ORGANIC LETTERS

2009
Vol. 11, No. 24
5722−5725

Suppressed β-Effect of Silicon in 3-Silylated Monocyclic β-Lactams: The Role of Antiaromaticity

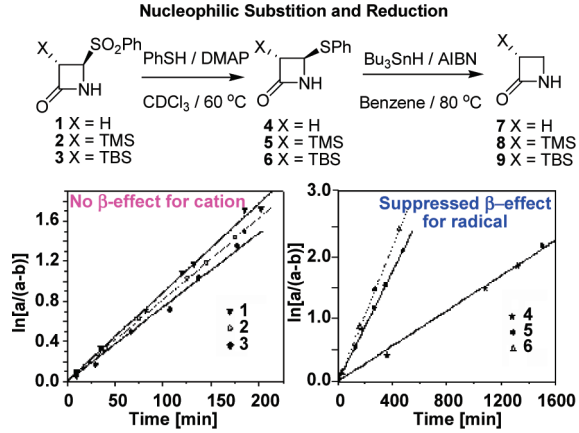
Subhendu Sekhar Bag,*,† Rajen Kundu,† Amit Basak,‡ and Zdenek Slanina§

Department of Chemistry, Indian Institute of Technology, Guwahati-781039, India, Department of Chemistry, Indian Institute of Technology, Kharagpur-721302, India, and Institute for Molecular Science, Okazaki-444-8585, Japan, and Institute of Chemistry, Academia Sinica, Taipei, Taiwan-ROC

ssbag75@iitg.ernet.in

Received October 22, 2009

ABSTRACT



The β-stabilizing effect of silicon substituent at C-3 on a C-4 cation and a radical in the 2-azetidinone systems is studied using NMR kinetics. While the β-effect is virtually nonexistent in the case of a cation, a foiled β-effect (only a 3-fold rate enhancement) is observed for a radical intermediate. From both the experimental and theoretical studies, it is demonstrated that antiaromaticity is playing the prime role in suppressing the β-stabilizing effect of silicon.

A great deal of effort has been put forth to know the nature of the intermediates, a radical or cation, involved in the enzymatic conversion of proclavaminate to dihydroclavaminate in the biosynthesis of clavulanic acid (Scheme S2, Supporting Information); however, a definitive answer is still to be found.[1] To offer some supportive light for the proposed radical mechanism and to find out the real cause of suppression of β-secondary isotope effects[2] which failed to settle the matter, we decided to use silicon-substituted β-lactams for a model study. The presence of a β-trimethylsilyl group has been shown to enhance the rate of solvolysis up to an order of 10^{12} as compared to a β-hydrogen which has been known for a long time and is at the heart of organosilicon chemistry.[3,4] Such rate enhancement is due to

† Indian Institute of Technology, Guwahati-781039.
‡ Indian Institute of Technology, Kharagpur-721302.
§ Institute for Molecular Science and Institute of Chemistry, Academia Sinica.

(1) (a) Krol, W. J.; Basak, A.; Salowe, S. P.; Townsend, C. A. *J. Am. Chem. Soc.* **1989**, *111*, 7625. (b) Basak, A.; Salowe, S.; Townsend, C. *J. Am. Chem. Soc.* **1990**, *112*, 1654. (c) Zhang, Z.; Ren, J.; Stammers, D. K.; Baldwin, J. E.; Harlos, K.; Schofield, C. J. *Nat. Struct. Biol.* **2000**, *7*, 127.

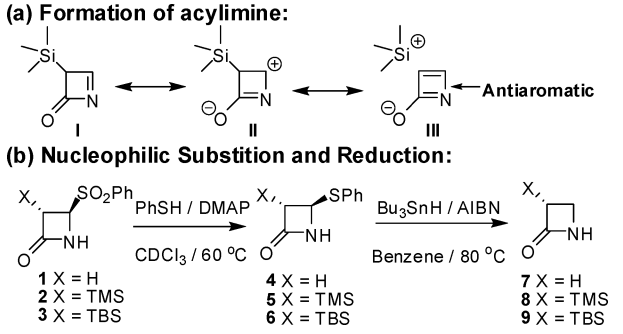
(2) (a) Iwata-Reuyl, D.; Basak, A.; Townsend, C. A. *J. Am. Chem. Soc.* **1999**, *121*, 11356. (b) Olofson, R. A.; Morrison, D. S.; Banerjee, A. *J. Org. Chem.* **1984**, *49*, 2652. (c) Alajarin, M. P.; Sánchez-Andrada, Cossío, F. P.; Arrieta, A.; Lecea, B. *J. Org. Chem.* **2001**, *66*, 8470.

