Original Research Article

A Theoretical Study of the Cycloaddition Reactions between 3-nitrofuran and several nucleophilic dienes. Reaction Mechanisms. A Discussion of a Solvation Model.

KEYWORDS: **Nitrofuran, Diels-Alder, theoretical calculations, mechanism**

ABSTRACT.

In this study the reactivity of 3-nitrofuran acting as electrophile in their reactions with different dienes, was analyzed in theoretical form. Specifically, the mechanism of each DA reaction was explored. Moreover, considering the polar character of this type of cycloaddition reaction we have discussed the modification of the dienophile reactivity when the solvent effect is considered by adding molecules of ILs to the dienophile optimizations.

Introduction

The Diels-Alder (DA) reaction allows the simple construction of a six-member ring from a compound with two conjugated double bonds (diene) and a simple olefine (dienophile), being one of the most significant and useful tools in synthetic organic chemistry.

Previous studies involving aromatic heterocycles such as indoles, pyrroles, furans and thiophenes in DA reactions demonstrate the viability of these systems as dienophiles when these compounds are properly substitute with electron-withdrawing groups.

According to the mechanisms, these reactions can be considered as a concerted asynchronous processes, that provides a polar character to the reaction –Polar Diels-Alder Reactions– (P-DA) being able to experiment solvent effects. Recently, ionic liquids (ILs) have shown that they can be a good alternative compared to conventional solvents due to their physical properties such as low vapor pressure, reutilization capacity, and less enviromental aggressive preparation and degradation ways.

Recently we analyzed the reactions between 3-nitrofuran and different dienes using protic ionic liquids (PILs) as solvents. In these cases, furan acts as an electrophilic dienophile. The experimental results observed show that the presence of an IL as reaction media improved the yields instead the reaction temperature and time decrease in relation with the employ of organic solvents. In conclusion it has been demonstrated that 3-nitrofuran react efficiently with the choose dienes in normal electron demand PDA reactions with the nitro group inducing side selectivity.

After that we developed a theoretical study on these reactions. The study of the behavior of dienes and dienophiles in DA reactions is not easy. A theoretical analysis through the Density Functional Theory (DFT) methods has been successful in explaining the feasibility of the cycloaddition process. The purpose of this work is to analyze in theoretical form the reactivity of 3-nitrofuran acting as electrophilic dienophile in their reactions with different dienes, specifically the mechanism of each reaction. Then and considering the effect of the PILs on this type of reactions and the polar character of these cycloaddition process we analyze the modification of the dienophile reactivity when the solvent effect is considered by adding molecules of PILs to the optimization of the dienophile.

Computational Methods

DFT calculations were carried out using the Gaussian 09 suite of programs, B3LYP exchange-correlation functional, together with the standard 6-31G* basis set.

The first step is to perform a geometrical optimization to get the conformation with the lowest energy. In order to verify that the structure is an energetic minimum and not a saddle point, frequency calculation was realized.

There are some indexes that are used to study the reactivity. The global electrophilicity index, ω, is given by the following simple expression $\omega = (\mu^2/2\eta)$, in terms of the electronic chemical potential μ and the chemical hardness η. Both quantities may be approached in terms of the one electron energies of the frontier molecular orbital HOMO and LUMO, ε_H and ε_L, as $\mu = (\varepsilon_H + \varepsilon_L)/2$ and $\eta = (\varepsilon_L - \varepsilon_H)$, respectively. Recently an empirical (relative) nucleophilicity index, *N*, has been introduced. It is based on the HOMO energies obtained within the Kohn-Sham scheme, and defined as $N = \varepsilon_{HOMO(Nu)} - \varepsilon_{HOMO(TCE)}$. The nucleophilicity is referred to tetracyanoethylene (TCE), because it presents the lowest HOMO energy in a large series of molecules already investigated in the context of polar cycloadditions. Local electrophilicity and nucleophilicity indexes, ω_k and N_k, were evaluated using the following expressions: $\omega_k=\omega f_k^+$ and $N_k=Nf_k^-$ where f_k^+ and f_k^- are the Fukui functions for a nucleophilic and electrophilic attacks, respectively. So, once the energetic parameters were get, the value of HOMO and LUMO orbitals were considered to quantify the reactivity indexes.

