First International Electronic Conference on Synthetic Organic Chemistry (ECSOC-1), www.mdpi.org/ecsoc/, September 1-30, 1997

[E0004]

Received: 25 August 1997 / Uploaded: 27 August 1997

Effects of Intramolecular and Intermolecular Interactions on Oxidations by Dimethyldioxirane.

Karol Miaskiewicz* and Douglas A. Smith

Contribution from The DASGroup, Inc.
1732 Lyter Drive
Johnstown, PA 15905
www.dasgroup.com

ABSTRACT

The Density Functional Theory B3LYP/6-31G method is used to provide a detailed understanding of the origins of intra- and intermolecular (solvent) effects on the epoxidation of C-C double bonds and oxidation of primary amines by dimethyldioxirane (DMDO). We find that the presence of hydrogen bond donors, either internal in the form of substituents on the substrate or external in the form of hydrogen bonding solvents, leads to dramatically decreased activation barriers for epoxidation of the C=C bond as well as for oxidation of amines. Solvent polarity, studied using the SCIPCM model, also lowers the activation barrier although this effect is substantially smaller than seen with hydrogen bonding interactions. The effect of solvent polarity is larger in the oxidation of primary amine than in the epoxidation reaction due to very polar transition state structure seen in the oxidation of amine.*

INTRODUCTION

Dioxiranes offer a powerful and often unique ability to transfer an oxygen atom to a wide variety of substrates, including carbon-carbon double bonds, carbon-hydrogen bonds in hydrocarbons, as well as atoms containing lone pairs, such as sulfides and sulfoxides and primary and secondary amines.

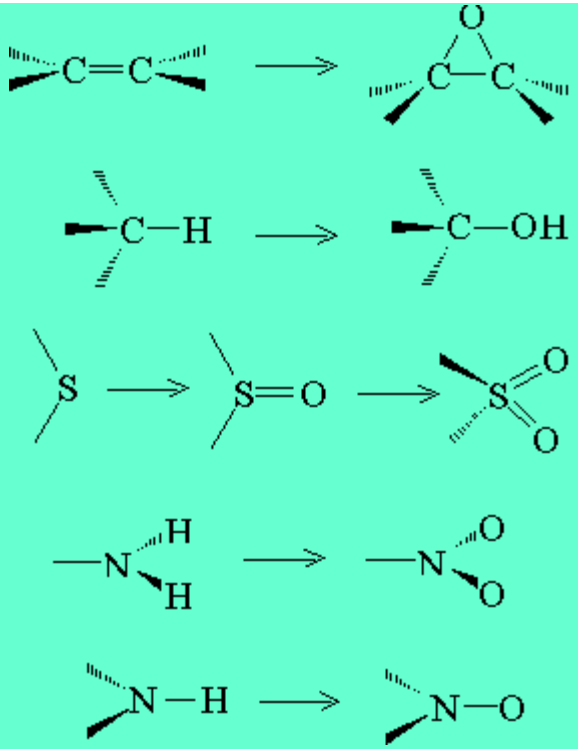
Control of regioselectivity and stereoselectivity by conformation and substituents in the molecular system undergoing oxidation, as well as by solvent used in the reaction, has been frequently observed in oxidations reactions by dioxiranes. Baumstark and co-workers observed highly accelerated epoxidation rates upon addition of water to the dimethyldioxirane (DMDO) solution in acetone.(1) Murray and Gu studied rates of DMDO epoxidation of ethyl-cinnamate and cyclohexene in a number of binary solvent systems. (2) Solvents with hydrogen bond donor capacity were found to increase reaction rates whereas the opposite effect, i.e., a decrease in reaction rates, was seen for solvents

