DFT Calculations Indicate that 1,4-Dihydropyridine Is a Promising Lead Antioxidant

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By density-functional-theory (DFT) calculations, 1,4-dihydropyridine (**1**) was found to be a powerful lead antioxidant with high H-atom-donating ability and relatively low pro-oxidant activity. Moreover, two ethoxycarbonyl (EtOCO) substituents at C(2) and C(6) should further enhance its H-atom-donating ability due to resonance effects.

Introduction. – In recent years, there has been growing interest in novel antioxidants used to prevent radical-induced oxidation of food and to retard radical-induced damage in organisms. Based on the well-known radical-scavenging mechanisms – direct H-atom transfer (*Eqn. 1*) and proton-transfer-coupled electron-transfer (*Eqn. 2*) – a rational design has been successfully introduced into this field [1–3].

$$ROO^{\bullet} + R'XH \rightarrow ROOH + R'X^{\bullet} \quad (1)$$

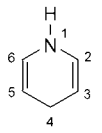
$$ROO^{\bullet} + R'XH \rightarrow ROO^{-} + R'XH^{\bullet+} \rightarrow ROOH + R'X^{\bullet} \quad (2)$$

In *Eqns. 1* and *2*, X represents an O-, S-, N-, or C-atom. Whereas the first pathway (*Eqn. 1*) dominates in nonpolar solvents [4–8], the second (*Eqn. 2*) is more abundant in polar solvents [9–11]. The first mechanism can be characterized by the X–H bond-dissociation enthalpy (*BDE*) of the antioxidant [12–17], and the second can be quantified by the adiabatic ionization potential (*IP*) of the antioxidant or of anions derived thereof [16][18]. Obviously, low X–H *BDE* values are beneficial to enhance the H-atom-donating power of these species. However, although low *IP* values of antioxidants are also favorable to raise the electron-transfer reactivity, they enhance the danger of generating a superoxide anion radical through transfer of the electron directly to surrounding O_2 [16]. By a compromise between *BDE* and *IP*, and taking the solubility and bioavailability of the antioxidant and the toxicity of antioxidant-derived products into consideration, one can rationally design novel antioxidants for a given chemical or biological system.

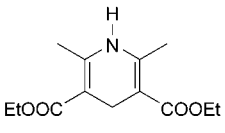
Up to now, there have been several successful examples in rational design of novel antioxidants [2][7][19–21]. However, all of them were phenol-type compounds. Considering the fact that nonphenolic compounds such as aminoxyl derivatives [22–24], edaravone (=2,4-dihydro-5-methyl-2-phenylpyrazol-3(3*H*)-one) [25][26], and γ-

terpinene [27] are also excellent antioxidants, nonphenolic antioxidants certainly deserve more attention. In this paper, we present the unexpected finding that 1,4-dihydropyridine (**1**) proper, according to our calculations, is a promising lead antioxidant with very low *BDE* and appropriate *IP* values.

Results and Discussion. – The vitamin E like antioxidant activity of diludin (=diethyl 1,4-dihydro-2,6-dimethylpyridine-3,5-dicarboxylate; **2**)[1]), has been reported more than 70 years ago [28][29]. However, there are only a few studies on the antioxidant action of 1,4-dihydropyridines (DHDs) [30][31] despite the fact that these compounds are widely being used as calcium antagonists (*e.g.*, compound **3**) to treat coronary heart disease and hypertension [32][33].



1



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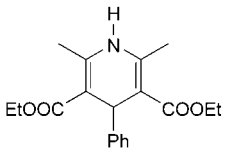

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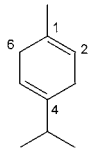
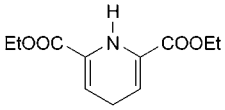


4
(γ-terpinene)



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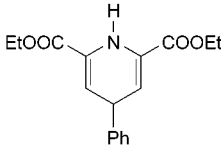

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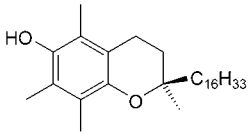

α-T
(α-tocopherol)

By means of a combined density-functional-theory (DFT) method, designated as (RO)B3LYP/6-311 + G(2d,2p)//AM1/AM1, we calculated the *BDE* and adiabatic *IP* values of compounds **2** and **3**. Compared with α-tocopherol (α-T), both DHDs were found to be safer than α-T with respect to pro-oxidant danger because of their higher *IP* values, but weaker than α-T as chain-breaking antioxidants due to their higher *BDE* values[2]) (see the *Table*). This may be the reason why the application of DHDs as antioxidants was hardly investigated during the past few decades.

We were surprised to find that the C–H *BDE* value for 1,4-dihydropyridine (**1**) is by 3–5 kcal/mol lower than those of α-T and γ-terpinene (**4**) (*Table*), suggesting that the H-atom at C(4) of **1** can be more readily abstracted than the counterparts in α-T and **4**. The low C–H *BDE* value of **1** can be rationalized in terms of resonance stabilization of the resulting radicals of type **5** (*Scheme 1*). Moreover, considering the structural similarity between **1** and **4**, it is reasonable to conjecture that the fate of the radicals **5** will be similar to that derived from **4**, *i.e.*, adduct formation with molecular

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[1]) Usually referred to as '2,6-dimethyl-3,5-bis(ethoxycarbonyl)-1,4-dihydropyridine'.

[2]) The experimental N–H dissociation enthalpies for **2** and **3** are several kcal/mol higher than the theoretical values [34]. However, these differences do not affect our conclusion. The much lower C(4)–H *BDE* value for **3** relative to **2** results from the strong π–p conjunction between the Ph group and the C(4)-radical.