For the mechanistic study, from the Potential Energy Surface (PES), the structures of transition states were located. IRC (Intrinsic Reaction Coordinates) calculations verify the transition states (TS).

The solvent effect was studied using an explicit model of solvation, the supermolecular method, which consist on adding molecules of ILs together with the dienophile and then optimize the system. The molecules of ILs were added progressively until a total amount of 4. The effect is analyzed only with the dienophile due to the capacity of this one to form hydrogen bonds. In order to compare the results of this model, we analyze the solvation effect using the *polarizable continuum model* (PCM) where the solute (dienophile) is placed into a cavity and the interaction with the solvents are considered only through their dielectric constants independently of their structure.

Results and Discussion

3.1. Dienophile and diene's properties

3.1.1. Dienophile

3-nitrofuran **(1)** (ω = 2.35 eV) is a strong electrophile, its global properties were calculated and the values are showed in Table 1.

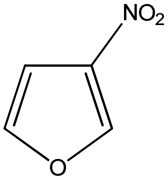
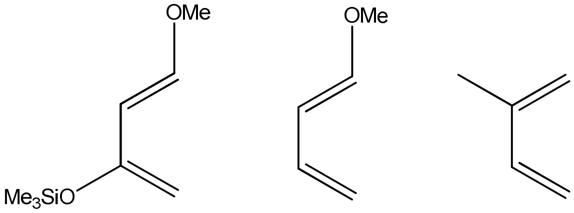


Figure 1

Table 1. *Global properties calculated using the B3LYP/6-31G* method.*

DIENOPHILE	**ε_{HOMO}(eV)**	**ε_{LUMO}(eV)**	**μ (eV)**	**η (eV)**	**ω (eV)**	***N* (eV)**
3-Nitrofuran	-0.26712	-0.08632	-0.1767	0.1808	2.35	1.85

3.1.2. Dienes



2 3 4

Figure 2

In the other side, the dienes (nucleophiles) are poor electrophiles. Danishefsky's diene **(2)** (ω =0.96 eV), is the diene with the major difference (Δ ω) related to the electrophilicity of the diene then the reactions with this diene would be more polar and more favorable than those with 1-methoxy-1,3-butadiene **(3)** (ω =1.07 eV) and with isoprene **(4)** (ω =1.27eV).

Table 2. *Global properties calculated using the B3LYP/6-31G(d) method. For the inclusion of chloroform as solvent the PCM method was applied.*

DIENE		**ε_{HOMO}(eV)**	**ε_{LUMO}(eV)**	**μ (eV)**	**η (eV)**	**ω (eV)**	***N* (eV)**
Isoprene	**Gas Phase**	-6.18	-0.41	-3.30	5.77	**0.94**	**2.93**
	Chloroform	-6.24	-0.50	-3.37	5.74	**0.99**	**2.88**
Danishefsky's diene	**Gas Phase**	-5.56	0.04	-2.76	5.60	**0.68**	**3.56**
	Chloroform	-5.65	-0.07	-2.86	5.58	**0.73**	**3.47**
1-Methoxy-1,3-butadiene	**Gas Phase**	-5.57	-0.14	-2.85	5.43	**0.75**	**3.55**
	Chloroform	-5.63	-0.26	-2.95	5.37	**0.81**	**3.49**

The electronic chemical potential (μ) presents the highest values for the dienophiles, what indicates that the charge transference is going to take place from the first ones to the aromatic heterocycles. Then the diene is going to be a nucleophile and the dienophile would act as electrophile.

3.1.3. Local Properties

The regioselectivity is expected to be higher for the processes that involve Danishefsky's diene due to the electron donor groups (-OMe y $–OSiMe_3$) and its relative positions, specially the influence of the –OMe group.

