DOI: 10.1002/ejic.200800534

A Theoretical Study on the Reactivity of a Rhenium Hydroxo-Carbonyl Complex Towards β-Lactams

Violeta Yeguas,[a] Pablo Campomanes,[b] and Ramón López*[a]

Keywords: β-Lactams / Cleavage reactions / Hydroxo complexes / Rhenium / Density functional calculations

The mechanism of the reaction between the complex $[Re(OH)(CO)_3(N_2C_2H_4)]$ and azetidin-2-one or 3-formylamino-*N*-sulfonatoazetidin-2-one was investigated by using the B3LYP density functional theory methodology in conjunction with the PCM-UAHF model to take into account solvent effects. According to our calculations, the rate-determining energy barrier for the azetidin-2-one case of 38.8 kcal mol^{-1}, becomes 25.7 kcal mol^{-1} in the case of the 3-formylamino-*N*-sulfonatoazetidin-2-one species. The presence of the sulfonato group is crucial for the cleavage of the β-lactam N1–C2 bond by the Re complex thanks to the interaction of the sulfonato group with the hydroxy and bidentate ligands of the complex. This could be of interest for the synthesis of β-amino acids and their derivatives from β-lactams under mild conditions and in solvents of low polarity promoted by organometallic complexes.

Introduction

The synthesis of organotransition metal complexes with terminal hydroxo ligands is a matter of great interest owing to the implication of such complexes in catalytic processes and in materials-related chemistry.[1–12] Besides this, organometallic hydroxo compounds are also important due to their rich OH-centred reactivity[13] which is dominated by the nucleophilic character of the hydroxo ligand. In recent years, several groups have started to investigate the chemistry of hydroxo complexes of the central (Groups 6 and 7) transition metals.[4,13–23] In particular, it has been reported that the hydroxo complex $[Re(OH)(CO)_3(Me_2\text{-bipy})]$ (Me_2-bipy = 4,4′-dimethyl-2,2′-bipyridine) reacts with a variety of organic electrophiles such as carbon disulfide, esters, aryl isocyanates, alkyl/aryl isothiocyanates, dimethyl acetylenedicarboxylate, ketenes, maleic anhydride and *rac*-lactide.[15–17] Some of these processes evolve through the cleavage of a single C–O bond[15,16] to form metal-carboxylate products which are subsequently demetalated by reaction with triflic acid to afford the corresponding free carboxylic acids.[16]

Although it is well-known that an amide is less reactive than an ester, it would be interesting to investigate the reactivity of the above-mentioned complex towards β-lactams, an important class of cyclic amides, given that the cleavage of the amidic C–N bond would afford β-amino acids which are recognised as valuable tools for the generation of new derivatives such as β-peptides as well as building blocks for β-lactam antibiotics.[24–32] To the best of our knowledge, neither experimental nor theoretical studies have addressed the reaction of a terminal hydroxo complex of rhenium with β-lactams. With regards to acyclic amides, we have previously reported a theoretical study on the reactivity towards formamide[33] showing that the most favourable reaction mechanism exhibits a relatively high rate determining energy barrier in dichloromethane solution of 39.1 kcal mol^{-1}.

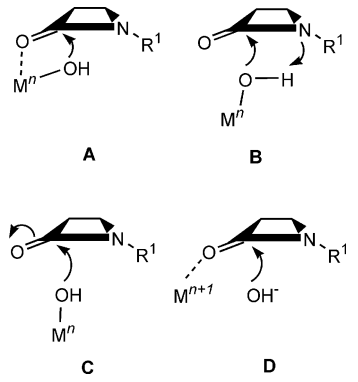
As an extension of our previous work mentioned above, we undertook a theoretical investigation of the reaction of a rhenium hydroxo-carbonyl complex with two β-lactams, azetidin-2-one and 3-formylamino-*N*-sulfonatoazetidin-2-one. Our aim was to try to answer the following question: could the rhenium complex cleave the amidic C–N bond of β-lactams? The β-lactam model, 3-formylamino-*N*-sulfonatoazetidin-2-one, was chosen due to the well-known active role played by the sulfonato group in the hydrolysis of monobactam antibiotics. The effect of the bulk solvent was taken into account using a continuum model (see the Computational Methods section for details).

Results and Discussion

Taking into account experimental studies on metal-promoted peptide hydrolysis[34–37] and theoretical investigations on the neutral[38,39] and enzymatic[40] hydrolysis of β-lactams, and the neutral hydrolysis of acyclic amides,[41–44] four different reaction mechanisms (see Scheme 1) can be envisaged for the reaction of [Re(OH)-

[a] Departamento de Química Física y Analítica, Universidad de Oviedo,
c/ Julián Clavería 8, 33006 Oviedo, Spain
[b] Laboratory of Computational Chemistry and Biochemistry, École Polytechnique Fédérale de Lausanne (EPFL),
1015 Lausanne, Switzerland
Supporting information for this article is available on the WWW under http://www.eurjic.org or from the author.

