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Mechanism of the Gold(I)-Catalyzed Rautenstrauch Rearrangement: A Center-to-Helix-to-Center Chirality Transfer

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Abstract: The mechanism of the stereospecific gold(I)-catalyzed Rautenstrauch rearrangement of (*E*)-1-ethynyl-2-methyl-but-2-en-yl acetate to 3,4-dimethyl-cyclopent-2-enone has been computationally addressed using DFT (B3LYP/6-31G*, SDD for Au). Our results indicate that the bond formation event follows the Au(I)-induced acetyl transfer to the vicinal alkyne and that it is the helicity of the pentadienyl cation intermediate which keeps memory of the chiral information. The fidelity of the center-to-helix-to-center chirality transfer requires that the rates of helix interconversion and pivaloyl rotation are slower than the cyclization, as calculations predict.

Introduction

Gold homogeneous catalysis with its many applications in organic synthesis, has received increasing attention these last years.[1,2] Although some of the reactions catalyzed by gold can be promoted by other transition metals,[3] both the reaction mechanisms and the product distributions may vary due to gold's low tendency for β-hydride elimination, fast protodemetalation, and reluctance to undergo the change of oxidation states needed in cross-coupling reactions.

Transition-metal-catalyzed cycloisomerization of enynes has become a method of choice for the synthesis of a variety of cyclic compounds. Most examples in the literature refer to reactions of 1,6- and 1,5-enynes, which in the presence of transition metals can undergo cycloisomerization processes leading to a variety of products.[6,7] When transition metal complexes of gold, ruthenium, or platinum are used for the activation of the alkyne, the cyclization mechanism usually involves the generation of metalacyclopropylcarbenoid intermediates resulting in the formation of cyclopropane-fused bicyclic compounds. However, depending on the nature of the enyne and the catalyst, cyclizations can follow other paths in the available manifold. 1,4-Enynes have been found to follow such alternate pathways, primarily due to the closer proximity of functional groups and a more conformationally restricted environment.[5,8,9]

An interesting example of these processes is the Rautenstrauch reaction,[8] the palladium-catalyzed cyclization of 1-ethynyl-2-propenyl acetates to 1,4-cyclopentadienyl acetates which evolve to 2-cyclopentenones, a common building block of many synthetic targets. A recent paper[5] describing a gold(I)-catalyzed variant of this reaction displaying a remarkable chirality transfer caught our attention in the course of a mechanistic study of a process with similar features,[4,10] the cyclopentannelation of allenolate allyl carbamates (**i** → **iii**, see Figure 1). Only one of the two enantiomeric cyclopentenones **v** was obtained upon treatment of enantiopure **iv** with 5% $Ph_3PAuSbF_6$ in CH_3CN at −20 °C. The configuration of the new stereocenter appears to be solely determined by the configuration of the protected alcohol at position 3 in **iv**. The chirality transfer was considered[5] to result from a C−C bond forming process that takes place either before or in concert with the cleavage of the stereogenic C−O bond in **iv** in which the leaving group occupies a position orthogonal to the olefin (see Figure 1, **B**).

We have computationally addressed the mechanistic issues of the **iv** → **v** rearrangement. Our results support that the bond formation event *follows* the Au(I)-induced pivaloyl transfer to the vicinal C_{sp} atom and that the chiral information is preserved on the helicity of the pentadienyl cation intermediate. For this center-to-helix-to-center chirality transfer to be efficient, both the helix interconversion and the pivaloyl rotation should be disfavored relative to cyclization, as calculations predict.

Results and Discussion

Figure 3 depicts the stationary points along the reaction path that transforms **1**, the simplest enyne of the original work,[5] into cyclopentenone **6**. Their relative energies in gas phase and solution, together with the activation barriers corresponding to the relevant transition structures, are shown in Table 1. To keep the computational cost low, the original pivaloate was substituted

(1) Hashmi, A. S. K. *Gold Bull.* **2004**, *37*, 51−65.
(2) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2005**, *44*, 6990−6993.
(3) Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654−8655.
(4) Schultz-Fademrecht, C.; Tius, M. A.; Grimme, S.; Wibbeling, B.; Hoppe, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 1532−1535.
(5) Shi, X.; Gorin, D. J.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 5802−5803.
(6) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813−834.
(7) Bruneau, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 2328−2334.
(8) Rautenstrauch, V. *J. Org. Chem.* **1984**, *49*, 950−952.
(9) Prasad, B. A. B.; Yoshimoto, F. K.; Sarpong, R. *J. Am. Chem. Soc.* **2005**, *127*, 12468−12469.
(10) Nieto Faza, O.; Silva López, C.; Álvarez, R.; de Lera, A. R. *Chem. Commun.* **2005**, 4285−4287.

