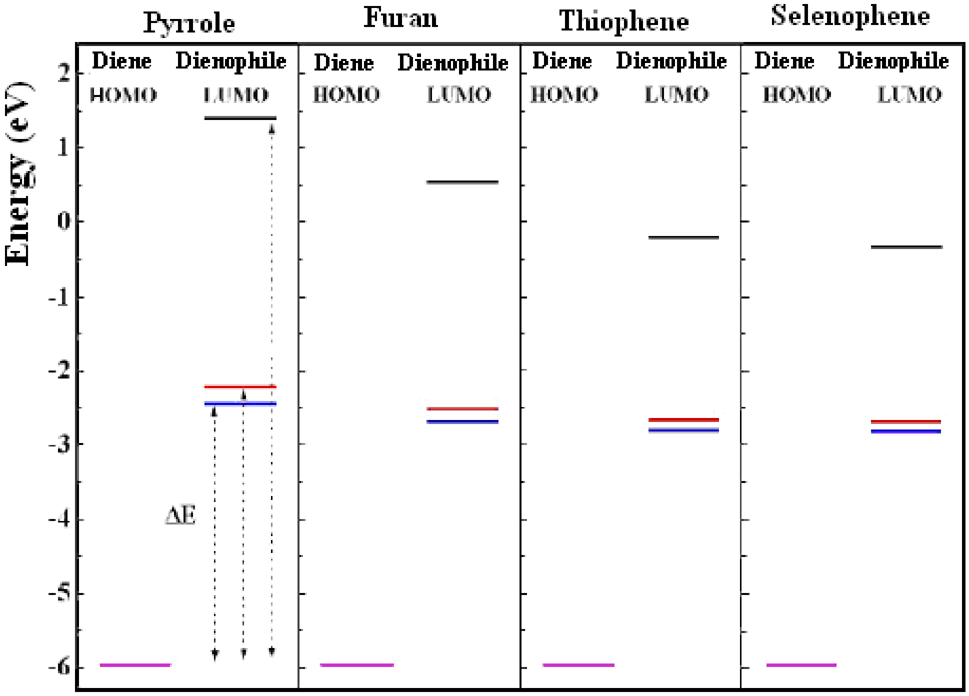

Figure 3. Effect of electroattractor substituents on the LUMO energy of the dienophile. In pink: isoprene; in black: dienophile without substitution; 4 in red: dienophile monosubstituted in 2-position with a nitro group, and in blue: dienophile disubstituted in 3-position with ethoxycarbonyl and in 5-position with nitro.

Conclusions

Global electrophilic index is a useful tool for explaining the effect of substituents in the diene/dienophile interacting pair. Upon increasing dienophile substitution with electroattractor groups, there is an increase in ω index, thus reflecting a higher electrophilic character. On the other hand, upon increasing diene substitution with electrodonor groups there is a decrase in ω index, thus reflecting a higher global nucleophilic nature.

Based on such theoretical calculations the influence of the combination and positional relationship of the substituents of each dienophile can be analysed in order to develop most suitable reactions for the design of possible precursor to be integrated in synthetic sequences.

Results are in agreement with those experimentally developed for each diene/dienophile pair in D-A thermal reactions. Depending on the observed Δω values, it can be assumed that these reactions occur *via* a concerted mechanism with the corresponding

Molecular Medicinal Chemistry
IDECEFYN
vol 12 January-April 2007, **54-57** http//:www.idecefyn.com.ar ISSN 1666-888X

asynchronous (asynchronic) transition state (zwitterionic).

Acknowledgements

To the Universidad Nacional del Litoral (Argentina) for financial support through CAI & D programs, and to CONICET (Argentina) for Doctoral Fellowships.

Note: This study was presented at the "XXVI Congreso Argentino de Química" , San Luis, Argentina, 2006

References

- Biolatto B., Kneeteman M. and Mancini P. (1999) Diels-Alder reactions of *N*-tosyl-3-nitroindole and dienamides: Diels-Alder reactions of *N*-tosyl-3-nitroindole and dienamides: synthesis of intermediates of Aspidospermine alkaloids. *Tetrahedron Lett.* **40**, 3343-3446.
- Della Rosa C., Paredes E., Kneeteman M. N. and Mancini P. M. E. (2004a) 2-Nitrofurans as dienophiles in Diels-Alder reactions. *8th International Electronic Conference on Synthetic Organic Chemistry* (ECSOC-8), A016.
- Della Rosa C., Paredes E., Kneeteman M. and Mancini P. M. E. (2004b) Behaviour of thiophenes substituted with electron-withdrawing groups in cycloaddition reactions. *Lett. Org. Chem.* **1**, 369-371.
- Della Rosa C., Kneeteman M. N. and Mancini P. M. E. (2005) 2-Nitrofurans as dienophiles in Diels-Alder reactions. *Tetrahedron Lett.* **46**, 8711-8714.
- Domingo L. R., Aurell M. J., Pérez P. and Contreras R. (2002a) Quantitative characterization of the global electrophilicity power of common diene/dienophile pairs in Diels-Alder reactions. *Tetrahedron* **58**, 4417-4423.
- Domingo L. R., Arnó M., Contreras R. and Pérez P. (2002b) Density Functional Theory study for the reaction of 1,3-butadienes and dimethyl acetylenedicarboxylate. Polar stepwise *vs* concerted mechanism. *J. Phys. Chem. A* **106**, 952-961.
- Domingo L. R. and Aurell M. J. (2002) Density functional theory study for the cycloaddition reaction of furan derivatives with masked *o*-benzoquinones. Does the furan act as dienophile on the cycloaddition reaction?. *J. Org. Chem.* **67**, 959-965.
- Domingo L. R. (2002) A density functional theory study for the Diels–Alder reaction between *N*-acyl-1-aza-1,3-butadienes and vinylamines. Lewis acid catalyst and solvent effects. *Tetrahedron* **58**, 3765-3774.
- Fleming I. (1999) *Pericyclic Reaction*. Oxford University, Oxford.
- Frisch M. J., Trucks G. W., Schlegel H. B., Scuseria G. E., Robb M. A., Cheeseman J. R., Zakrzewski V. G., Montgomery J**r**. 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., Rabuck A. 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. Y., Nanayakkara A., González C., Challacombe M., Gill P. M. W., Johnson B. G., Chen W., Wong M. W., Andrés J. L., Head-Gordon M., Replogle E. S. and Popple J. A. (1998) *Gaussian* 98 (Revision A.7). Gaussian Inc., Pittsburgh, PA, USA.
- Prof. Dr. Kenichi Fukui (1982) *Kenichi Fukui, The Nobel Prize in Chemistry 1981. The Nobel Prizes 1981*, Editor Wilhelm Odelberg, Nobel Foundation, Stockholm.
- Maynard A. T., Huang M., Rice W.G. and Covell D.G. (1998) Reactivity of the HIV-1 nucleocapsid protein p7 zinc finger domains from the perspective of density-functional theory. *Proc. Natl. Acad. Sci. USA* **95**, 11578-11583.
- Parr R. G. and Yang W. (1989) *Density Functional Theory of Atoms and Molecules.* Oxford University Press, New York.
- Parr R. G., von Szentpály L. and Liu S. (1999) Electrophilicity index. *J. Am. Chem. Soc.* **121**,1922-1924.