[G017]

GLOBAL REACTIVITY INDEXES CALCULATED ON DIELS-ALDER PRIMARY ADDUCTS TO STUDY THE REGIO- AND STEREOCHEMISTRY OF THE REACTIONS BETWEEN FURAN DERIVATIVES AND DANISHEFSKY'S DIENE.

Romina Brasca,[1,2] María N. Kneeteman,[1] Pedro M. E. Mancini[1,*] and Walter M. F. Fabian[3,*]

1. Área de Química Orgánica, Departamento de Química, Facultad de Ingeniería Química, Universidad Nacional del Litoral, Santiago del Estero 2829, (S3000AOM) Santa Fe, Argentina.
2. Doctoral scholarship holder from the National Council of Scientific and Technical Research (CONICET).
3. Institut für Chemie, Karl-Franzens-Universität Graz, Heinrichstrasse 28, (8010) Graz, Austria.

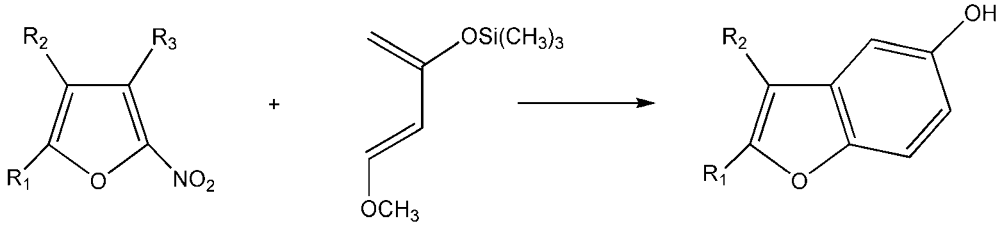
ABSTRACT

The reaction of substituted furans **a-c** and Danishefsky's diene which yield 5-benzofuranol derivatives has been studied using the hardness, the polarizability and the electrophilicity of the corresponding D-A primary adducts as global reactivity indexes. The main objective of this work is to investigate the power of these global indexes in predicting the major regioisomer. It has been demonstrated that both the hardness as well as the electrophilicity power of the adducts are appropriate descriptors for predicting the major product of the reactions at least in the cases study here. The maximum hardness principle and the minimun electropilicity principle are obeyed in these regiospecific Diels–Alder reactions. The stereoselectivity of the D-A reactions has also been studied.

INTRODUCTION

A great number of natural products and biologically significant synthetic compounds possess a benzofuran ring as part of their structures.[1] Consequently, a large number of procedures have been developed for the preparation of benzofuran derivatives.[2]

The main purpose of this work is to analyze the regiochemical outcomes obtained by one of the procedures that were proposed for synthesizing benzofuran derivatives, using some DFT-based global descriptors of the reaction products.[2(b)] This procedure involves Diels-Alder (D-A) reactions using furans substituted with electron withdrawing groups as dienophiles and Danishefsky's diene. In the three cases studied here, cycloaddition products showed extrusion of the nitro group, hydrolysis of the silyl enol ether and elimination of methanol to give the corresponding 5-hydroxybenzofurans (Scheme 1).



a. R_1=R_2=R_3=H
b. R_1=CO_2CH_3, R_2=R_3=H
c. R_1=R_3=H, R_2=CO_2CH_3

a. R_1=R_2=H
b. R_1=CO_2CH_3, R_2=H
c. R_1=H, R_2=CO_2CH_3

Scheme 1. Experimentally observed products of the D-A reactions between furan derivatives and Danishefsky's diene.[2(b)]

Despite the fact that the transition state theory is widely used as a strict and successful approach to study the regiochemistry in cycloaddition reactions, the location of the transition structures is not always so easy.

Therefore, new Density Functional Theory (DFT) based concepts and indexes have been developed recently in order to model the chemical reactivity and site selectivity in different cycloaddition reactions.[3] For instance, we have demonstrated that some local and global indexes calculated on the reactants can be used to rationalize the regioselectivity for the D-A reactions studied here.[4]

More recently, the analysis based on the use of global reactivity indexes has been extended to the reaction products and it has been confirmed that the electrophilicity index could be utilized as an indicator of regioselectivity and stereoselectivity in a serie of reactions. [5]

This theoretical background motivated us to study the regio- and stereoselectivity of certain D-A reactions using some global reactivity indexes of the corresponding cycloadducts as a complement of the study that has been previously done and moreover, as a contribution to the general knowledge in the field.