$(CO)_3(N_2C_2H_4)$] with azetidin-2-one and 3-formylamino-*N*-sulfonatoazetidin-2-one. The mechanism related to the proposal **D** in Scheme 1 was not investigated here because the energy required for the cleavage of the HO–Re bond of the complex is higher than the 65.0 kcal mol^{-1} reported in a theoretical study of the reactivity of molybdenum and rhenium hydroxo-carbonyl complexes with phenyl acetate.[45] Figure 1 depicts the optimised structures of the species involved in the reaction mechanisms for the reaction between [Re(OH)$(CO)_3(N_2C_2H_4)$] and azetidin-2-one. Table S1 in the Supporting Information lists the corresponding energy data. The rhenium complex has the hydroxy ligand oriented on the same side as the carbonyl ligands. We will discuss the mechanisms found as in the sequence depicted in Scheme 1. Unless otherwise stated in the text, the energy of all solvated species with respect to the separate reactants will be given in parentheses.



Scheme 1. Mechanistic proposals investigated for the reaction between the Re complex and β-lactams. The superscript *n* indicates the charge on the metal, M.

The most favourable reaction mechanism starts with the addition of the HO–Re bond to the β-lactam C=O (see **A** in Scheme 1) through either the TS **TS1a** (38.8 kcal mol^{-1}) or **TS1′a** (34.8 kcal mol^{-1}). In the former, the bidentate ligand is oriented on the same side of the complex system as the amidic C–N bond while the latter TS exhibits the opposite orientation. On one hand, **TS1a** connects the separate reactants with the intermediate **M1a** (17.9 kcal mol^{-1}) in which the Re and $O_{hydroxy}$ atoms are now linked to the $O_{carbonyl}$ and C_{amidic} atoms at distances of 2.119 and 1.445 Å, respectively. Intermediate **M1a** then evolves through the TS **TS2a** (25.2 kcal mol^{-1}) for the N_{amidic} inversion to give the intermediate **M2a** (18.4 kcal mol^{-1}). The next step corresponds to the rotation of the O–H bond with respect to the C–OH group of the system through TS **TS3a** (19.6 kcal mol^{-1}) to give the intermediate **M3a** (14.3 kcal mol^{-1}) in which the hydroxy O–H bond is oriented towards the amidic C–N. **M3a** leads to the product **P** (–22.3 kcal mol^{-1}) by means of TS **TS4a** (35.0 kcal mol^{-1}) for the cleavage of the amidic C–N bond and simultaneous H transfer from the $O_{hydroxy}$ atom to the N_{amidic} atom. At this TS, the amidic C···N, hydroxy O···H and $H_{hydroxy}$···N_{amidic} distances are 1.985, 0.973 and 2.286 Å, respectively. On the other hand, **TS1′a** gives rise to the intermediate **M1′a** (14.3 kcal mol^{-1}) in which the distances of the newly formed Re–$O_{carbonyl}$ and $O_{hydroxy}$–$C_{carbonyl}$ bonds are 2.115 and 1.437 Å, respectively. **M1′a** proceeds through the TS **TS2′a** (39.9 kcal mol^{-1}) for the β-lactam ring opening and simultaneous H transfer results in the product **P′** (–23.9 kcal mol^{-1}). At **TS2′a**, the amidic C···N, hydroxy O···H and $H_{hydroxy}$···N_{amidic} distances are 1.908, 1.146 and 1.397 Å, respectively. The mechanistic proposal type **B** in Scheme 1 indicates formation of the product **P′** directly through the TS **TSc** (41.7 kcal mol^{-1}) for the addition of the hydroxy O–H bond of the complex to the amidic C–N. Finally, the least favourable reaction mechanism found (see **C** in Scheme 1) starts with the TS **TS1b** (43.9 kcal mol^{-1}) for the addition of the hydroxy O–H bond to the β-lactam C=O which becomes the minimum energy structure **M1b** (13.8 kcal mol^{-1}). At this intermediate, the distances of the two newly formed bonds $O_{hydroxy}$–$C_{carbonyl}$ and $H_{hydroxy}$–$O_{carbonyl}$ are 1.350 Å and 0.968 Å, respectively. Then, the system undergoes a rotation of the O–H bond around the C–OH group through the TS **TS2b** (17.8 kcal mol^{-1}) to give the intermediate **M2b** (16.8 kcal mol^{-1}) wherein the hydroxy group is oriented on the same side as the N_{amidic}–H bond of the β-lactam moiety. **M2b** proceeds through the TS **TS3b** (21.4 kcal mol^{-1}) for the N_{amidic} inversion to give **M1′a** (14.3 kcal mol^{-1}) which subsequently evolves to **P′** (–23.9 kcal mol^{-1}) through the TS **TS2′a** as discussed above.

According to our results, the reaction between [Re(OH)$(CO)_3(N_2C_2H_4)$] and azetidin-2-one proceeds more favourably through the addition of the HO–Re bond of the complex to the β-lactam C=O bond and this can occur in two ways. In the most favourable, which has a rate-determining energy barrier in solution of 38.8 kcal mol^{-1}, the bidentate ligand lies on the same side of the complex as the amidic C–N bond while in the other way, the rate-determining energy barrier of which is 39.9 kcal mol^{-1}, the bidentate ligand is oriented towards the opposite side of the amidic C–N bond. The magnitude of these energy values is very similar to that found for the reaction of the Re complex with formamide (39.1 kcal mol^{-1})[33] thus suggesting long reaction times are involved. Concerning the rate-determining energy barriers, we suggest that the addition step involving **TS1a** (38.8 kcal mol^{-1}) is the rate-determining step for the most favourable addition pathway while for the other one the β-lactam ring opening step, involving **TS2′a** (39.9 kcal mol^{-1}), is the rate-determining stage. An NBO analysis of the TSs involved in the addition (**TS1a** and **TS1′a**) and β-lactam ring opening (**TS4a** and **TS2′a**) steps indicates the presence of several types of "donor-acceptor" interactions between the N_{amidic} atom and the bidentate ligand at **TS4a** (see Figure 2) which are not present in the remaining TSs. The second order perturbation energy of all these stabilising interactions, $\sigma(C–N_{amidic})\rightarrow\pi^*(C_{bidentate}–N_{bidentate})$, $\sigma(N_{amidic}–H)\rightarrow\pi^*(C_{bidentate}–N_{bidentate})$ and $LP(N)\rightarrow\pi^*(C_{bidentate}–N_{bidentate})$ amounts to 3.4 kcal mol^{-1} thus explaining why **TS4a** is 3.8 kcal mol^{-1} more stable than **TS1a**. On the contrary, in the other pathway, the pres-