Dioxiranes

R1, R2 = H, F, CH_3, CF_3

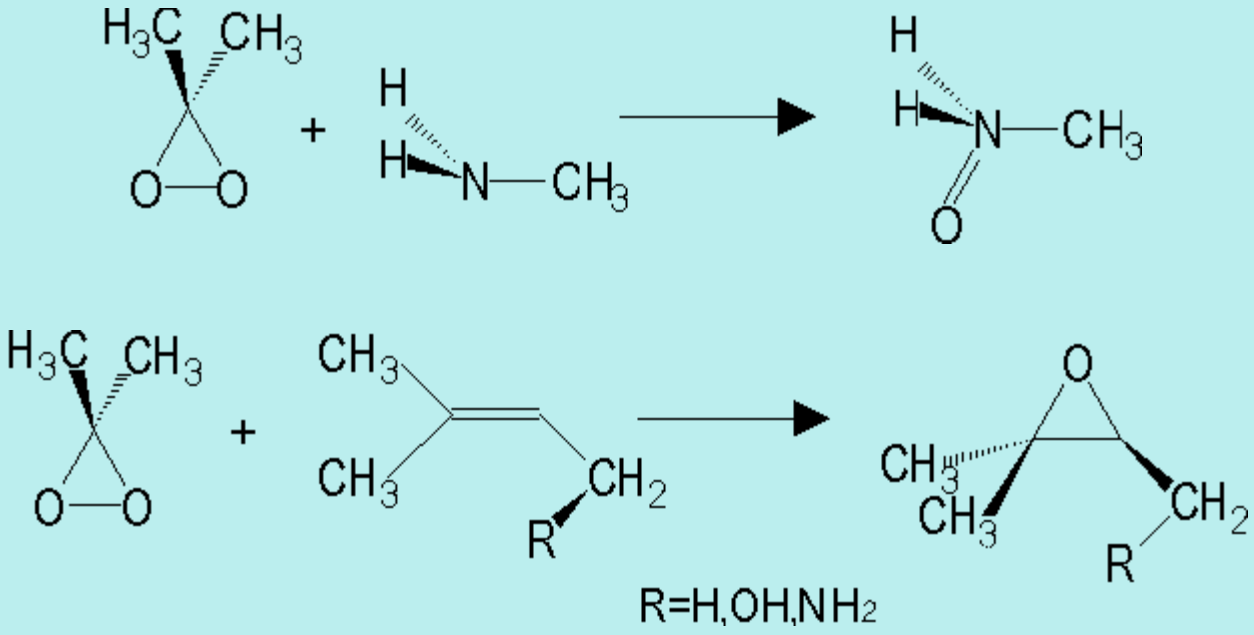
Typical Oxidations by Dioxiranes

with hydrogen bond acceptor capacity. (2) Interestingly, only a slight effect of solvent's polarity on reaction rates was detected. A pronounced dependence of epoxide diastereoselectivity on substituent has been recently reported in DMDO epoxidations of cyclohexenes. In addition, a strong solvent influence on this stereoselectivity has been also observed.(3) Adam and Smerz have documented similar substituent and solvent effects in regio- and diastereselective epoxidation of allylic alcohols by DMDO. (4) The observed control of regio- and stereoselectivity has been postulated to occur primarily through hydrogen bonding interactions with the hydroxyl substituents of allylic alcohols and/or with molecules of a protic solvents.(3,4)



The present computational study elucidates the atomistic details of intra- and intermolecular interactions that affect reactivity and selectivity in DMDO oxidations of alkenes and amines. The transition state barriers for selected DMDO oxidation are calculated in the presence of dielectric medium, solvent molecules with hydrogen bond donor properties, as well as in the presence of hydrogen bond donor substituents on the reactant. Results of the present study provide an elegant atomistic explanation of experimentally observed substituent and solvent effects in dioxirane oxidations.

MODELED REACTIONS



COMPUTATIONAL METHODS

Dioxiranes are challenging problems for ab initio calculations. Hartree-Fock methods are inadequate for dioxiranes; methods that incorporate electronic correlation energy, at least to some extent, are required. After extensive tests and validations we selected the density functional B3LYP/6-31G* method to model reactions of dioxiranes. This computational level provides reasonable quality results (at least as good as the MP2 level calculations) at relatively moderate computational cost. (5)

Calculations were performed using Gaussian 94. (6) Oxidation of alkenes was studied on the model reaction between DMDO and 2-methyl-2-butene and its hydroxy and amino derivatives. Oxidation of primary amines was modeled by the reaction between DMDO and methylamine. Transistion states described by one imaginary frequency were located for the model reactions. Corrections for the Zero Point Vibrational Energy (ZPE) were obtained from B3LYP/6-31G* frequency calculations.