GENERAL EXPERIMENTAL PROCEDURE

The gas-phase equilibrium geometries of all species described here were obtained by full optimization at the B3LYP/6-31G(d)[6] level using the GAUSSIAN03 program.[7] All stationary points found were characterized as true minima by frequency calculations.

When investigated the solvent effects by means of single-point (SP) calculations on the optimized gas-phase structures, using a self-consistent continuum method[8] in its conductor-like approximation (CPCM).[9] The solvent used was benzene, as in the experiments.[2(b)]

The chemical hardness, the chemical potential, the global electrophilicity index and the polarizability of the species of interest have been calculated using Eqs. 1-4.

$$\eta = \left(\varepsilon_{LUMO} - \varepsilon_{HOMO}\right) \qquad (1)$$

$$\mu = \frac{\left(\varepsilon_{LUMO} + \varepsilon_{HOMO}\right)}{2} \qquad (2)$$

$$\omega = \frac{\mu^{2}}{2\eta} \qquad (3)$$

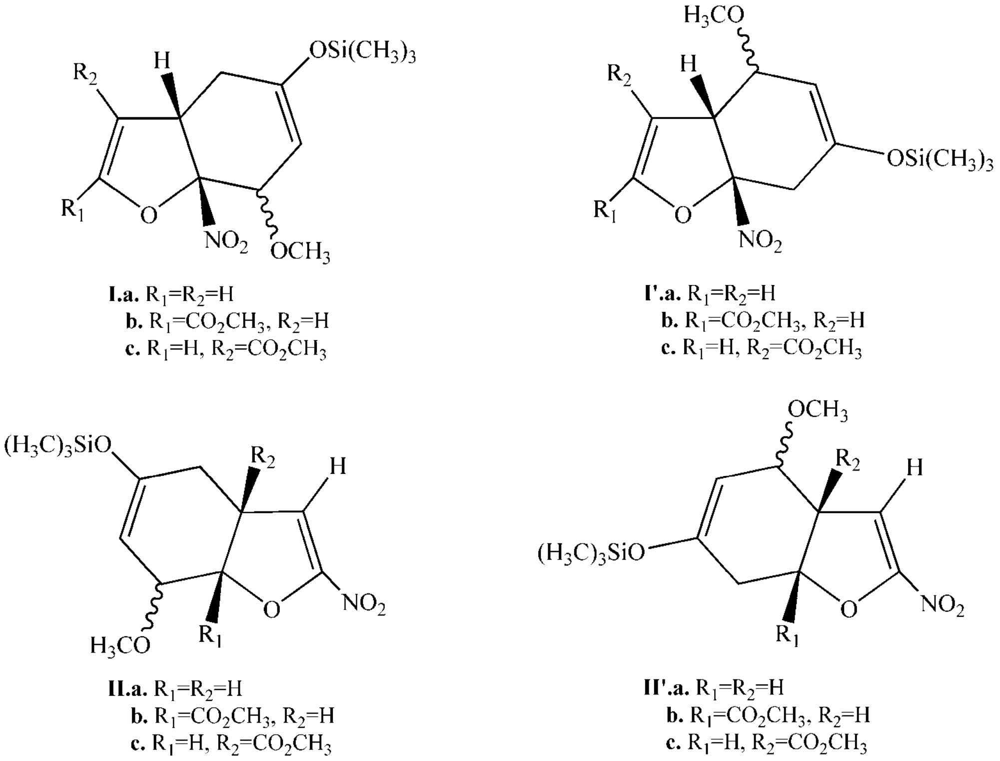
$$\alpha = \frac{\left(\alpha_{xx} + \alpha_{yy} + \alpha_{zz}\right)}{3} \qquad (4)$$

where α_{xx}, α_{yy} and α_{zz} are the diagonal components of the polarizability tensor.

RESULTS AND DISCUSSION

For each reaction (Scheme 1) four channels, which lead to the regioisomers **I**, **I'**, **II** and **II'** are feasible (Scheme 2). Clearly, depending on the orientation of the nitro and methoxy groups, two stereoisomers can be obtained in each channel (i.e. *endo* and *exo* adducts).