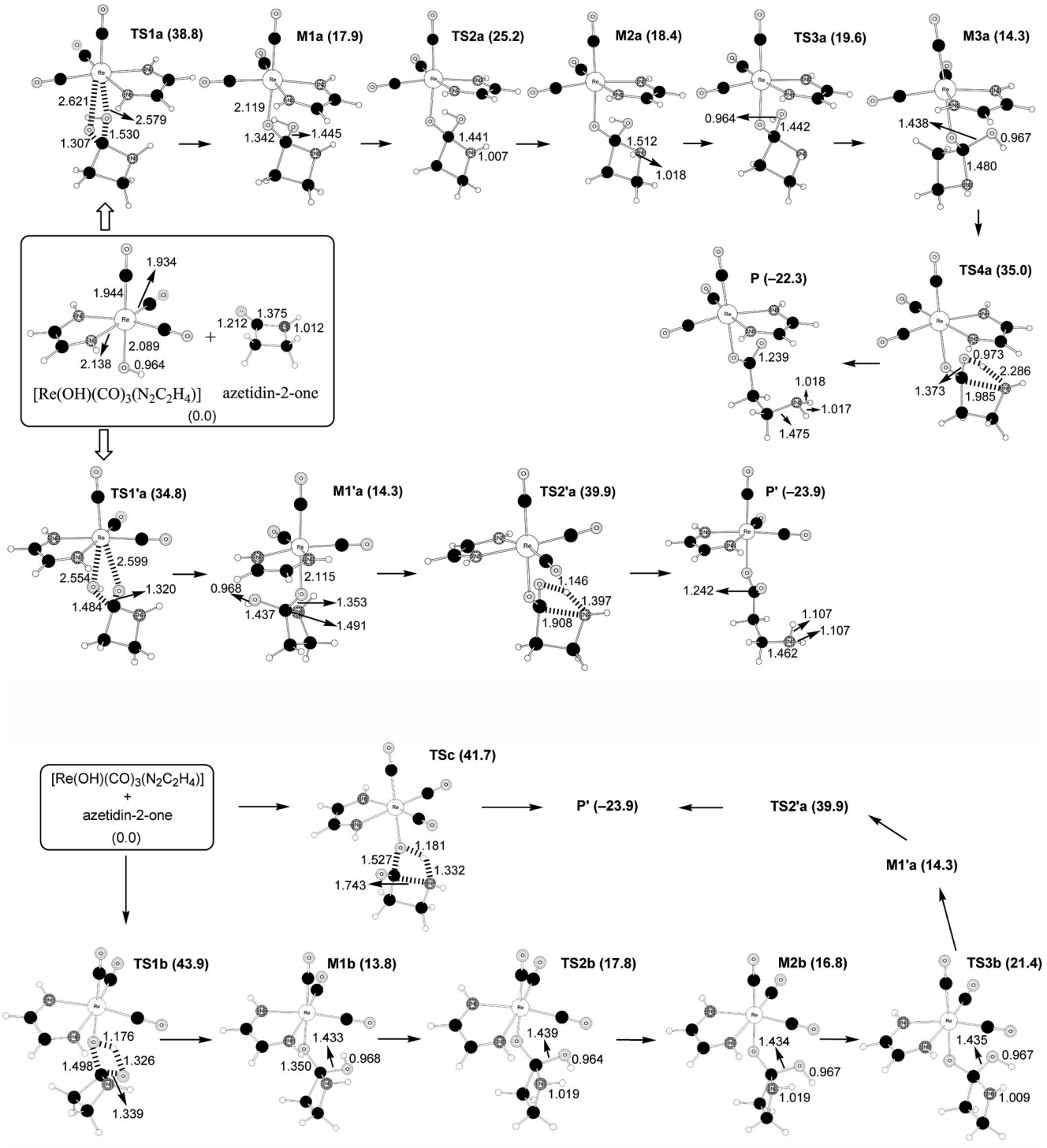


Figure 1. Schematic view of the optimised structures involved in the reaction mechanisms found for the reaction between azetidin-2-one and $[Re(OH)(CO)_3(N_2C_2H_4)]$. Relative energies in solution [kcal mol^{-1}] and the most relevant distances [Å] are also displayed.

ence of the carbonyl ligands on the same side of the complex as the amidic C–N bond prevents the appearance of the above-mentioned interactions and provokes a certain destabilisation of the system when going from **TS1′a** to **TS2′a** due to electronic repulsions between the lone pair of the N_{amidic} atom and the two O atoms of the carbonyl ligands.