Effects of dielectric solvent were simulated using the SCIPCM model as implemented in Gaussian 94. SCIPCM calculations were single point calculations, i.e., geometry was not re-optimized in the dielectric field. Analysis of electronic properties and molecular orbitals was performed via natural bond orbital (NBO) analysis. (7)

RESULTS AND DISCUSSION

Epoxidation of butenes

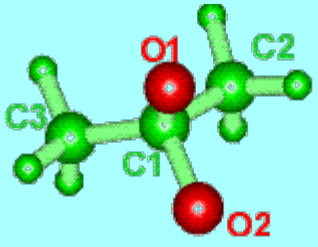
Effect of intra- and intermolecular hydrogen bonding.

Transition state (TS) structures were calculated for DMDO epoxidation of 2-methyl-2-butene (TS-1), 3-methyl-2-buten-1-ol (TS-2 and TS-3), 1-amino-3-methyl-2-butene (TS-4), and 2-methyl-2-butene in the presence of methanol (TS-5).

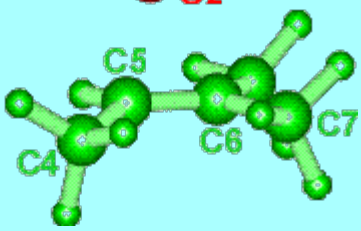
Substituents with hydrogen bond donor properties present in the alkene system have a profound effect on activation energies (see Table 1). The hydroxyl group at C4, in a conformation that allows for it to interact with the attacking DMDO (TS-2), brings down the activation energy from 13.6 kcal/mol to 6.7 kcal/mol. This is not an electronic effect, i.e., changes in electronic density distribution within the alkene, but is clearly due to direct interaction between DMDO and the OH group. When the OH group is rotated away from DMDO (TS-3), such that it cannot interact with DMDO, the activation barrier returns to 13.0 kcal/mol. The interaction between OH and DMDO has the form of hydrogen bonding, although the hydrogen bond angle of 120° is quite far from an optimal linear configuration. An amino group at C1 shows a similar interaction with DMDO that decreases the activation barrier. However, the decrease is smaller when compared to the hydroxyl group (10.0 vs. 7.6 kcal/mol) which is explained by a weaker hydrogen bonding interaction as evidenced by a longer H4--O2 distance and even less favorable angle. One may expect similar effects on the reaction barrier with other substituents that possess hydrogen bond donor

TS-1

DMDO + 2-methyl-2-buten



O2-C5 = 1.946 Å
O2-C6 = 2.194 Å
O1-O2 = 1.879 Å



TS-2

capability.

An even more profound effect than observed with hydrogen bond donor substituents is observed in the presence of methanol - the ﷺexternalﷺ hydrogen bond donor. The activation energy is just 0.8 kcal/mol when methanol is hydrogen bonded to DMDO in TS-5. Methanol is geometrically less constrained than substituents on the alkene and thus forms a stronger hydrogen bond interaction (the H9--O2 distance is just 1.865 ﷺ and the O9--H9--O2 angle is 168.7°) with DMDO.

Table 1. B3LYP/6-31G activation energies (ZPE corrected) of calculated transition states for DMDO oxidations.*

Transition State	Activation Energy (kcal/mol)
Epoxidations	
TS-1	13.6
TS-2	6.74
TS-3	13.0
TS-4	10.0
TS-5	0.81
Oxidation of amine	
TS-6	14.4
TS-7	2.14
TS-8	1.33

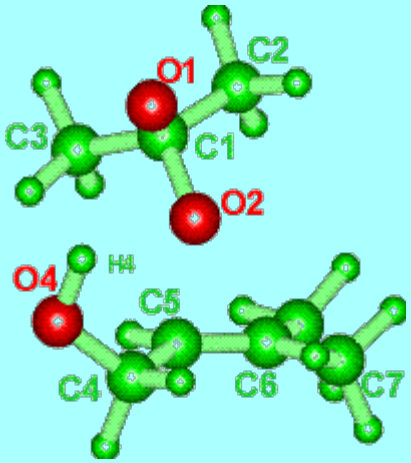
Effect of solvent polarity.