As a part of our general interest in the D-A reactions between furan derivatives and Danishefsky's diene, we explored the electronic features of the isomeric adducts using some DFT-based descriptors. The data are summarized in Tables 1-4. [Total energies are shown in Kcal/mol. α, η and ω are shown in eV. The Zero Point Energy (ZPE) was added to the total energy].



I.a. $R_1=R_2=H$
b. $R_1=CO_2CH_3$, $R_2=H$
c. $R_1=H$, $R_2=CO_2CH_3$

I'.a. $R_1=R_2=H$
b. $R_1=CO_2CH_3$, $R_2=H$
c. $R_1=H$, $R_2=CO_2CH_3$

II.a. $R_1=R_2=H$
b. $R_1=CO_2CH_3$, $R_2=H$
c. $R_1=H$, $R_2=CO_2CH_3$

II'.a. $R_1=R_2=H$
b. $R_1=CO_2CH_3$, $R_2=H$
c. $R_1=H$, $R_2=CO_2CH_3$

Scheme 2. Possible regioisomeric D-A adducts.

Table 1. Global properties for the D-A adducts **I** and **I'**
[gas-phase calculations, B3LYP/6-31g(d)].

Dienophile	**D-A Adduct**	**[E + ZPE]**	η	ω	α
a	**I.** *endo*	-745907.351	**4.536**	**1.592**	4374.388
	I’. *endo*	-745908.042	4.484	1.679	4370.307
	I. *exo*	-745905.160	**4.558**	**1.662**	4334.009
	I’. *exo*	-745907.973	4.468	1.706	4347.505
b (s-cis)	**I.** *endo*	-888873.335	**4.506**	**1.690**	5233.546
	I’. *endo*	-888873.681	4.471	1.771	5243.674
	I. *exo*	-888871.168	**4.531**	**1.765**	5132.040
	I’. *exo*	-888873.681	4.503	1.839	5140.867
b (s-trans)	**I.** *endo*	-888872.690	**4.517**	**1.668**	5226.108
	I’. *endo*	-888873.497	4.481	1.758	5233.721
	I. *exo*	-888870.868	**4.541**	**1.739**	5127.599
	I’. *exo*	-888873.820	4.487	1.812	5136.924
c (s-cis)	**I.** *endo*	-888875.249	**4.550**	**1.696**	5198.710
	I’. *endo*	-888875.388	4.371	1.879	5168.755
	I. *exo*	-888875.065	**4.452**	**1.854**	5147.774
	I’. *exo*	-888875.388	4.370	1.894	5148.991
c (s-trans)	**I.** *endo*	-888875.642	**4.517**	**1.671**	5205.409
	I’. *endo*	-888875.065	4.354	1.853	5180.185
	I. *exo*	-888875.434	**4.435**	**1.831**	5141.874
	I’. *exo*	-888875.434	4.370	1.856	5152.322

Table 2. Global properties for the D-A adducts **II** and **II'**
[benzene calculations, SP CPCM/B3LYP/6-31g(d)].

Dienophile	D-A Adduct	[E + ZPE]	η	ω	α
b	**II.** *endo*	-888866.514	3.679	2.493	5217.186
	II'. *endo*	-888866.152	3.857	2.374	5225.608
	II. *exo*	-888863.287	3.808	2.424	5127.664
	II'. *exo*	-888866.996	3.898	2.348	5155.630
c	**II.** *endo*	-888866.357	3.840	2.441	5240.966
	II'. *endo*	-888866.138	3.838	2.387	5283.492
	II. *exo*	-888864.328	3.731	2.528	5170.019
	II'. *exo*	-888867.808	3.873	2.367	5184.136

Table 3. Global properties for the D-A adducts **I** and **I'**
[benzene calculations, SP CPCM/B3LYP/6-31g(d)].