10.1021/ol902411r
Published on Web 11/16/2009

the stabilization of the developing carbocation β-to silicon primarily via hyperconjugation of a C−Si σ-bond with the unfilled p-orbital of the β-carbon atom.[5]

However, in small cyclic systems, such as 2-azetidinone, the hyperconjugative stabilization of a cation or a radical at C-4 by β-silicon at C-3 might be difficult, and hence stabilization might be expected to be less and expressed to different extents.[2a,b,6] Previously, Fedor and others[7] have shown that the formation of an acylimine intermediate via the E1cB mechanism is the rate-determining step in monocyclic β-lactams. Therefore, the generated acylimine intermediate can be thought to be stabilized by a silicon substituent (Scheme 1a; structure II), and hence a rate

Scheme 1. (a) Presentation of Acylimine Formation and (b) Nucleophilic Substitution and Reduction of Different β-Lactams



enhancement is expected as the transition state leading to the intermediate will have partial positive character at C-4. The same argument holds for the reactions going through a radical at C-4.[8]

Since silicon has a strong β-effect, we thought that it would be worthwhile to study the effect of a silicon substituent at C-3 on reactions involving a cation (partial) or a radical at C-4 in monocyclic β-lactams. The specific question we wanted to address was: could silicon at C-3 stabilize a cation or a radical at C-4 in β-lactams? The difference between the two effects might be large and hence easily determinable, e.g., by NMR. As β-lactams occur relatively rarely in nature, it is not surprising that the biological activity of these compounds should be attributed to their chemical reactivity. Thus, this model study may shed some light on the nature of intermediates involved in the oxygen insertion at C-4 in actual enzymatic reaction.[1]

Therefore, we have synthesized the β-lactams **1**−**3** following literature procedures,[9] with some modifications, for studying the kinetics of reactions passing through a cationic intermediate (Scheme S1, Supporting Information). The β-lactams **4**−**6** served as substrates for studying the radical reactions. With all the substrates in hand, we proceeded to find out the reactivity of **1**−**3** (Scheme 1b) toward nucleophilic displacement of the phenylsulfonyl group. The kinetics was followed by treating various β-lactams with thiophenol and DMAP as base in $CDCl_3$ under identical conditions of concentration and temperature and recording the ^1H NMR at different times. We observed that all the three substrates reacted at nearly equal rates, and their reactions essentially followed first-order kinetics as revealed in the plot (Figure 1a; Table 1, entries **1**−**3**). Thus, the presence of the β-silyl

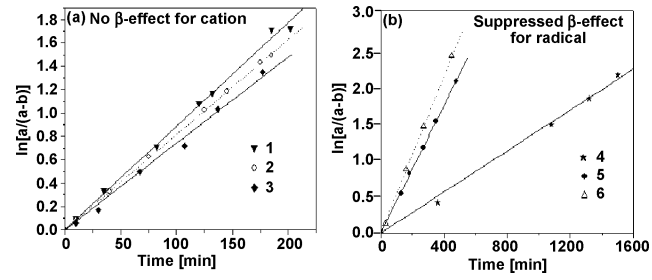


Figure 1. Reaction kinetics of (a) nucleophilic displacement of **1**−**3** with thiophenol and (b) reduction of **4**−**6** by Bu_3SnH.

Table 1. Rate Constants for Reactions of **1**−**3** with Thiophenol at 60 °C and Reduction of **4**−**6** with *n*-Bu_3SnH at 80 °C

entry	rate constants (k_{obs}) (min^{-1})	entry	rate constants (k_{obs}) (min^{-1})
1	8.89×10^{-3}	**4**	1.39×10^{-3}
2	8.17×10^{-3}	**5**	4.31×10^{-3}
3	7.41×10^{-3}	**6**	4.60×10^{-3}

substituent has practically no influence on the kinetics of the reaction which reflects its inability to stabilize the acylimine intermediate. To our knowledge, this is the first example of a β-lactam system where the β-effect of silicon is virtually nonexistent.