Taking into consideration the results obtained for the reaction with azetidin-2-one, we only investigated the two most favourable reaction mechanisms for the reaction between the Re complex and 3-formylamino-*N*-sulfonatoazetidin-2-one. These correspond to the mechanistic proposals **A** and **B** in Scheme 1. Figure 3 shows the optimised geometries of the species involved in them and Table S2 in the

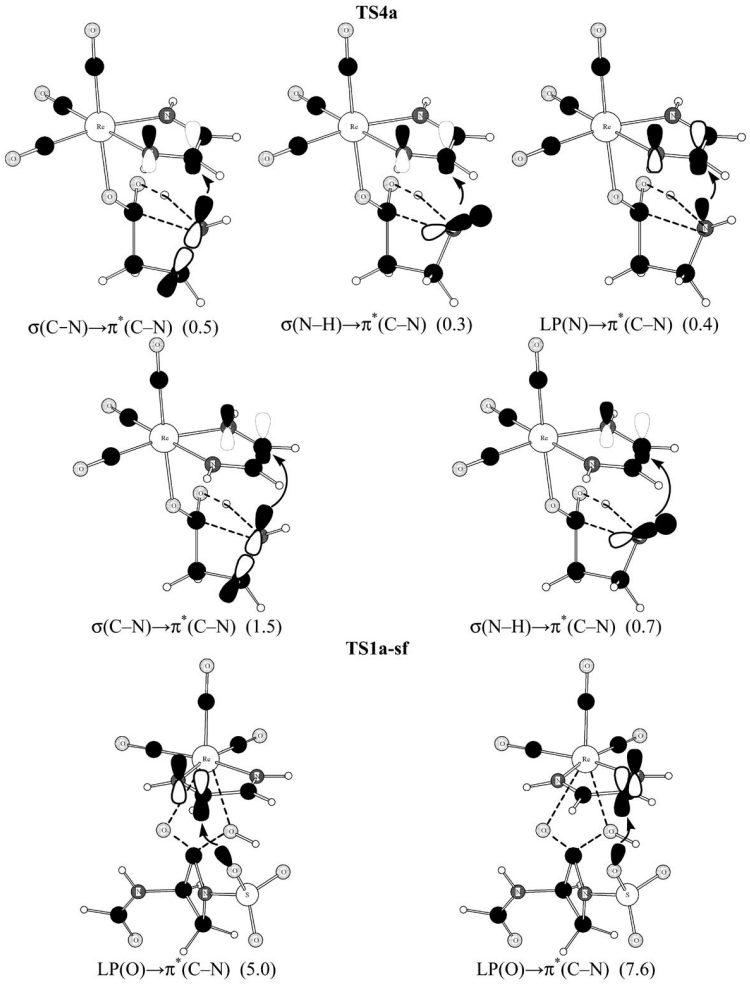


Figure 2. Most significant structures' "donor-acceptor" (bond-antibond) interactions in the NBO basis for the TSs **TS4a** and **TS1a-sf**. The second-order perturbation energies [kcal mol^{-1}] are also included in parentheses.

Supporting Information lists the corresponding energy data. Once again, the energy of all solvated species with respect to the separate reactants will be given in parentheses.

The most favourable reaction mechanism again corresponds to the addition of the HO–Re bond to the carbonyl C=O. As in the azetidin-2-one case, the Re complex can add to 3-formylamino-*N*-sulfonatoazetidin-2-one with the bidentate ligand oriented on the same side as the sulfonato group through the TS **TS1a-sf** (25.7 kcal mol^{-1}) or with both groups on different faces of the complex system through the TS **TS1′a-sf** (35.5 kcal mol^{-1}). At both TSs, it is interesting to note that the presence of the sulfonato group attached to the N_{amidic} atom favours a hydrogen bonding interaction between the $H_{hydroxy}$ atom and one of the $O_{sulfonato}$ atoms even if the Re complex approaches the β-lactam without the OH ligand oriented towards the sulfonato group. Besides this, another hydrogen bonding interaction is located between the O atom linked to Re and the $H(N)_{formylamino}$ atom. Given the similarity of these two addition mechanisms, we will describe them together. **TS1a-sf/TS1′a-sf** leads to **M1′a-sf/M1a-sf** (10.3/16.5 kcal mol^{-1}) in which the O atom linked to the metal at a distance of 2.122/2.093 Å interacts with the $H(N)_{formylamino}$ atom at a distance of 2.056/2.161 Å and also, in the case of **M1a-sf**, one of the $O_{sulfonato}$ atoms interacts simultaneously with the $H_{hydroxy}$ atom and one of the $H(N)_{bidentate}$ atoms at distances of 1.792 and 1.883 Å, respectively. **M1a-sf/M1′a-sf** can evolve through either the TS **TS2a1-sf/TS2′a1-sf** (16.7/26.9 kcal mol^{-1}) for the β-lactam ring opening with simultaneous H transfer from the $O_{hydroxy}$ atom to one of the $O_{sulfonato}$ atoms or the TS **TS2a2-sf/TS2′a2-sf** (13.6/22.9 kcal mol^{-1}) for the N_{amidic} inversion. On one hand, **TS2a1-sf/TS2′a1-sf** leads to the intermediate **M2a1-sf/M2′a1-sf** (0.4/3.2 kcal mol^{-1}) in which the $H_{hydroxy}$ atom is transferred to the sulfonato group and the amidicC–N bond is nearly or totally broken. **M2a1-sf/M2′a1-sf** becomes the product **P-sf/P′-sf** (–23.3/–22.6 kcal mol^{-1}) through the TS **TS3a1-sf/TS3′a1-sf** (19.7/–23.3 kcal mol^{-1}) for the H migration of the $O_{sulfonato}$ atom to the N_{amidic} atom. Although **TS2′a2-sf** is 2.1 and 2.9 kcal mol^{-1} less