Table 3. *Local indexes for dienes*

DIENE	Atom	N_k (eV)
Isoprene	C1	1.20
	C4	0.92
Danishefsky's diene	C1	0.56
	C4	1.46
1-Methoxy-1,3-butadiene	C1	0.74
	C4	0.94

The 3-nitrofuran has its major local electrophilicity in C2. It is expected that the most nucleophilic site of the diene reacts, at first, with the most electrophilic center of the dienophile.

3.2. Mechanism of reaction

In the cycloaddition reactions as D-A with the nitro-dienophiles in general it was observed that is not possible to get the primary adducts retaining the nitro group, and an elimination stage of it as nitrous acid, is consider. They are a domino processes that involve consecutive reactions. If asymmetric dienes such as Danishefsky's diene were used, an extra stage of the elimination of -OMe group and hydrolysis of $–OSiMe_3$ group is also taken into account. In this study we analyze the reaction mechanism considering only the process of the formation of the primary adducts because this is the determinant step of the reaction. It is necessary taken into account that the irreversible character of these reactions is due to the elimination of the nitrous acid and subsequent aromatization of the products.

- ***3-nitrofuran + isoprene***

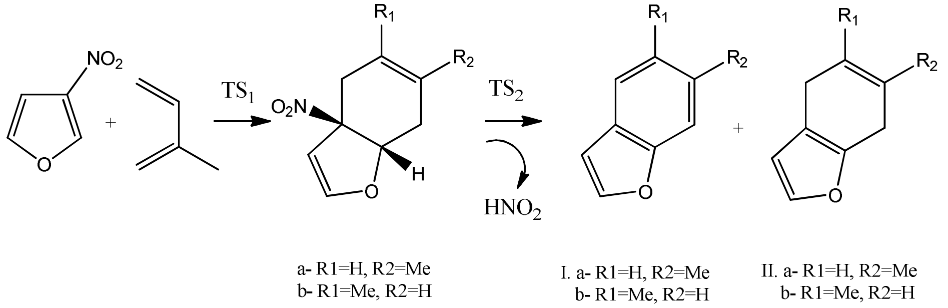


Figure 3

First the Δ ω of the reactions was calculated, in this case 1.41 eV. The C2 of the 3-nitrofuran is the most electrophilic site, so is going to be the one that reacts with the most nucleophilic carbon of the diene. The ΔN_k for isoprene between C1 and C4 is near 0.30 eV. As the difference is not big enough we expect both isomers as products.

Trough an analysis of the potential energy surface the TS1 (Figure 4) corresponding to the formation of the *para* and *meta* product indicates that we are in front of a concerted cycloaddition process because both formatting bonds vibrate at the same time and in an asymmetric form [(Δr_{para}= 1.23 Å), (Δr_{meta}= 1.37 Å), ($\Delta r = (r_1 - r_2)$)] where r_1 is the distance between C2 ^{dienophile} -C1 ^{diene} and r_2 is the distance between C3 ^{dienophile} -C4 ^{diene}.

Figure 4

This is due to the fact that the formation of the bond between the most electrophilicity center of the dienophile (C3) and the most nucleophilicity center of the diene (C4). The energy barrier of the *meta* isomer is a little higher than the *para* one.