Dienophile	D-A Adduct	[E + ZPE][a]	η	ω
a	**I.** *endo*	-745911.663	**4.310**	**1.772**
	I'. *endo*	-745912.217	4.277	1.850
	I. *exo*	-745909.541	**4.277**	**1.862**
	I'. *exo*	-745912.309	4.200	1.901
b (s-cis)	**I.** *endo*	-888878.409	**4.288**	**1.865**
	I'. *endo*	-888879.262	4.266	1.935
	I. *exo*	-888876.449	**4.268**	**1.955**
	I'. *exo*	-888879.078	4.278	2.018
b (s-trans)	**I.** *endo*	-888877.971	**4.297**	**1.852**
	I'. *endo*	-888879.032	4.267	1.934

	I. *exo*	-888876.149	**4.272**	**1.944**
	I'. *exo*	-888879.078	4.262	2.004
c (s-cis)	**I.** *endo*	-888880.692	**4.305**	**1.899**
	I'. *endo*	-888880.277	4.168	2.043
	I. *exo*	-888880.254	**4.193**	**2.051**
	I'. *exo*	-888880.577	4.124	2.079
c (s-trans)	**I.** *endo*	-888880.992	**4.288**	**1.885**
	I'. *endo*	-888880.461	4.169	2.020
	I. *exo*	-888880.438	**4.187**	**2.034**
	I'. *exo*	-888880.554	4.127	2.045

Table 4. Global properties for the D-A adducts **II** and **II'**
[benzene calculations, SP CPCM/B3LYP/6-31g(d)].

Dienophile	**D-A Adduct**	**[E + ZPE]**	η	ω
b	**II.** *endo*	-888871.283	3.505	2.676
	II'. *endo*	-888871.444	3.632	2.614
	II. *exo*	-888868.608	3.589	2.647
	II'. *exo*	-888872.090	3.67553	2.609
c	**II.** *endo*	-888871.998	3.604	2.678
	II'. *endo*	-888871.052	3.602	2.622
	II. *exo*	-888869.576	3.529	2.742
	II'. *exo*	-888872.989	3.646	2.638

Study of the regioselectivity of the D-A reactions

The regioisomer that have the higher value of η and the lower values of ZPE, α and ω, should correspond to the major product.[10] The calculated hardness and electrophilicity power correctly predict the regioisomers **I.a-I.c** as the main adducts of the D-A reactions (the corresponding values are highlighted in bold in Tables 1 and 3). However, the calculated total energies and polarizabilities show a random behaviour. Therefore, neither of these two parameters can predict the predominant regioisomer of the D-A reactions in a correct way.

The results obtained in gas phase revealed the same tendency as in benzene. The chemical hardness and the electrophilicity power are useful parameters to predict which regioisomers will lead to the main product of the D-A reactions.

We can conclude that the predominant regioisomeric adduct of the reactions between furan derivatives and Danishefsky's diene has always the less electrophilicity and high hardness values. Therefore, the regioselectivity experimentally observed can be confirmed by this approach.

Study of the stereoselectivity of the D-A reactions

The obtained energies show that the **I.***endo* isomer is more stable than the **I.***exo* one (Tables 1-4). Moreover, the more stable **I.***endo* isomer has lower electrophilicity value than the **I.***exo* isomer in all cases. Regarding the hardness, we found that only in the presence of benzene media the maximum hardness principle is obeyed.

ACKNOWLEDGMENTS

This work received financial support from Universidad Nacional del Litoral through CAI+D Projects (CAID 12/ H409 and CAID 12/H619) and PICTO 36102R. R. Brasca thanks the Austrian Exchange Service (ÖAD) and the Austrian Federal Ministry of Science and Research (BMWF) for the Ernst-Mach Stipendien and CONICET for the Doctoral Grant Program.