When the β-lactams **4**−**6** (Scheme 1b) were treated with tri-*n*-butyltinhydride keeping identical conditions of temperature and concentrations, rate enhancement of about 3-fold, independent of the concentration of tinhydride, was observed for both the silyl-substituted derivatives. Thus, the reaction

(3) (a) White, J. M. *Aust. J. Chem.* **1995**, *48*, 1227-A. (b) Colvin, E. *Silicon in Organic Synthesis*, Butterworths Monograph in Chemistry; Butterworth: Boston, 1981. (c) Creary, X.; O'Donnell, B. D.; Vervaeke, M. *J. Org. Chem.* **2007**, *72*, 3360.

(4) Lambert, J. B.; Wang, G. T.; Finzel, R. B.; Teramura, D. H. *J. Am. Chem. Soc.* **1987**, *109*, 7838.

(5) (a) Lambert, J. B.; Chelius, E. C. *J. Am. Chem. Soc.* **1990**, *112*, 8120. (b) Creary, X.; Butchko, M. A. *J. Org. Chem.* **2002**, *67*, 112. (c) Fujio, M.; Umezaki, Y.; Alam, Md. A.; Kikukawa, K.; Fujiyama, R.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1091. (d) Dichiarante, V.; Salvaneschi, A.; Protti, S.; Dondi, D.; Fagnoni, M.; Albini, A. *J. Am. Chem. Soc.* **2007**, *129*, 15919.

(6) Auner, N.; Walsh, R.; Westrup, J. *Chem. Commun.* **1986**, 207.

(7) (a) Fedor, L. R. *J. Org. Chem.* **1984**, *49*, 5094. (b) Rao, S. N.; O'Ferrall, R. A. M. *J. Am. Chem. Soc.* **1990**, *112*, 2729. (c) Page, M. I.; Laws, A. P. *Tetrahedron* **2000**, *56*, 5631.

(8) Hwu, J. R.; Gilbert, B. A.; Lin, L. C.; Liaw, B. R. *Chem. Commun.* **1990**, 161.

(9) (a) Clauss, K.; Grimm, D.; Prossel, G. *Liebigs Ann. Chem.* **1974**, *4*, 539. (b) Iwata-Reuyl, D.; Basak, A.; Silverman, L. S.; Engle, C. A.; Townsend, C. A. *J. Nat. Prod.* **1993**, *56*, 1373. (c) Shibasaki, M.; Nishida, A.; Ikegami, S. *Chem. Commun.* **1982**, 1324.

again essentially followed pseudo-first-order kinetics (Figure 1b; Table 1, entries **4**−**6**). Since the rates of tin hydride mediated reactions depend primarily upon the stability of the radical intermediates[10] unlike in the case of cations, the β-silicon substituent is able to stabilize to some extent the radical at C-4 which is manifested in the observation of rate enhancement by 3-fold. The magnitude of β-stabilization was, however, much less than expected (calculated β-stabilization energy was ~3.2 kJ/mol vs 12.3 kJ/mol reported for 2-trimethylsilyl-2-methyl propyl radical[6]).

From the above results, it is clear that while the β-effect of silicon is absent in the case of a cationic intermediate the effect is considerably suppressed in the case of a radical intermediate. Three possible factors, (a) the antiaromaticity, (b) involvement of N-lone pair, and (c) the dihedral angle, might be considered, all of which could potentially suppress the β-effect. It is indeed true that the dihedral angle[11] plays a dominant role in controlling the magnitude of the β-effect. The optimized structure (Figure 2a) of the β-lactam containing an empty p-orbital indicated that the concerned dihedral angle was ~32°, which suggests that the β-effect should still be substantial at this dihedral angle, of the order of $\sim 10^4$.[11] Thus, the dihedral angle could not alone explain the suppression of the β-effect.

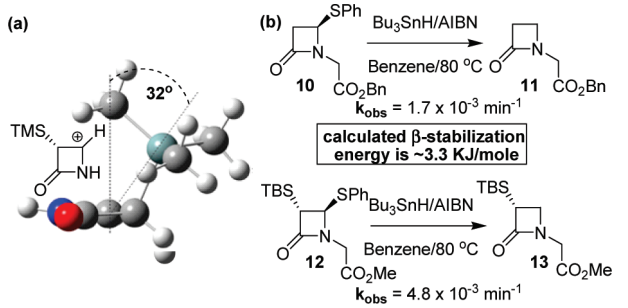


Figure 2. (a) Calculated dihedral angle of the β-silyl cation. (b) Kinetics of radical displacement of N-substituted β-lactams.