- ***3-nitrofuran + 1-methoxy-1,3-butadiene***

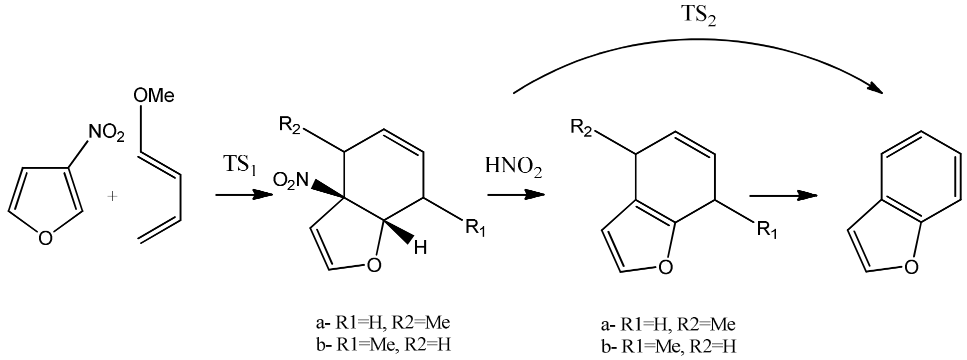


Figure 5

In this case the Δω of the reaction reach the 1.60 eV. It is expected a good yield of the cycloaddition product and that the –OMe group is going to be eliminated as MeOH to reach the aromatic final product. In this case the mixture of isomers of the dihydro compounds (ΔN_k=0.29 eV) subsequent derivates in the same final aromatic product.

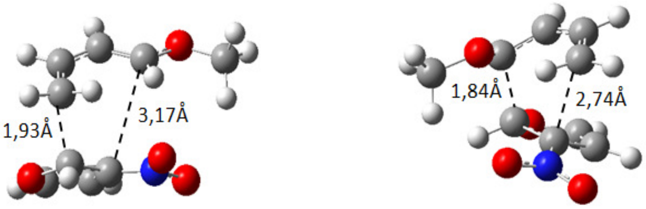


Figure 6

For this diene one transition state (previous to the formation of the nitrate primary adduct) is also observed (TS$_1$ -Figure 6-) and it indicates that we are in front of a concerted cycloaddition process. Both forming bonds vibrate at the same time and in an asymmetric form [(Δr_{ortho}=1,24 Å), (Δr_{meta}=0,90 Å), ($\Delta r= (r_1 - r_2)$)] where r_1 is the distance between

$C_2^{dienophile}$- C_1^{diene} and r_2 is the distance between $C_3^{dienophile}$-C_4^{diene}. The *meta* isomer is also showed and its energy barrier is a little higher than the *para* one.

- ***3-nitrofuran + Danishefsky's diene***

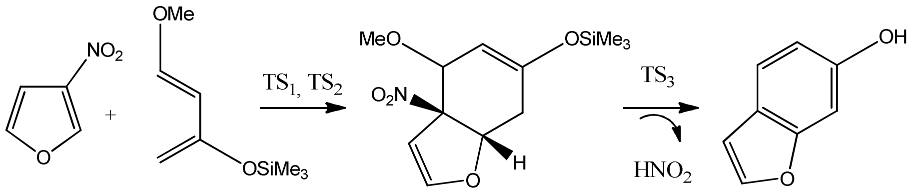
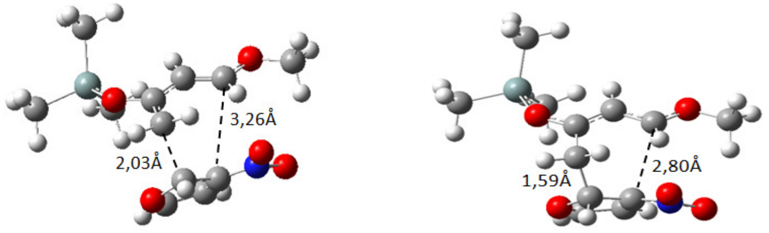


Figure 7

When Danishefsky's diene is used ($\Delta\omega$=1,67), only the formation of one isomer is expected (ΔN_k=0.89 eV). This product corresponds to the union of C4 of the diene and C2 of the dienophile. The reaction must be completely regioselective and with the loose of the $-NO_2$ and –OMe groups form the aromatic compound that corresponds to the *para* adduct.

Finally, with Danishefsky's diene the mechanism is surprisingly. There are two transition states [(Δr_{TS1}=1,24 Å), (Δr_{TS2}=0,90 Å)] corresponding to each sigma bond formation and an intermediate state, which was not possible to optimize. We are in presence of a *two-step non-intermediate mechanism*. This fact does not agree with the pericyclic reaction concept.