Solvent polarity affects the activation barrier for epoxidation of 2-methyl-2-butene (TS-1), as revealed by calculations using the SCIPCM model (Table 2). Activation energy for TS-1 decreases from 13.6 kcal/mol in the gas phase to 9.3 kcal/mol when a dielectric constant of 40 is used. The decrease in the activation barrier reflects the polarity of TS-1 with dipole moment of 4.2D (dipole moments of DMDO and 2-methyl-2-butene are 2.9D and 0.18D, respectively). The solvent-induced decrease in activation energy for TS-1 is substantially smaller than observed with when solvent with hydrogen bond donor capacity, such as methanol, is present (TS-5).

Table 2. B3LYP/6-31G activation energies (ZPE corrected) of TS-1 calculated in the presence of dielectric medium using the SCIPCM model.*

Dielectric constant ε in SCIPCM calculations	Common solvent with a close value of ε	Activation energy (kcal/mol) of TS-1

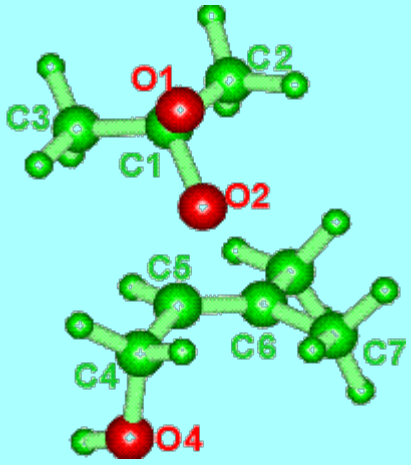
DMDO + 3-methyl-2-buten-1-ol



O2-C5 = 1.938 Å
O2-C6 = 2.275 Å
H4-O2 = 2.112 Å
H4-O1 = 2.525 Å

TS-3

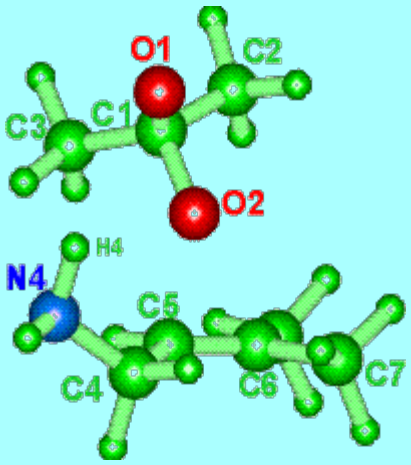
DMDO + 3-methyl-2-buten-1-ol



O2-C5 = 1.909 Å
O2-C6 = 2.258 Å
H4-O2 = 4.349 Å

TS-4

DMDO + 1-amino-3-methyl-2-buten



O2-C5 = 1.944 Å
O2-C6 = 2.246 Å
H4-O2 = 2.318 Å
H4-O1 = 2.700 Å

TS-5

DMDO + 2-methyl-2-buten +

gas phase	gas phase	13.6
10	CH_2Cl_2 e=9.08	9.98
20	acetone e=20.7	9.53
40	CH_3CN e=36.02	9.26

Oxidation of primary amines

Effect of hydrogen bonding.

A dramatic effect on the barrier for oxidation of methylamine is seen with explicit solvent molecules hydrogen bonded to DMDO at the TS structure. The barrier is just 1-2 kcal/mole (without the ZPE contribution the barrier is even slightly negative at the B3LYP level) in the presence of water or methanol interacting with DMDO (Table 1). This barrier is 14.4 kcal/mol in the absence of such hydrogen bonding interaction.

Effect of solvent polarity.

The activation barrier for DMDO oxidation of amine is substantially lowered in the dielectric medium (although not as dramatically as seen with hydrogen bonded solvent molecules) and shows significant decrease with increasing value of e (Table 3). This is a result of a highly polar TS with a large dipole moment of 8.1D.