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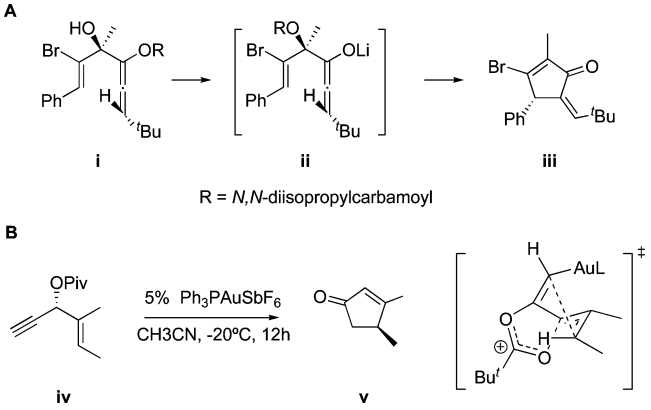

Figure 1. Chirality transfer in the cyclopentannelation of allenolate allyl carbamates (**A**) and gold(I)-catalyzed Rautenstrauch rearrangement (**B**) as described by Hoppe et al.[4] and Toste et al.,[5] respectively.

Table 1. Thermodynamic Properties (Relative Free Energies and Activation Free Energies in Gas Phase and in Solution) of the Structures in Figure 3[a]

structure	ΔG^{rel}_{gas}	$\Delta G^{rel}_{sol.}$	$\Delta G^{‡}_{gas}$	$\Delta G^{‡}_{sol.}$
ts12	6.04	6.42		
2	0.00	0.00		
ts23	7.40	6.16	5.09	4.56
3	−9.80	−9.94		
ts34	−3.87	−3.25	5.93	6.69
(*P*/*M*)-**4-anti**	−6.16	−6.05		
(*P*/*M*)-**4-syn**	−3.11	−4.09		
h-ts	3.04	3.13	9.20	9.18
r-ts	−1.04	−1.58	5.12	4.47
(*P*/*M*)-**ts45-anti**	−1.40	−2.46	4.76	3.59
(*P*/*M*)-**ts45-syn**[b]	0.11	−1.16		
(*R*/*S*)-**5**	−40.75	−41.85		

[a] These values, in kcal/mol, were calculated at the B3LYP/6-31G* (SDD for Au) level of theory, using single-point PCM calculations with UAKS radii to model the effect of the solvent (CH_3CN). [b] No syn transition structures were found for the cyclization. This entry corresponds to a single-point calculation of a structure built by rotation of the acetate group from the fixed geometry of the corresponding anti conformer. The free energies in this entry were calculated using electronic energies together with the solvation free energy for the involved structures.

with a simpler acetate (the reaction still takes place, despite a lower yield[5]) and gold's ligand PPh_3 with PH_3. Although the gold(I) complexes considered are more stable with a phosphine ligand, the same structures are found if the latter is omitted (the bare gold(I) cation acting then as a catalyst), affording reaction profiles with similar reaction energies and activation barriers. The transfer of chiral information in this system can then be similarly justified.

The first step of the mechanism involves the face-selective complexation of gold to the alkyne assisted by the acetate group through **ts12** (see Figure 3). The cationic complex **2** evolves to the *E*-alkene **3** through a concerted transition structure where the attack of a lone pair on the carboxyl oxygen to the activated alkyne triggers the formation of a σ metal−carbon bond. The orientation of the metal in **2**, together with the required anti disposition of the two forming σ bonds, precludes the formation of the *Z*-isomer.[11] Experimental evidence of this stereospecific carbonyl-oxygen backside attack to the gold(I) π-coordinated alkyne has been reported for propargyl amides.[12]