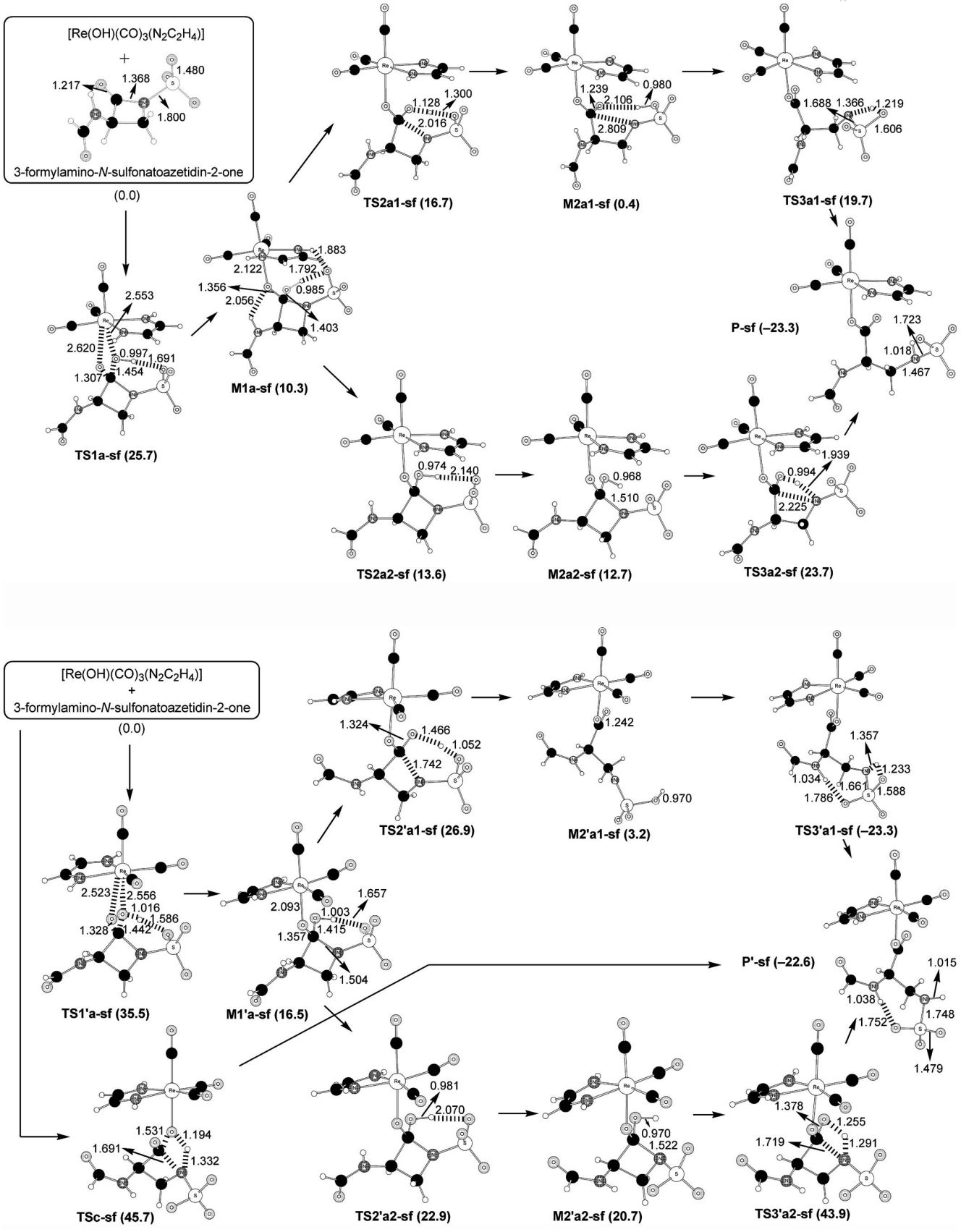


Figure 3. Schematic view of the optimised structures involved in the most favourable reaction mechanism found for the reaction between 3-formylamino-*N*-sulfonatoazetidin-2-one and $[Re(OH)(CO)_3(N_2C_2H_4)]$. Relative energies in solution [kcal mol^{-1}] and the most relevant distances [Å] are also displayed.

stable in electronic energy than **M2′a1-sf** and **P′-sf**, respectively, it becomes a transient species when solute-solvent interactions are taken into account in the calculations. On the other hand, **TS2a2-sf/TS2′a2-sf** gives **M2a2-sf/M2′a2-sf** (12.7/20.7 kcal mol^{-1}) by the N_{amidic} inversion which subsequently transforms into **P-sf/P′-sf** through the TS **TS3a2-sf/TS3′a2-sf** (23.7/43.9 kcal mol^{-1}) for the cleavage of the amidic C–N bond and simultaneous H transfer from the $O_{sulfonato}$ atom to the amidic N atom. The concerted mechanism evolves through the TS **TSc-sf** (45.7 kcal mol^{-1}) for the cleavage of the amidic C–N and hydroxy O–H bonds with simultaneous formation of the $C_{carbonyl}$–$O_{hydroxy}$ and $H_{hydroxy}$–N_{amidic} bonds, thus giving the product **P′-sf**.