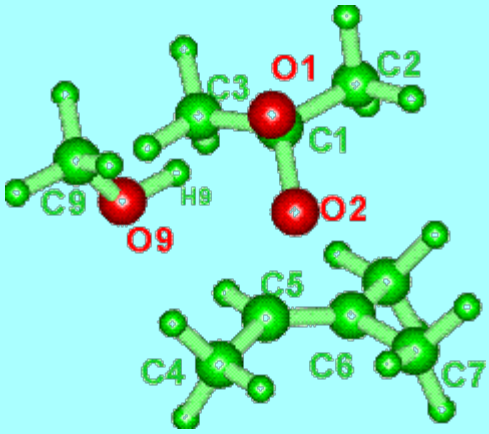
Table 3. B3LYP/6-31G activation energies (ZPE corrected) of TS-6 calculated in the presence of dielectric medium using the SCIPCM model.*

Dielectric constant e in SCIPCM calculations	**Common solvent with a close value of e**	**Activation energy (kcal/mol) of TS-6**
gas phase	gas phase	14.4
5	CCl_4 e=2.24	7.09
10	CH_2Cl_2 e=9.08	5.42
20	acetone e=20.7	4.43
40	CH_3CN e=36.02	3.93

Frontier orbitals in DMDO oxidations.

In the oxidation reactions studied here, DMDO is the electrophile and the alkene p system or the nitrogen lone pair in methylamine is the nucleophile. The TS geometries provide optimal interaction between frontier orbitals, i.e., the LUMO of DMDO and the HOMO of the

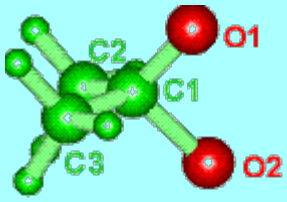
methanol



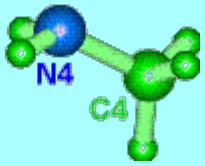
O2-C5 = 2.046 Å
O2-C6 = 2.261 Å
H9-O2 = 2.453 Å
H9-O1 = 1.865 Å

TS-6

DMDO + methylamine

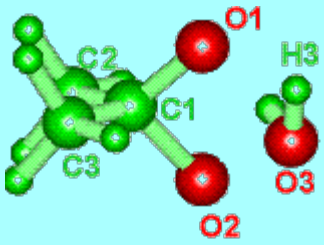


O2-N4 = 1.710 Å
O1-O2 = 2.011 Å

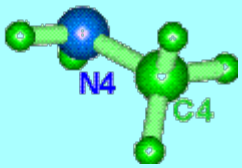


TS-7

DMDO + methylamine + water



O2-N4 = 1.792 Å
O1-O2 = 1.920 Å
H3-O2 = 2.238 Å
H3-O1 = 1.947 Å

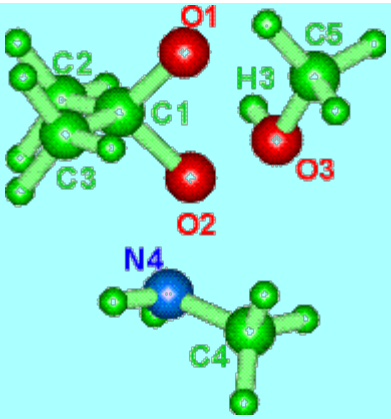


TS-8

DMDO + methylamine + methanol

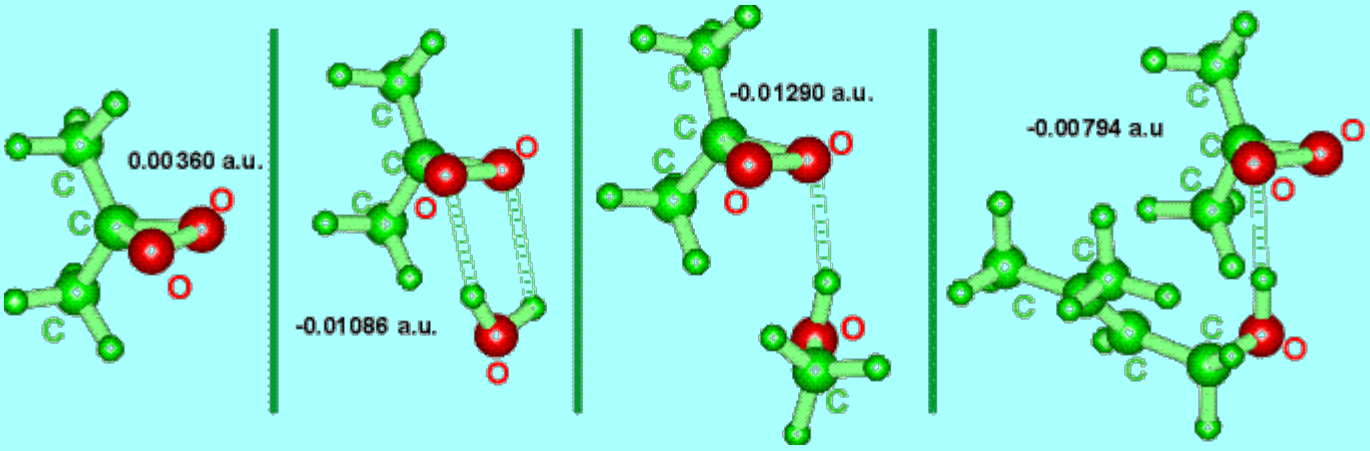
alkene/methylamine. Hydrogen bonding interactions with the dioxirane exert their effect on the reaction barrier by lowering the energy of DMDO's LUMO (primarily anti-bonding O-O). The LUMO energy is decreased by 0.0165 a.u. in the complex between DMDO and methanol (see figure below) when compared to isolated DMDO. A similar effect is seen when water interacts with DMDO and in the hydrogen bonded complex formed with 2-methyl-2-butene. In these cases, the DMDO LUMO energy decreases by 0.0145 and 0.0115 a.u., respectively.