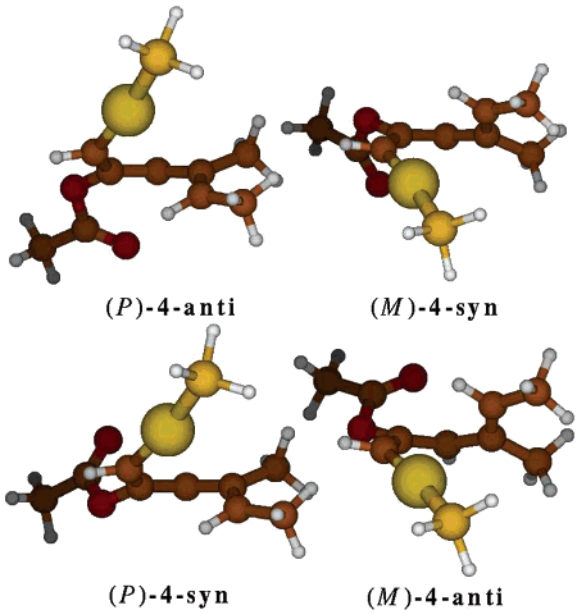

Figure 2. Conformational isomers of chiral gold(I)-bound helical pentadienyl cation **4**.

Two paths were conceived for the evolution of **3**: cyclization concerted with bond breaking in a scheme that can resemble both a S_N2' reaction and the electrocyclization of an incipient pentadienyl cation[10] or the breaking of the C_3−O bond to yield a pentadienyl cation. Whatever path is followed, the distinct selectivity observed would stem from an anti preference in the bond-breaking−bond-forming process: the gold-activated alkene attacks the C_1−C_2 alkene on the opposite side of the molecular plane the acetate is placed on. This stereoelectronic effect would be consistent with a concerted mechanism but more difficult to conciliate with an open cationic intermediate that could evolve through conformational scrambling.

However, after a thorough search, no cyclization transition structure was found that preserved the cyclic C_3−O bond,[13] and the reaction follows instead the path of **ts34**, which, through a low-energy barrier (6.69 kcal/mol), leads to (*P*)-**4-anti** (Figure 2), a pentadienyl cation where both the right-handed helix (*plus*) and the orientation of the acetate group are determined by the original configuration (*S*) of the stereocenter in **1**.

The most remarkable feature of this mechanism is the competition that now arises between the cyclization of (*P*)-**4-anti** and the conformational changes that can either invert the helicity (**h-ts**) or switch the orientation of the acetate (**r-ts**) from anti to syn (these last descriptors have been chosen to describe the orientation of the gold-bound alkene with respect to the face of the molecular plane where the carbonyl is located). (*P*)-**4-anti** then directly proceeds along the cyclization path ((*P*)-**ts45-anti**) to (*S*)-**5**, instead of attempting to cross the higher conformational barrier **h-ts** (3.59 vs 9.18 kcal/mol), which would lead (through a lower energy transition structure, **r-ts**) to the other reactive conformation, (*M*)-**4-anti**, and, eventually, to the cyclopentenone (*R*)-**6**, the enantiomer of the experimentally observed product (Figure 3).

(11) The reaction path from **3** to **6** has also been followed for the *Z*-isomer *Z*-**3** with analogous results (see Supporting Information). The only differences worth noting are the lower energies of the minima involved.
(12) Hashmi, A. S. K.; Weyrauch, J. P.; Frey, W.; Bats, J. W. *Org. Lett.* **2004**, *6*, 4391−4394.
(13) Only a transition state that would correspond to a very strained structure somehow resembling the (syn) insertion of an imposible gold carbene on the C_1−C_2 alkene could be located. The high energy of this stationary point (it corresponds to an activation barrier of 74.28 kcal/mol) led us to discard this possibility.