In accordance with our results for the reaction with 3-formylamino-*N*-sulfonatoazetidin-2-one, the two types of addition of the HO–Re bond to the β-lactam carbonyl are again the most favourable reaction mechanisms, the rate-determining steps for both routes being the first ones. The route in which the bidentate ligand lies on the same side as the amidic C–N bond is now much more stable than the other by 9.8 kcal mol^{-1}. As can be seen in Figure 2, an NBO analysis of **TS1a-sf** reveals the presence of donor-acceptor interactions between the lone pairs of one of the $O_{sulfonato}$ atoms and the two C–N π antibonding orbitals of the bidentate ligand with a second-order perturbation energy of 12.6 kcal mol^{-1}. At **TS1′a-sf**, the orientation of the bidentate ligand is opposite to the sulfonato group and, therefore, does not allow the interaction mentioned above. In agreement with this, **TS1a-sf** is 9.8 kcal mol^{-1} more stable than **TS1′a-sf**. Besides this, a comparison of **TS1a-sf** and **TS1′a-sf** with the analogous **TS1a** and **TS1′a**, for the azetidin-2-one case, reveals the crucial role played by the formylamino group and mainly the sulfonato group in conjunction with the bidentate ligand. For both routes, the presence of the formylamino and sulfonato groups favours the establishment of hydrogen bonding interactions which would lead to a greater relative stability of **TS1a-sf** and **TS1′a-sf** with respect to **TS1a** and **TS1′a**, respectively. In the **TS1a-sf** vs. **TS1a** case, the hydrogen bonding interactions in conjunction with the stabilising interactions between one of the $O_{sulfonato}$ atoms and the C–N bonds of the bidentate ligand explains why **TS1a-sf** is 13.1 kcal mol^{-1} more stable relative to **TS1a**. However, in the **TS1′a-sf** vs. **TS1′a** case, the former TS is 0.7 kcal mol^{-1} less stable relative to the latter due to the appearance of significant electronic repulsions between the O atoms of the carbonyl ligands and the sulfonato group which slightly predominates over the hydrogen bonding interactions. Therefore, the resultant rate-determining energy barrier in solution for the reaction between [Re(OH)(CO)$_3$(N$_2$C$_2$H$_4$)] and 3-formylamino-*N*-sulfonatoazetidin-2-one is 25.7 kcal mol^{-1} (**TS1a-sf**) which is close to the experimental activation energy obtained for the alkaline hydrolysis of the monobactam aztreonam (22.4 kcal mol^{-1}).[46] This suggests the use of the Re complex as an effective agent to cleave β-lactam N1–C2 bonds in particularly mild conditions and in solvents of low polarity.

Conclusions

According to the computed energy barriers obtained in this work, the presence of a sulfonato group attached to the amidic N atom is required for the efficient cleavage of the β-lactam N1–C2 bond by the rhenium hydroxo-carbonyl complex. This catalytic effect is mainly due to the establishment of a hydrogen bond between the sulfonato and hydroxy groups and to the interaction of one of the sulfonato oxygen atoms with antibonding C–N π* orbitals of the bidentate ligand, thus stabilising the energy profile with respect to the separate reactants. A similar effect could be envisaged for other β-lactams such as the bicyclic nucleus of penicillins and cephalosporins thanks to the location of a negatively charged carboxylate group adjacent to the β-lactam amide group.

Computational Methods

The computational investigation was performed with the simplified complex [Re(OH)(CO)$_3$(N$_2$C$_2$H$_4$)] (N$_2$C$_2$H$_4$=HN=CH–CH=NH) which was chosen to mimic the one used experimentally in the reactions with esters and other organic electrophiles[15–17] and to minimise the computational time. Besides, several theoretical studies have demonstrated the adequacy of replacing bidentate ligands such as phenanthroline (phen) or bipyridine (bpy) by the diimine (HN=CH–CH=NH).[45,47,48]

Quantum chemical computations were carried out with the Gaussian 03 series of programs.[49] Full geometry optimisations of stable species and transition states (TS) were performed in the gas phase by employing the hybrid density functional B3LYP[50–52] with the 6-31+G(d,p) basis set[53] (LANL2DZ for Re augmented by *f* polarisation functions with exponent 0.869)[54,55] and by using the standard Schlegel algorithm.[56] The B3LYP functional combines Becke's three-parameter nonlocal hybrid exchange potential with the nonlocal correlation functional of Lee, Yang and Parr. The nature of the stationary points was verified by analytical computations of harmonic vibrational frequencies. Intrinsic reaction coordinate (IRC) calculations with the Gonzalez and Schlegel method[57,58] were carried out to check the two minimum energy structures connecting each TS.