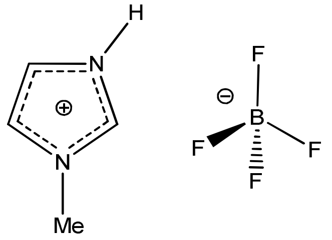
TS₁ ***TS₂***

Figure 8

In all the cases it is observed that the relative stability of the nitrate adduct respect to the final product with elimination of nitric acid is considerably lower. It is because of this fact that the primary cycloadduct is not observed. The extrusion of nitrous acid is the irreversible step of the D-A reaction (impulsive force) and the aromaticity of the final product explained the stability.

3.3. Influence of neoteric solvents

The IL employed for the solvent effect analysis was tetrafluoroborate of 1-methyllimidazolium -[HMIM][BF_4]- (Figure 9). This selection is related to the possibility of hydrogen bonding formation that presents this IL.



[HMIM][BF_4]

Figure 9

If the classical interaction between the electrophile and the IL is considered which mean that the IL cation interact via hydrogen bonding with the nitro group of the electrophile the global electrophilicity index is too high (ca. ω=10, for tetrafluoroborate of 1-methyllimidazolium and ethyl ammonium nitrate). These results are not compatible with the experimental data (although the rate of the reaction is higher than those when a molecular solvent is used, the yields and the temperature of the reactions do not change enough), probably because the anion is not considered formally.

For this reason, the supermolecular approach was explored. In this case the anion is considered. When one par *anion-cation* of IL is taken into account the anion interacts only with the cation (electrostatic interactions) without affecting the 3-nitrofuran, enabling planar arrangement of hydrogen bond between the cation and the dienophile (Figure 10).

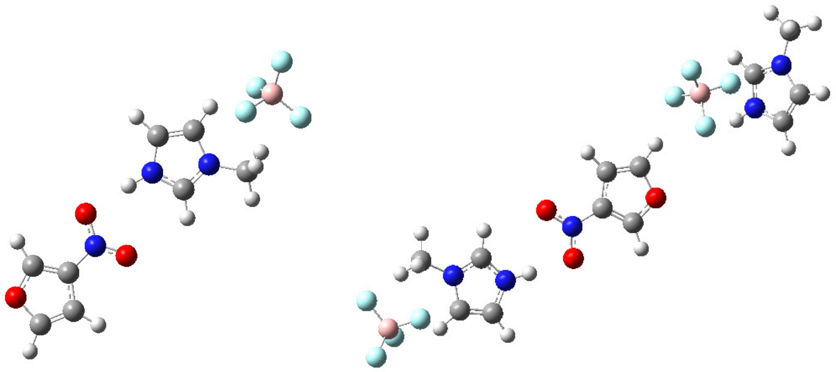


Figure 10

When a second IL par *anion-cation* is added, an additional electrostatic interaction with the dienophile appears and, therefore, the value of ω decreases from 5.01 to 3.78 eV. This trend continues when the 3rd and 4th IL molecules are added, with values of ω of 3.11 and 2.84 eV respectively (Figure 11).

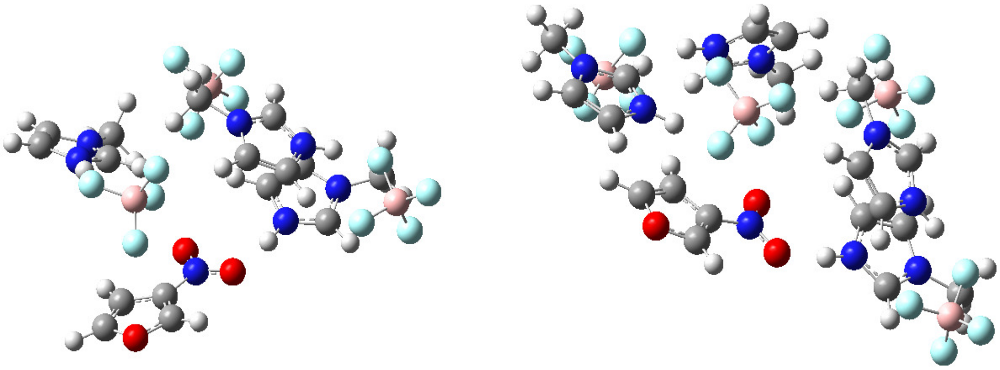


Figure 11

Based on these results, it can be considered that, when predominates a specific interaction of hydrogen bonding on the dienophile, the value of the global electrophilicity increases while when we are also in the presence of electrostatic interactions the effect is counteracted.