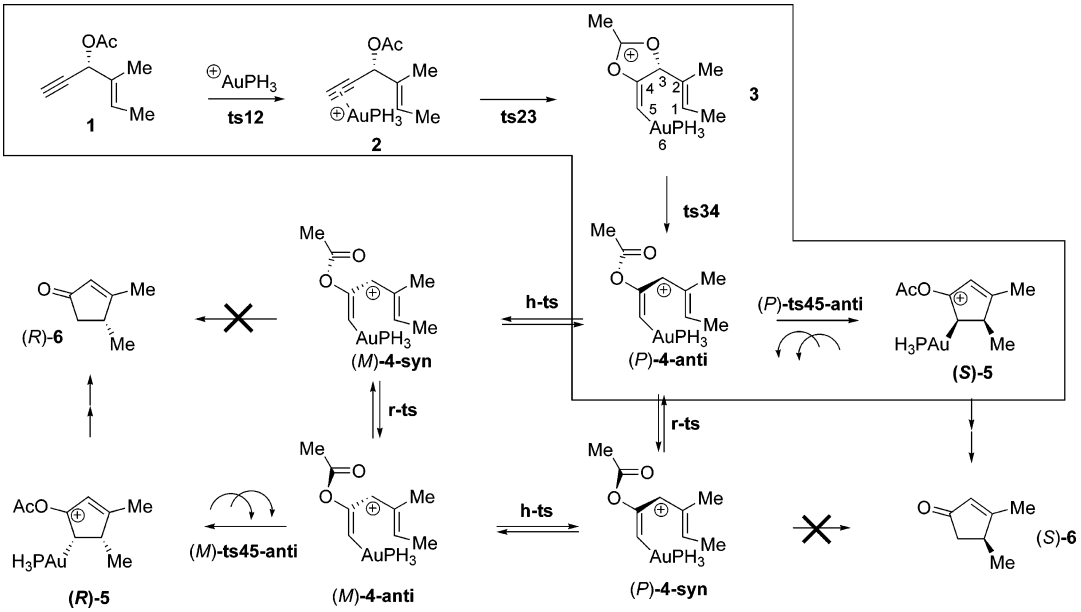

Figure 3. Mechanistic manifold for the gold-catalyzed Rautenstrauch rearrangement of (*E*)-1-ethynyl-2-methylbut-2-enyl acetate **1**.

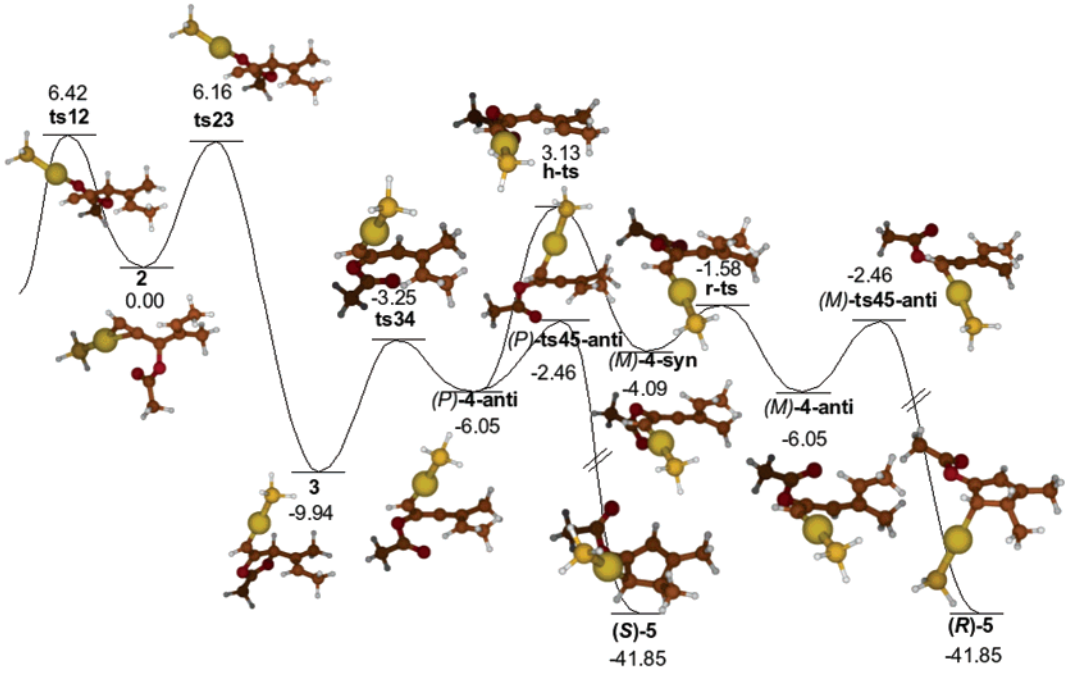

Figure 4. Reaction energy profile for the gold(I)-catalyzed rearrangement of (*E*)-1-ethynyl-2-methylbut-2-enyl acetate **1** (Figure 3).