Although it has been suggested that the hydroxyl group in allylic alcohols should lower the nucleophilicity of the double bond through inductive electron withdrawal, (4) we do not find the hydroxyl group exercising any meaningful electronic effect on the HOMO (π C=C orbital) of the allylic alcohol. In addition, the atomic partial charges on C2 and C3 do not change significantly with the introduction of the hydroxyl group at C4. As a result, our calculations indicate that the inductive effect of the OH group in allylic alcohol is very small, if any, and the primary mechanism by which this group may affect the reaction barrier for epoxidation is through a direct interaction with DMDO in the TS.



O2-N4 = 1.790 Å
O1-O2 = 1.920 Å
H3-O2 = 2.239 Å
H3-O1 = 1.906 Å

Energy of the LUMO orbital in DMDO and hydrogen bonded complexes with H_2O, CH_3OH and 3-methyl-2-buten-1-ol



CONCLUSIONS

- As revealed by performed here modeling studies, epoxidations and oxidation of primary amine by dimethyldioxirane are very sensitive to intra- and inter-molecular interactions. The observed sensitivity provides an explanation for substituent and solvent effects observed experimentally in oxidation reactions by dioxiranes.

- The activation barrier is dramatically lowered in the presence of hydrogen bond donors that interact with the DMDO molecule. Such hydrogen bond interactions can occur with

appropriate substituents present on the reactant (such as the hydroxyl group on the allylic alcohol). They can also occur with molecules of solvent with hydrogen bond donor properties, as seen here with methanol and water molecules.

Increasing the polarity of the solvent also lowers the reaction barrier. However, this effect is much less profound than is lowering of the reaction barrier seen for hydrogen bonding interactions. Lowering of reaction barrier due to solvent polarity is more significant in oxidation of amine than in epoxidation of the C=C bond. This is the effect of highly polar transition state structure observed in oxidation of amine.

REFERENCES

1. Baumstark, A. L.; Vasquez, P. C. *J. Org. Chem.* **1988**, *53*, 3437.
2. Murray, R. W.; Gu, D. *J. Chem. Soc. Perkin Trans. 2* **1993**, 2203.
3. Murray, R. W.; Singh, M.; Williams, B. L.; Moncrieff, H. M. *J. Org. Chem.* **1996**, *61*, 1830.
4. Adam, W.; Smerz, A. K. *J. Org. Chem.* **1996**, *61*, 3506.
5. Miaskiewicz, K.; Teich, N.; Smith, D.A. *J. Org. Chem.* in press.
6. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T. A.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challocombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A.; **Gaussian 94**, Gaussian, Inc., Pittsburgh, PA, 1995.
7. Glendening, E. D.; Reed, A. E.; Carpenter, J. E.; Weinhold, F. **NBO Version 3.1.**

Comments

During 1-30 September 1997, all comments on this poster should be sent by e-mail to ecsoc@listserv.arizona.edu with **E0004** as the message subject of your e-mail. After the conference, please send all the comments and reprints requests to the author(s).