Table 4. Global electrophilicity of 3-nitrofuran with different solvents.

Method	Solvent	ω(eV)
PCM	[HMIM][BF_4]	2,49
	Water	2,51
	Benzene	2,41
Supramolecular	[HMIM][BF_4]x1	5,01
	[HMIM][BF_4]x2	3,78
	[HMIM][BF_4]x3	3,11
	[HMIM][BF_4]x4	2,84

It is noted that the global electrophilicity of dienophiles increases when the solvent effect is considered respect to the gas phase. Furthermore, the highest values correspond to the influence of the IL.

There is a second ω value that is related to the structure where a same anion is interacting with both, the dienophile and the cation, which reduces the effect of the hydrogen bonding interaction due to the rotation in the plane (Figure 12).

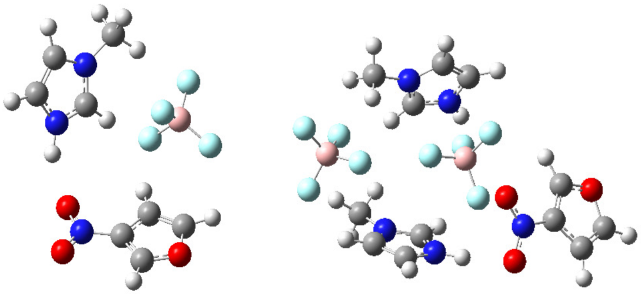


Figure 12

In this case, ω values are lower, 3-nitrofuran+[HMIM][BF_4]x1 (2.91 eV) - 3-nitrofuran+[HMIM][BF_4]x2 (2.92 eV), 3-nitrofuran+[HMIM][BF_4]x3 (2.75 eV), 3-nitrofuran+[HMIM][BF_4]x4 (2.74 eV). This seems to be due to the diminution of the interaction between the orbital of both, the dienophile and the solvent that results as a consequence of the non-planar arrangement

Moreover, incorporating other IL molecules, the number of electrostatic interactions increases, including new solvent-solvent interactions (Figure 12). The ω values fluctuate around 2.80 eV due to the different relation between electrostatic effects and hydrogen bonds.

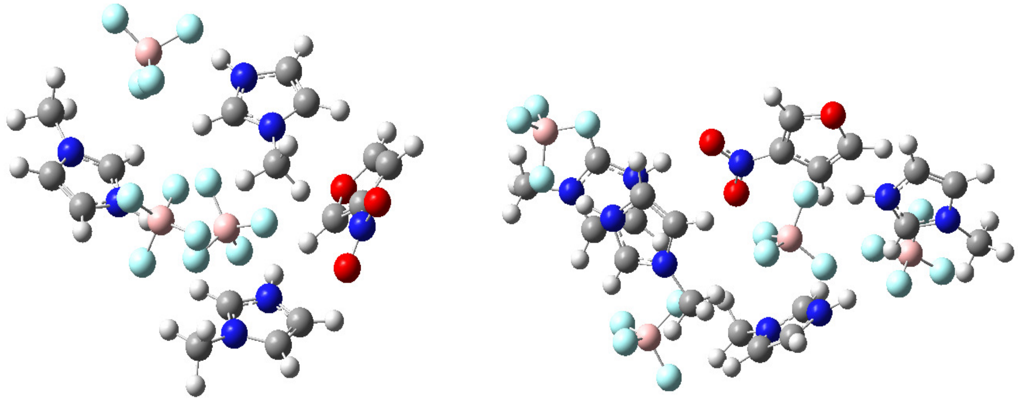


Figure 13

Additionally, the global electrophilicity value of 3-nitrofuran in the presence of IL using the PCM method is lower than the one obtained using the explicit method, its value is in fact similar to water, because it is a polar solvent and, with this method, those solvents having similar dielectric constant values will provide similar results regardless of their structures.