The involvement of the N-lone pair in stabilization of the cation or radical should be of the same order, if at all, in all the cases since we were dealing with similar systems. Moreover, even where such stabilization is weak, we still observed considerable suppression of the β-effect as revealed in the radical-mediated reaction shown in Figure 2b (stabilization is only about 3.3 kJ/mol). It is interesting to note that our results on the β-effect of silicon followed the same trend as the reported suppressed β-secondary deuterium isotope effects[2a] in β-lactam systems for a cationic or a radical intermediate. The absence of any downfield shift of NH in **1**−**3** in the presence of excess thiophenol points out again no additional participation of N-lone pair with the carbonyl.

Therefore, with the N-lone pair effect also failing to satisfactorily explain our observation, one has to invoke the role of antiaromaticity in these systems, which is in our view mainly responsible for suppression of β-effect. Although the suppression of the β-effect of silicon is beyond any doubt, the subtle difference in its extent in the radical and the cationic regime is not clear; the geometry of the radical and cation at C-4 might be playing an important role which accounts for the difference in percent antiaromatic destabilization and thus can explain the suppressed β-effect to a different extent.

To ascertain the relative reactivities of the β-lactams with and without β-silyl groups at C-3, we carried out theoretical calculations at the ROMP2=FC/6-31G**//B3LYP/3-21G* level[12] using Gaussian 98. Thus, the result showed no significant change in charge distribution, especially at C-4 which is β to silicon for both silylated and nonsilylated systems with a cation or a radical generated at C-4. Although charge distribution in the ground state is not an accurate method for predicting the reactivity, development of any extra charge at C-4 indicated the absence of any β-effect of silicon in these systems. The results are in good agreement with our experimental findings. The computational results also showed no significant change in energetics whether silicon is present in the β-position or not. Computation on cyclobutylamine systems as our β-lactam model also showed no change in energetics. Although the numbers refer to the thermodynamic changes, it is unlikely that there would be a substantial change in kinetic barrier (Table S4, Supporting Information).

The isodesmic calculation on the radical reaction using B3LYP/3-21G* (using Gaussian 03)[13] optimized geometries pointed out strongly repressed β-silyl effect (stabilization energies were only 3.36 kJ/mol for N-unprotected and 4.52 kJ/mol for N-protected β-lactam) supporting our experimental results (Scheme S4, Supporting Information). Therefore, the β-silyl effect has essentially been faded away because of the

(10) (a) Kuivila, H. G.; Menapace, L. W.; Warner, C. R. *J. Am. Chem. Soc.* **1962**, *84*, 3584. (b) Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 7739.

(11) Lambert, J. B.; Zhao, Y.; Emblidge, R. W.; Salvador, L. A.; Liu, X.; So, J.-H.; Chelius, E. C. *Acc. Chem. Res.* **1999**, *32*, 183.

(12) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.5; Gaussian, Inc.: Pittsburgh, PA, 1998.

(13) 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.; Bakken, V.; 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 03*, revision C.02; Gaussian, Inc.: Wallingford, CT, 2004.

antiaromatic character of the cations or radicals that would necessarily come along with β-silyl stabilization.

To account for the antiaromatic origin of the subtle difference in the extent of β-effect of silicon in the radical and cationic regime, we studied the magnetic properties of an acylimine and the other cationic and radical intermediates by calculating the NICS (nucleus independent chemical shift) at different points along the z-axis, magnetic exaltations (Λ), and antiaromatic destabilization energies (ASE) at different levels of theory using the Gaussian 03 program package.[13] The result (GIAO-B3LYP/6-31+G*//B3LYP/6-311+G**) showed that except the radical intermediate, $\mathbf{4}_{\mathbf{rad.}}$ (Figure 3b),

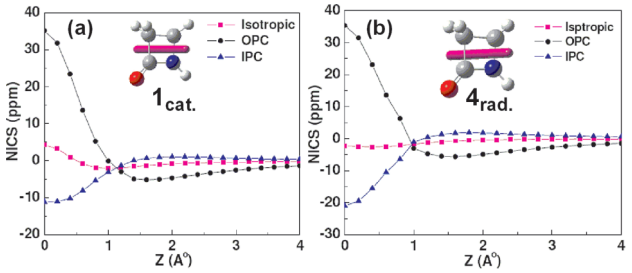


Figure 3. Plot of NICS values (osotropic, out-of-plane, and in-plane components) as a function of distance (z, Å).