No cyclization transition structure could be located for the (*P*)- and (*M*)-**4-syn** species. Although irrelevant to the chirality transfer issue, this can be explained resorting to the combined effect of electrostatic interactions that result in a higher dipole moment for the syn transition structure (3.27 vs 2.85 D)[14] and the low barrier for the acetate rotation (2.51 kcal/mol for the syn−anti conversion). A single-point calculation of a rough hypothetical syn transition structure, built by rotation of the acetate group on the fixed geometry of the anti structure, would yield an activation barrier for the cyclization of (*P*)-**4-syn** about 4.38 kcal/mol higher than that corresponding to the anti product, which would ensure complete selectivity at the experimental conditions.

(14) Dipole moments of charged species must be cautiously dealt with.

Thus, the chiral information present in the original enyne is conveyed through **3** to the pentadienyl cation (*P*)-**4-anti**, where it is stored in the helicity of the main carbon chain. The concurrent existence of a barrier to cyclization lower than that corresponding to the inversion of the helix (**h-ts**) ensures the faithful transfer of this information to the final product (Figure 4).

Besides the striking chirality transfer through a pentadienyl cation intermediate, this mechanism shows other features that have interest on their own. The first of these is the noncarbene character of the gold complexes. In contrast with the most usual mechanisms for the reaction of enynes with transition metals,[6,7] where the metal center has a central role organizing the relevant transition structures, the only function of gold in this mechanism is to sanction the formation of **3**, a system similar to the

Table 2. Optimized Bond Distances (Å) and NBO Bond Orders for the Most Relevant Structures in Figure 3[a]

	bond distances (Å)				
structure	d_{4-5}	d_{3-4}	d_{3-2}	d_{2-1}	d_{5-6}
3	1.32	1.51	1.51	1.35	2.05
ts34	1.34	1.47	1.44	1.37	2.04
(*P*/*M*)-**4-anti**	1.37	1.43	1.42	1.38	2.04
(*P*/*M*)-**4-syn**	1.38	1.42	1.42	1.38	2.03
(*P*/*M*)-**ts45-anti**	1.40	1.41	1.40	1.41	2.05

	NBO bond orders				
structure	4–5	3–4	3–2	2–1	5–6
3	1.93	0.99	1.03	1.82	0.59
ts34	1.80	1.10	1.24	1.62	0.61
(*P*/*M*)-**4-anti**	1.56	1.31	1.31	1.54	0.63
(*P*/*M*)-**4-syn**	1.61	1.25	1.31	1.54.	0.64
(*P*/*M*)-**ts45-anti**	1.46	1.31	1.41	1.39	0.56

[a] The atom numbering is that displayed on **3**. These values were calculated at the B3LYP/6-31G* (SDD for Au) level of theory, using single-point PCM calculations with UAKS radii to model the effect of the solvent (CH_3CN).

intermediate of carbamoyl transfer (see **i** → **ii** in Figure 1) proposed by Hoppe,[4] before the Nazarov-like reaction takes place. After **ts23**, the gold behaves as a simple spectator whose electron-donor properties favor the ionic cyclization.[15] The bond order scheme, stemming from both an NBO analysis of the wave function and the examination of the bond distances on the carbon chain, fully supports the proposed structure (see Table 2).

Despite the defined pentadienyl cation structure of intermediate **4**, the mechanism of this process cannot be clearly described as ionic or pericyclic. However, the fact that the charge difference between C_1 and C_5 is noticeable (between 0.23 and 0.38 for **4** and **ts45**) together with a minimum value for the NICS[16] along an axis normal to the molecular plane ($NICS_{min}$) of **ts45-anti** higher than that found for similar processes would hint toward an ionic mechanism.

The calculated $NICS_{min}$ value for **ts45** (above −8 ppm) differs not much from the −8.2 ppm of the tropylium cation or the −7.6 ppm of the cyclooctatetraenyl dication,[17] but it is lower than those (about −11 ppm) corresponding to the transition structures of related processes such as the electrocyclization of hydroxyl-substituted pentadienyl cations (deemed to be pericyclic).[18]

We suggest then that this reaction would be best classified as the intramolecular attack of a nucleophile (an enol acetate with some additional charge donation from the gold complex) to an allyl cation, whose key step involves the imprint of the chiral information of the original stereocenter in the helical conformation of a pentadienyl cation. Transition state **ts23** guarantees the *E* geometry of **3**, and the balance between the energies of **ts45-anti** and **h-ts** and **r-ts**, together with the nonexistence of syn cyclization transition structures, makes avoiding the expected conformational scrambling possible.