Global electrophilicity values obtained by the last result, provide more consistent results with experience, where the reaction yields are slightly higher and the reaction conditions, time and temperature, decrease.

Conclusions

The theoretical calculations are consistent with the experimental results observed for these reactions in relation with the selectivity and products obtained. Nitrofuran explored has enough electrophilicity character to act in polar DA reactions. The analysis of the reaction mechanism in this P-DA process shows that when isoprene is used as diene only one transition state is observed. On the other hand when 1-methoxy-1,3-butadiene and Danishesfky's diene is possible observed two transition states without a classic intermediate state. The mechanism corresponding to the last reactions could be considered as stage mechanisms. The reactivity indexes are a good tool to explain and predict the behavior of the involved molecules in a cycloaddition reaction. It can be established, from the chemical potential values, which of the molecules are going to act as dienes or dienophiles and how polar the reaction could be (Δω). Local indexes result representatives of the reaction regioselectivity.

The supermolecular approach is more consistent to explain the solvent effect that produce a protic IL when act as reaction medium of a cycloaddition reaction in which the electrophile is the 3-nitrofuran.

References

1. O. Diels, K. Alder, *Justus Liebigs Ann Chem* 1928, *460*, 98.
2. W. Carruthers, *Some Modern Methods of Organic Synthesis*. (2nd edn), Cambridge University, Press Cambridge, UK. 1978, (b) W Carruthers, *Cycloaddition Reactions in Organic Synthesis*. Pergamon,Oxford, UK, 1990.
3. Domingo, L. R.; Saez, J. A.; *Org. Biomol. Chem.,* 2009, 7, 3576.
4. Domingo, L. R.; Saéz, J. A.; Zaragozá, R. J.; Arnó *J. Org. Chem.* 2008, *73*, 8791.
5. L. R. Domingo, M. J. Aurell, M. N. Kneeteman and P. M. E. Mancini, *THEOCHEM*, 2008, 853, 68.
6. B. Biolatto, M. Kneeteman, E. Paredes and P. M. E. Mancini, *J. Org. Chem.*, 2001, 66, 3906; (b) E. Paredes, R. Brasca, M. N. Kneeteman and P. M. E. Mancini, *Tetrahedron*, 2007, 63, 3790; (c) C. Della Rosa, C. Ormachea, M. N. Kneeteman, C. Adam and P. M. E. Mancini, *Tetrahedron Lett.*, 2011, 52, 6754; (d) C. D. Della Rosa, C. M. Ormachea, A. S. Sonzogni, M. N. Kneeteman, L. R. Domingo and P. M. E. Mancini, *Lett. Org. Chem*., 2012, 9, 691; (e) Della Rosa, C.; Kneeteman, M.; Mancini, P. *Tetrahedron Lett*., 2007, 48, 1435.
7. (a) C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B: Condens. Matter Mater. Phys.*, 1988, *37*, 785; (b) A. D. Becke, *J. Chem. Phys.*, 1993, *98*, 5648.
8 (a) C. E. Check, T. M. Gilbert, *J. Org. Chem.*, 2005, *70*, 9828; (b) G. O. Jones, V. A. Guner, K. N. Houk, *J. Phys. Chem. A*, 2006, *110*, 1216; (c) G. A. Griffith, I. H. Hillier, A. C. Moralee, J. M. Percy, R. Roig, M. K. Vicent, *J. Am. Chem. Soc.*, 2006, *128*, 13130; (d) Mar Ríos-Gutiérrez, P. Pérez, L. R. Domingo, *RSC Adv.*, 2015, 5, 58464.