all other β-lactams-**7**, $\mathbf{7}_{\mathbf{aze.}}$ (Figure S26, Supporting Information), and $\mathbf{1}_{\mathbf{cat.}}$ (Figure 3a) exhibited positive NICS values at all the points calculated indicating their strong antiaromatic character. The β-silyl unsubstituted and substituted β-lactam radicals, $\mathbf{4}_{\mathbf{rad.}}$ (Figure 3b, Table 2) and $\mathbf{5}_{\mathbf{rad.}}$ (Table 2), respectively, showed a much less (−) ve isotropic chemical shift at the ring center indicating their nonaromatic character.[14]

Table 2. DFT Calculated NICS(0), Magnetic Exaltation (Λ), ASE, and y % of Various β-Lactams

compound	NICS (0)[a]	Λ[b]	ASE[c]	y % [d]
$\mathbf{1}_{\mathbf{cat.}}$	4.240	1.539	-41.340	-30.874
$\mathbf{4}_{\mathbf{rad.}}$	-2.217	0.251	61.748	39.599
TMS $\mathbf{2}_{\mathbf{cat.}}$	0.844	0.140	-29.964	-23.097
TMS $\mathbf{5}_{\mathbf{rad.}}$	-3.819	-0.613	69.075	44.608

[a] NICS (ppm) at center. [b] Λ (ppm cgs).[15] [c] ASE = antiaromatic destabilization energy (kJ/mol). [d] y % = % antiaromaticity/aromaticity.

For a better understanding and comparing the antiaromatic characters between the radicals and cations, we have plotted isotropic chemical shifts of respective NICS probes (bq's) and their in-plane and out-of-plane components against the distance, z, perpendicular to the xy-plane.[14] The shape of the plots (NICS vs z) clearly indicates that the β-lactam cation is strongly antiaromatic in character (Figure 3a).[14] However, the shape is quite different in the case of the β-lactam radical ($\mathbf{4}_{\mathbf{rad.}}$, Figure 3b)—the out-of-plane shielding decays rapidly as the distance between the probe and the ring plane increases which is characteristic of a nonaromatic compound.[14] This indicated that the electronic structure of the radical is neither aromatic nor antiaromatic and that the π-character of the C3−C4 bond is not yet very developed in the transition structure. Thus, from the NICS study it is concluded that percent antiaromaticity and hence the destabilization is much less in the case of a radical compared to that of a cation supporting our observed suppressed β-silyl effect to a different extent.

The antiaromatic destabilization energy (ASE) based on the hydrogenation reaction calculated at the B3LYP/6-311+G** level[13] also indicated the higher destabilization of the cation compared to the radical intermediate (Table 2).[15] It is also clear from the % antiaromaticity (y %) that the radicals are much less antiaromatic or rather nonaromatic, while the cations are strongly antiaromatic (Table 2).[15] The calculated values of magnetic exaltations (Λ)[16] at the CSGT-SCF level also indicated similar findings (Table 2). Therefore, all the theoretical magnetic criteria are conclusive to the relatively greater antiaromatic character of the cation compared to the radical intermediates supporting their reactivity to different extents.

In conclusion, we have shown that the β-radicals are better stabilized (with a strong suppression) by silicon in our system compared to the β-cation. Thus, this model study supports the preferable formation of a radical over a cationic intermediate in the conversion of proclavaminate to clavaminate in the actual enzymatic pathway. From both the experimental and theoretical studies, it was demonstrated that antiaromaticity is playing the prime role by ruling out several other possible factors in suppressing the β-stabilization effect of silicon and hence in controlling the reactivity at C-4 of monocyclic β-lactam systems. The subtle difference in suppressed β-silicon effect between the cationic and radical regime was also clearly explained by considering their antiaromatic destabilization and % antiaromaticity to different extents. To the best of our knowledge, this is the first example where there is no β-effect of silicon in β-lactam systems.

Acknowledgment. Support has been provided by DST (SR/SI/OC-69/2008), Govt. of India, and IIT Guwahati.

Supporting Information Available: Synthetic Schemes S1 and S2, experimental procedure, kinetic equation, $^1H/^{13}C$ NMR spectra, and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

OL902411R

(14) (a) Wiest, O. *J. Phys. Chem. A* **1999**, *103*, 7907. (b) Stanger, A. *J. Org. Chem.* **2006**, *71*, 883.
(15) Mucsi, Z.; Viskolcz, B.; Csizmadia, I. G. *J. Phys. Chem. A* **2007**, *111*, 1123.
(16) Proft, F. De.; Schleyer, P. v. R.; Lenthe, J. H. v.; Stahl, F.; Geerlings, P. *Chem.—Eur. J.* **2002**, *8*, 3402.