To take into account condensed phase effects, single point calculations were also performed on the gas phase optimised geometries using the Polarisable Continuum Model (PCM) of Tomasi et al.[59,60] with the united atom Hartree–Fock (UAHF) parametrisation.[61] The energy in solution comprises the electronic energy of the polarised solute, the electrostatic solute-solvent interaction energy $<\Psi_f|H+\frac{1}{2}V_f|\Psi_f>$ and the nonelectrostatic terms corresponding to cavitation, dispersion and short range repulsion. A relative permittivity of 8.93 was assumed in the calculations to simulate dichloromethane which was the solvent used experimentally in related reactions between [Re(OH)(CO)$_3$(Me$_2$-bipy)] and several organic electrophiles.[15–17]

The computational scheme chosen in this work is similar to that used in a theoretical study on the reactivity of [Re(OH)(CO)$_3$(N$_2$C$_2$H$_4$)] towards phenyl acetate,[45] wherein the validity of the B3LYP mechanistic predictions compared with X-ray experimental data and more sophisticated quantum-chemical computations was confirmed. Thus, a similar trend could be expected for the present investigation.

For interpretation purposes, a natural bond orbital (NBO) analysis was performed on some of the most important critical structures along the reaction coordinates at the B3LYP level of theory.[62,63]

Supporting Information (see also the footnote on the first page of this article): Absolute and relative electronic energies, Gibbs energies of solvation and energies in solution of all the structures presented in this work.

Acknowledgments

Financial support from the Spanish Ministerio de Educación y Ciencia (MEC) (project and grant CTQ2004-06309) is highly appreciated.

[1] F. Bottomley, L. Sutin, *Adv. Organomet. Chem.* **1988**, *28*, 339–396.
[2] H. E. Bryndza, W. Tam, *Chem. Rev.* **1988**, *88*, 1163–1188.
[3] J. W. Gilje, H. W. Roesky, *Chem. Rev.* **1994**, *94*, 895–910.
[4] R. Gupta, C. E. MacBeth, V. C. J. Young, A. S. Borovik, *J. Am. Chem. Soc.* **2002**, *124*, 1136–1137.
[5] E. N. Jacobsen in *Comprehensive Organometallic Chemistry II*, vol. 12, chapter 11 (Eds.: G. Wilkinson, F. G. A. Stone, E. W. Abel, L. S. Hegedus), Pergamon, New York, **1995**.
[6] B. A. Katsuki, S. G. Sligar, J. S. Olsen, G. N. Philips, *Chem. Rev.* **1994**, *94*, 699.
[7] M. L. Ludwig, A. L. Metzger, K. A. Pattridge, W. C. Stallings, *J. Mol. Biol.* **1991**, *219*, 335–338.
[8] B. Meunier, S. P. de Visser, S. Saik, *Chem. Rev.* **2004**, *104*, 3947–3980.
[9] H. W. Roesky, S. Singh, K. K. M. Yusuff, J. A. Maguire, N. S. Hosmane, *Chem. Rev.* **2006**, *106*, 3813–3843.
[10] M. Whitlow, A. J. Howard, B. L. Finzel, T. L. Poulos, E. Winbourne, G. I. Gillilard, *Proteins: Struct. Funct. Genet.* **1991**, *9*, 153–173.
[11] N. Mahé, O. Guillou, C. Daiguebonne, Y. Gérault, A. Caneschi, C. Sangregorio, J. Y. Chane-Ching, P. E. Car, T. Roisnel, *Inorg. Chem.* **2005**, *44*, 7743–7750.
[12] D. Morales, B. Pleune, R. Poli, P. Richard, *J. Organomet. Chem.* **2000**, *596*, 64–69.
[13] J. R. Fulton, A. W. Holland, D. J. Fox, R. G. Bergman, *Acc. Chem. Res.* **2002**, *35*, 44–56.
[14] K. L. Breno, M. D. Pluth, C. K. Landorf, D. R. Tyler, *Organometallics* **2004**, *23*, 1738–1746.
[15] L. Cuesta, D. C. Gerbino, E. Hevia, D. Morales, M. E. Navarro-Clemente, J. Pérez, L. Riera, V. Riera, D. Miguel, I. del Río, S. García-Granda, *Chem. Eur. J.* **2004**, *10*, 1765–1777.
[16] L. Cuesta, E. Hevia, D. Morales, J. Pérez, L. Riera, D. Miguel, *Organometallics* **2006**, *25*, 1717–1722.
[17] D. C. Gerbino, E. Hevia, D. Morales, M. E. Navarro-Clemente, J. Pérez, L. Riera, V. Riera, D. Miguel, *Chem. Commun.* **2003**, 328–329.
[18] D. H. Gibson, X. Yin, *J. Am. Chem. Soc.* **1998**, *120*, 11200–11201.
[19] D. H. Gibson, X. Yin, H. Hen, M. S. Mashuta, *Organometallics* **2003**, *22*, 337–346.
[20] R. Gupta, A. S. Borovik, *J. Am. Chem. Soc.* **2003**, *125*, 13234–13242.
[21] P. J. Heard, P. Sroisuwan, D. A. Tocher, *Polyhedron* **2003**, *22*, 1321–1327.
[22] D. Morales, M. E. Navarro-Clemente, J. Pérez, V. Riera, D. Miguel, *Organometallics* **2002**, *21*, 4934–4938.