9. Y. Zhao and D. G. Truhlar, *J. Phys. Chem. A*, 2004, *108*, 6908.
10. W. J. Hehre, L. Radom, P. v. R. Schleyer, J. A. Pople, *Ab initio Molecular Orbital Theory*; Wiley: New York, 1986.
11. (a) H. B. Schlegel, *J. Comput. Chem.* 1982, *3*, 214; (b) H. B. Schlegel, *In Modern Electronic Structure Theory* (Ed.: Yarkony, D. R.); World Scientific Publishing: Singapore, 1994
12. K. Fukui, *J. Phys. Chem.* 1970, *74*, 4161.
13. (a) C. González, H. B. Schlegel, *J. Phys. Chem.* 1990, *94*, 5523; (b) C. González, H. B. Schlegel, *J. Chem. Phys.* 1991, *95*, 5853.
14. (a) J. Tomasi, M. Persico, *Chem. Rev.*, 1994, *94*, 2027. (b) B. Y. Simkin, I. Sheikhet, *Quantum Chemical and Statistical Theory of Solutions-A Computational Approach* Ellis Horwod: London, 1995.
15. (a) E. Cances, B. Mennucci, J. Tomasi, *J. Chem. Phys.*, 1997, *107*, 3032. (b) M. Cossi, V. Barone, R. Cammi, J. Tomasi, *Chem. Phys. Lett.*, 1996, *255*, 327. (c) V. Barone, M. Cossi, J. Tomasi, *J. Comput. Chem.*, 1998, *19*, 404.
16. (a) A. E. Reed, R. B. Weinstock, F. Weinhold, *J. Chem. Phys.* 1985, *83*, 735; (b) A. E. Reed, L. A. Curtiss, F. Weinhold, *Chem. Rev.* 1988, *88*, 899.
17. M. J. Frisch, *et al.*, Gaussian 09, Revision A.02, Gaussian, Inc., Wallingford CT, 2009.
18. R. G. Parr, L. von Szentpaly, S. Liu, *J. Am. Chem. Soc.* 1999, *121*, 1922.
19. (a) R. G. Parr, R. G. Pearson, *J. Am. Chem. Soc.* 1983, *105*, 7512; (b) R. G. Parr, W. Yang, *Density Functional Theory of Atoms and Molecules*; Oxford University Press: New York, 1989.
20. (a) L. R. Domingo, E. Chamorro, P. Pérez, *J. Org. Chem.* 2008, *73*, 4615; (b) Domingo, L. R.; Pérez, P. *Org. Biomol. Chem.* 2011, *9*, 7168.
21. W. Kohn, L. J. Sham, *Phys. Rev.* 1965, *140*, 1133.
22. L. R. Domingo, P. Pérez, J. A. Sáez, *RSC Adv.* 2013, *3*, 1486.
23. L. R. Domingo, P. Pérez, D. Ortega *J. Org. Chem.* 2013, *78*, 2462.
24. L. R. Domingo, J. A. Sáez, S. R. Emamian *Org. Biomol. Chem.* 2015, *13*, 2034.
25. L. R. Domingo, *RSC Adv.* 2014, *4*, 32415.
26. (a) P. Geerlings, F. De Proft, W. Langenaeker, *Chem. Rev.* 2003, *103*, 1793; (b) D. H. Ess, G. O. Jones and K. N. Houk, *Adv. Synth. Catal.* 2006, *348*, 2337.
27. L. R. Domingo, M. J. Aurell, P. Pérez, R. Contreras *Tetrahedron* 2002, *58*, 4417.
28. P. Jaramillo, L. R. Domingo, E. Chamorro, P. Pérez, *J. Mol. Struct. (Theochem)* 2008, *865*, 68.

29. Bini R., Chiappe, C., Mestre, V. L., Pomelli, C. S., Welton, T. “A theoretical study of the solvent effect on Diels-Alder reaction in room temperature ionic liquids using a supermolecular approach”. Theor. Chem. Acc. **2009**, 123, 347.

30. C. Della Rosa, M. Kneeteman, P. Mancini*, Tetrahedron Letters* **2005,** 46, 8711-8714.