REFERENCES

---

[1] (a) Hu, Y.; Xiang, J.S.; Di Grandi, M.J.; Du, X.; Ipek, M.; Laakso, L.M.; Li, J.; Li, W.; Rush, T.S.; Schmid, J.; Skotnicki, J.S.; Tam, S.; Thomason, J.R.; Wang, Q.; Levin, J.I. *Bioorg. Med. Chem.* **2005**, *13*, 6629. (b) Gfesser, G.A.; Faghih, R.; Bennani, Y.L.; Curtis, M.P.; Esbenshade, T.A.; Hancock, A.A.; Cowart, M.D. *Bioorg. Med. Chem. Lett.* **2005**,*15*, 2559. (c) Collini, M.D.; Kaufman, D.H.; Manas, E.S.; Harris, H.A.; Henderson, R.A.; Xu, Z.B.; Unwalla, R.J.; Miller, C.P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4925. (d) Shimazu, S.; Tsunekawa, H.; Yoneda, F.; Katsuki, H.; Akaike, A.; Janowsky, A. *Eur. J. Pharm.* **2003**, *482*, 9. (e) Shimazu, S.; Tsunekawa, H.; Yoneda, F.; Katsuki, Tsunekawa, H.; Tanigawa, A.; Yoneda, F.; Knoll, J.; Akaike, A. *Eur. J. Pharm.* **2001**, *421*, 181. (f) Vaccarini, C.; Alarcón, R.; Sosa, V. *Molecules* **2000**, *5*, 435.

[2] (a) De Luca, L.; Giacomelli, G.; Nieddu, G. *J. Org. Chem.* **2007**, *72*, 3955. (b) Della Rosa, C.; Kneeteman, M.K.; Mancini, P.M.E. *Tetrahedron Lett.* **2005**, *46*, 8711. (c) Kraus, G.A.; Zhang, N.; Verkade, J.G., Nagarajan, M.; Kisanga, P.B. *Org. Lett.* **2000**, *2*, 2409. (d) Horton, D.A.; Bourne, G. T.;

Smythe, M.L. *Chem. Rev.* **2003**, *103*, 893. (e) Zhang, H.C.; Maryanoff, B.E. *J. Org. Chem.* **1997**, *62*, 1804. (f) Fancelli, D.; Fagnola, M.C.; Severino, D.; Bedeschi, A. *Tetrahedron Lett.* **1997**, *38*, 2311.

[3] (a) Pérez, P.; Domingo, L.R.; Duque-Noreña, M.; Chamorro, E. *J. Mol. Struct. (Theochem)* **2009**, *895*, 86. (b) Benmeddah, A.; Mekelleche, S.M.; Benchouk, W.; Mostefa-Kara, B.; Villemin, D. *J. Mol. Struct. (Theochem)* **2007**, *821*, 42. (c) Domingo, L.R.; Pérez, P.; Contreras, R. *Eur. J. Org. Chem.* **2006**, 498. (d) Noorizadeh, S.; Maihami, H. *J. Mol. Struct. (Theochem)* **2006**, *763*, 133. (e) Domingo, L.R.; Perez, P.; Contreras, R. *Lett. Org. Chem.* **2005**, *2*, 68. (f) Arroyo, P.; Picher, M.T.; Domingo, L.R.; Terrier, F. *Tetrahedron* **2005**, *61*, 7359. (g) Domingo, L.R.; Pérez, P.; Contreras, R. *Lett. Org. Chem.* **2005**, *2*, 68. (h) Pérez, P.; Domingo, L.R.; Aurell, M.J.; Contreras, R. *Tetrahedron* **2003**, *59*, 3117. (i) Chamorro, E.; Chattaraj, P.K.; Fuentealba, P. *J. Phys. Chem. A* **2003**, *107*, 7068. (j) Domingo, L.R.; Aurell, M.J.; Pérez, P.; Contreras, R. *Tetrahedron* **2002**, *58*, 4417. (k) Domingo, L.R.; Aurell, M.J.; Pérez, P.; Contreras, R. *J. Phys. Chem. A* **2002**, *106*, 6871. (l) Parr, R.G.; Von Szentpaly, L.; Liu, S. *J. Am. Chem. Soc.* **1999**, *121*, 1922. (m) Kurtz, H.; Dudis, D. *Quantum mechanical methods for predicting nonlinear optical properties*; Lipkowitz, K.B.; Boyd, D.B. (Eds.), Reviews in Computational Chemistry, Wiley-VCH: New York, **1998.** (n) Parr, R.G.; Yang, W. *Density Functional Theory of Atoms and Molecules*; Oxford University Press: Oxford, U.K., **1989.** (o) Parr, R.G.; Yang, W. *Density Functional Theory of Atoms and Molecules*; Oxford University Press: Oxford, U.K., **1989.** (p) Parr, R.G.; Yang, W. *J. Am. Chem. Soc.* **1984**, *106*, 4049. (q) Parr, R.G.; Pearson, R.G. *J. Am. Chem. Soc.* **1983**, *105*, 7512. (r) Parr, R.G.; Pearson, R.G. *J. Am. Chem. Soc.* **1983**, *105*, 7512. (s) Pearson, R.G. *J. Am. Chem. Soc.* **1963**, *85*, 3533. (t) Pearson, R.G. *J. Am. Chem. Soc.* **1963**, *85*, 3533. (u) Domingo, L.R.; Aurell, M.J.; Pérez, P.; Contreras, R. J. Org. Chem. **2003**, *68*, 3884.