[23] D. Morales, B. Plusne, R. Poli, P. Richard, *J. Organomet. Chem.* **2000**, *596*, 64–69.
[24] S. Abele, D. Seebach, *Eur. J. Org. Chem.* **2000**, 1–15.
[25] B. Alcaide, P. Almendros, C. Aragoncillo, *Chem. Rev.* **2007**, *107*, 4437–4492.
[26] D. J. Hart, D. C. Ha, *Chem. Rev.* **1989**, *89*, 1447–1465.
[27] E. Juaristi, *Enantioselective Synthesis of β-Amino Acids*, VCH-Wiely, New York, **1997**.
[28] J. L. Matthews, M. Overhand, F. N. M. Kühnle, *Liebigs Ann./Recueil* **1997**, 1371–1379.
[29] I. Ojima, F. Delaloge, *Chem. Soc. Rev.* **1997**, *26*, 377–386.
[30] C. Palomo, J. M. Aizpurúa, I. Ganboa, M. Oiarbide, *Curr. Med. Chem.* **2004**, *11*, 1837–1872.
[31] F. H. van der Steen, G. van Koten, *Tetrahedron* **1991**, *47*, 7503–7524.
[32] W. B. Wang, E. J. Roskamp, *J. Am. Chem. Soc.* **1993**, *115*, 9417–9420.
[33] V. Yeguas, P. Campomanes, M. I. Menéndez, T. L. Sordo, *THEOCHEM* **2007**, *811*, 241–247.
[34] J. Chin, *Acc. Chem. Res.* **1991**, *24*, 145–152.
[35] K. B. Grant, M. Kassai, *Curr. Org. Chem.* **2006**, *10*, 1035–1039.
[36] M. Ruf, H. Vahrenkamp, *Chem. Ber.* **1996**, *129*, 1025–1028.
[37] L. M. Sayre, *J. Am. Chem. Soc.* **1986**, *108*, 1632–1635.
[38] J. Pitarch, M. F. Ruiz-López, J. L. Pascual-Ahuir, E. Silla, I. Tuñón, *J. Phys. Chem. B* **1997**, *101*, 3581–3588.
[39] J. Pitarch, M. F. Ruiz-López, E. Silla, J. L. Pascual-Ahuir, I. Tuñón, *J. Am. Chem. Soc.* **1998**, *120*, 2146–2155.
[40] J. Pitarch, J. L. Pascual-Ahuir, E. Silla, I. Tuñón, V. Moliner, *J. Chem. Soc. Perkin Trans. 2* **1999**, 1351–1356.
[41] S. Chalmet, W. Harb, I. Tuñón, M. F. Ruiz-López, *J. Phys. Chem. A* **2001**, *105*, 11574–11581.
[42] L. Gorb, A. Asensio, I. Tuñón, M. F. Ruiz-López, *Chem. Eur. J.* **2005**, *11*, 6743–6753.
[43] J. I. Mujika, J. M. Mercero, X. Lopez, *J. Am. Chem. Soc.* **2005**, *127*, 4445–4453.
[44] D. Zahn, *Eur. J. Org. Chem.* **2004**, 4020–4023.
[45] V. Yeguas, P. Campomanes, R. López, *Organometallics* **2007**, *26*, 5271–5277.
[46] R. Méndez, T. Alemany, J. Martín-Villacorta, *Chem. Pharm. Bull.* **1992**, *40*, 3222–3227.
[47] E. Hevia, J. Pérez, V. Riera, D. Miguel, P. Campomanes, M. I. Menéndez, T. L. Sordo, S. García-Granda, *J. Am. Chem. Soc.* **2003**, *125*, 3706–3707.
[48] M. A. Iron, A. Sundermann, J. M. L. Martin, *J. Am. Chem. Soc.* **2003**, *125*, 11430–11441.
[49] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. J. Montgomery, T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millan, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, H. M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, J. R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvado, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaroni, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, *Gaussian 03*, *Revision C.02*, Gaussian, Inc., Wallingford CT, **2004**.
[50] A. D. Becke, *Phys. Rev. A* **1988**, *38*, 3098–3100.
[51] A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652.
[52] C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785–789.
[53] W. J. Hehre, L. Radom, J. A. Pople, P. v. R. Schleyer, *Ab initio Molecular Orbital Theory*, Wiley, New York, **1986**, p.
[54] A. W. Ehlers, M. Böhme, S. Dapprich, A. Gobbi, A. Höllwarth, V. Jonas, K. F. Köhler, *Chem. Phys. Lett.* **1993**, *208*, 111–114.
[55] P. J. Hay, W. R. Wadt, *J. Chem. Phys.* **1985**, *82*, 299–310.
[56] H. B. Schlegel, *J. Comput. Chem.* **1982**, *3*, 214–218.

[57] C. Gonzalez, H. B. Schlegel, *J. Chem. Phys.* **1989**, *90*, 2154–2161.
[58] C. Gonzalez, H. B. Schlegel, *J. Phys. Chem.* **1990**, *94*, 5523–5527.
[59] J. Tomasi, R. Cammi, *J. Comput. Chem.* **1995**, *16*, 1449–1458.
[60] a) J. Tomasi, M. Persico, *Chem. Rev.* **1994**, *94*, 2027; b) J. Tomasi, R. Cammi, *J. Comput. Chem.* **1995**, *16*, 1449; J. Tomasi, R. Cammi, *Chem. Rev.* **1994**, *94*, 2027–2094.
[61] V. Barone, M. Cossi, J. Tomasi, *J. Chem. Phys.* **1997**, *107*, 3210–3221.
[62] E. Reed, L. A. Curtiss, F. Weinhold, *Chem. Rev.* **1988**, *88*, 899–926.
[63] F. Weinhold, J. E. Carpenter in *The Structure of Small Molecules and Ions* (Eds.: R. Naaman, Z. Vager), New York, **1988**.
Received: May 27, 2008
Published Online: August 29, 2008