Computational Methods

All the calculations in this study were carried out with DFT methods as implemented in the Gaussian 03[19] suite of programs. All the structures depicted in Figure 2 were optimized using the Becke three-parameter exchange functional[20] and the nonlocal correlation functional of Lee, Yang, and Parr[21] (B3LYP) with the 6-31G* basis set for all atoms save gold, for which the Stuttgart−Dresden effective core potential[22] was used both to accurately take relativistic effects into account and to substantially reduce the number of electrons in the system.

The stationary points were characterized by means of harmonic analysis, and for all the transition structures, the vibration related to the imaginary frequency corresponds to the nuclear motion along the reaction coordinate under study. In several significant cases intrinsic reaction coordinate (IRC)[23] calculations were performed to unambiguously connect transition structures with reactants and products. Bond orders were calculated with the natural bond orbital (NBO),[24] and charges were evaluated using the APT method.[25] Nucleus-independent chemical shifts (NICS)[16] were calculated by means of the gauge-independent atomic orbitals (GIAO) method.[26] The solvation energies were calculated for all the structures in acetonitrile resorting to single-point calculations with PCM[27−29] and UAKS radii.[30,31] As no anti structure was found for **ts45**, a qualitative approximation to (*P*/*M*)-**ts45-syn** was achieved through a single-point calculation on a (*P*/*M*)-**ts45-anti** geometry only modified by the rotation of the acetate group. As a result, no vibrational frequencies were obtained for this structure, and thus, the energy comparisons, instead of referring to free energies (as elsewhere), use electronic energies (corrected with the solvation free energies) where this structure is involved.

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Supporting Information Available: Coordinates, thermodynamic, and geometric parameters and frequency data of the studied structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) We are dealing here with cyclization barriers of 3.6 kcal/mol, compared to the computed 12.2 kcal/mol of Hoppe's system,[10] the 0.6 kcal/mol of a 2-hydroxy-pentadienyl cation, or the 19.5 kcal/mol of a 1-hydroxy-pentadienyl cation.[18]

(16) Schleyer, P. v. R.; Maerker, C.; Dransfeld, A.; Jiao, H.; Hommes, N. J. R. v. E. *J. Am. Chem. Soc.* **1996**, *118*, 6317−6318.
(17) Cations tend to display lower NICS values than their neutral or anionic counterparts; the NICS for benzene was calculated to be −11.5 ppm,[16] while values as high as −21 ppm were computed for the transition structures of 1,3-dipolar cycloadditions.[32]
(18) Nieto Faza, O.; Silva López, C.; Álvarez, R.; de Lera, A. R. *Chem. Eur. J.* **2004**, *10*, 4324−4333.
(19) Frisch, M. J. et al. *Gaussian 03*, revision B.01; Gaussian, Inc.: Pittsburgh, PA, 2003.
(20) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652.
(21) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789.
(22) Andrae, D.; Häussermann, U.; Dolg, M.; Stoll, H.; Preuss, H. *Theor. Chim. Acta* **1990**, *77*, 123−141.
(23) Gonzalez, C.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154−2161.
(24) Glendening, E. D.; Reed, A. E.; Carpenter, J. E.; Weinhold, F. *NBO*, version 3.1.
(25) Cioslowski, J. *J. Am. Chem. Soc.* **1989**, *111*, 8333−8336.
(26) Wolinski, K.; Hinton, J. F.; Peter, P. *J. Am. Chem. Soc.* **1990**, *112*, 8251−8260.
(27) Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027−2094.
(28) Mineva, T.; Russo, N.; Sicilia, E. *J. Comput. Chem.* **1998**, *19*, 290−299.
(29) Cossi, M.; Scalmani, G.; Rega, N.; Barone, V. *J. Chem. Phys.* **2002**, *117*, 43−54.
(30) Klamt, A.; Jonas, V.; Bürger, T.; Lohrenz, J. C. W. *J. Phys. Chem. A* **1998**, *102*, 5074−5085.
(31) Barone, V.; Cossi, M. *J. Phys. Chem. A* **1998**, *102*, 1995−2001.
(32) Cossío, F. P.; Morao, I.; Jiao, H.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1999**, *121*, 6737−6746.