[4] Brasca, R.; Kneeteman, M.N.; Mancini, P.M.E.; Fabian, W.M.F. *J. Mol. Struct. (Theochem)* **2009**, *911*, 124.

[5] (a) Noorizadeh, S. *Chin. J. Chem.* **2008**, *10*, 1439. (b) Xia, Y.; Yin, D.; Rong, C.; Xu, Q.; Yin, D.; Liu, S. *J. Phys. Chem. A* **2008**, *112*, 9970. (c) Noorizadeh, S. *J. Phys. Org. Chem.* **2007**, *20*, 514. (d) Cong, Y.; Yang, Z.; Wang, C.; Liu, X.; Bao, X. *Chem. Phys. Lett.* **2002**, *357*, 59.

[6] (a) Becke, A.D. *J. Chem. Phys.* **1993**, *98*, 5648-5652. (b) Lee, C.; Yang, W.; Parr, R.G. *Phys. Rev. B* **1988**, *37*, 785.

[7] Gaussian 03, Revision B.04, Frisch, M.J.; Trucks, G.W.; Schlegel, H.B.; Scuseria, G.E.; Robb, M.A.; Cheeseman, J.R.; Montgomery, J.A. (Jr.); Vreven, T.; Kudin, K.N.; Burant, J.C.; Millam, J.M.; Iyengar, S.S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G.A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J.E.; Hratchian, H.P.; Cross, J.B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R.E.; Yazyev, O.; Austin, A.J.; Cammi, R.; Pomelli, C.; Ochterski, J.W.; Ayala, P.Y.; Morokuma, K.; Voth, G.A.; Salvador, P.; Dannenberg, J.J.; Zakrzewski, V.G.; Dapprich, S.; Daniels, A.D.; Strain, M.C.; Farkas, O.; Malick, D.K.; Rabuck, A.D.; Raghavachari, K.; Foresman, J.B.; Ortiz, J.V.; Cui, Q.; Baboul, A.G.; Clifford, S.; Cioslowski, J.; Stefanov, B.B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R.L.; Fox, D.J.; Keith, T.; Al-Laham, M.A.; Peng, C.Y.; Nanayakkara, A.; Challacombe, M.; Gill, P.M.W.; Johnson, B.; Chen, W.; Wong, M.W.; Gonzalez, C.; Pople, J.A. Gaussian, Inc., Pittsburgh PA, **2003.**

[8] Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027.

---

[9] (a) Klamt, A.; Schüürmann, G. *J. Chem. Soc., Perkin Trans. 2* **1993**, 799. (b) Klamt, A.; Jonas, V.; Buerger, T.; Lohrenz, J.C.W. *J. Phys.Chem. A* **1998**, *102*, 5074.

[10] (a) Elango, M.; Parthasarathi, R.; Subramanian, V.; Chattaraj, P. K. *J. Mol. Struct. (Theochem)* **2007**, *820*, 1. (b) Chattaraj, P. K.; Maiti, B. *J. Am. Chem. Soc.* **2003**, *125*, 2705. (c) Chamorro, E.; Chattaraj, P. K.; Fuentealba, P *J. Phys. Chem. A* **2003**, *107*, 7068. (d) Ayers, P. W.; Parr, R. G. *J. Am. Chem. Soc.* **2000**, *122*, 2010. (e) Liu, S. B.; Parr, R. G. *J. Chem. Phys.* **1997**, *106*, 5578. (f) (32) Chattaraj, P. K.; Sengupta, S. *J. Phys. Chem.* **1996**, *100*, 16126. (g) Chattaraj, P. K.; Liu, G. H.; Parr, R. G. *Chem. Phys. Lett.* **1995**, *237*, 171.