Table. *Calculated Bond-Dissociation Enthalpies* (*BDE*; in kcal/mol) *and Adiabatic Ionization Potentials* (*IP*; in kcal/mol) *of the 1,4-Dihydropyridines* **1**–**3**, **6** *and* **8**, *and of* γ*-Terpinene* (**4**) *and* α*-Tocopherol* (α-T). The parameters *TE* (total electronic energy; in hartree), *ZPVE* (zero-point vibrational energy; in hartree), and *TCE* (thermal correction to energy; in hartree) are also given. All values were calculated by means of the B3LYP/6-311 + G(2d,2p)//AM1/AM1 method at 298.15 K (for details, see the *Exper. Part*).

Compound	*TE*	*ZPVE*	*TCE*	*BDE*	*IP*
1	– 249.535810	0.112490	0.117321		
1$^{\bullet+}$ [a])	– 249.276910	0.110411			161.19
(1)-**1**$^{\bullet}$ [b])	– 248.898750		0.103186	78.85	
(4)-**1**$^{\bullet}$ [b])/)	– 248.914449		0.105020	70.12	
(1,4)-**1** [c]	– 248.358617		0.094551	30.12 (N–H)	
2	– 862.751283	0.313911	0.334162		
2$^{\bullet+}$	– 862.488496	0.309965			162.49
(1)-**2**$^{\bullet}$	– 862.107188		0.319132	82.72	
(4)-**4**$^{\bullet}$	– 862.083755		0.320716	98.39	
3	– 1093.860664	0.397688	0.422399		
3$^{\bullet+}$	– 1093.599611	0.393176			161.06
(1)-**3**$^{\bullet}$	– 1093.213483		0.407010	84.44	
(4)-**3**$^{\bullet}$	– 1093.227085		0.408535	76.83	
6	– 784.097467	0.257822	0.274832		
6$^{\bullet+}$	– 783.835736	0.254407			162.15
(1)-**6**$^{\bullet}$	– 783.439501		0.259771	91.40	
(4)-**6**$^{\bullet}$	– 783.491951		0.262009	59.86	
(1,4)-**6**	– 782.898360		0.250925	53.44 (N–H)	
8	– 1015.210145	0.341358	0.362980		
8$^{\bullet+}$	– 1014.951391	0.337721			160.15
(1)-**8**$^{\bullet}$	– 1014.551633		0.347616	91.56	
(4)-**8**$^{\bullet}$	– 1014.612555		0.349483	54.47	
4	– 390.794360	0.237567	0.248831		
4$^{\bullet+}$	– 390.501030	0.232412			180.92
(3)-**4**$^{\bullet}$	– 390.165391		0.234810	73.84	
(6)-**4**$^{\bullet}$	– 390.163738		0.234839	74.90	
(3,6)-**4**	– 389.622292		0.225753	22.99 (C(6)–H)	
α-T d)	– 696.206230	0.317187	0.334113		
α-T$^{\bullet+}$	– 695.959770	0.315177			153.43
α-T$^{\bullet}$	– 695.575655		0.320504	75.10	

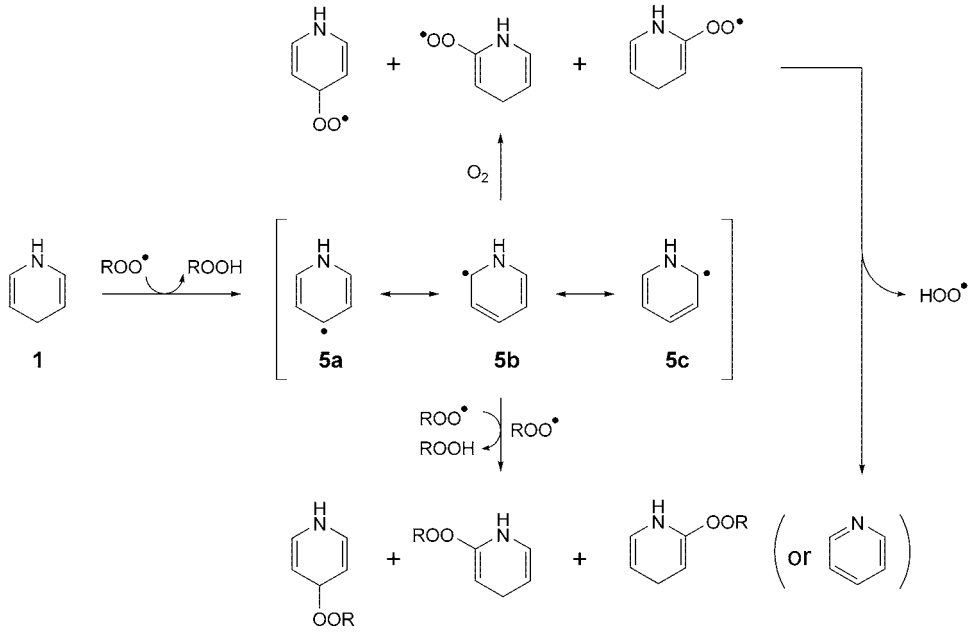
[a]) Radical cation generated after electron transfer. [b]) Radical generated by H-atom abstraction; the location of the radical is indicated in parenthesis. [c]) Nonradical product after second H-atom abstraction (abstraction sites indicated in parenthesis). [d]) Since the phytyl group ($C_{16}H_{33}$) has little effect on the *BDE* and *IP* values, it was formally replaced by a Me group in all calculations involving α-T.

oxygen (O_2), resulting in the formation of the peroxide radical (HOO$^{\bullet}$) and pyridine (*Scheme 1*) [27]. Surprisingly, although the peroxide-initiating reaction is thermodynamically favorable[3]) for the radical derived from **4**, the analogous reaction with **1** was not found to be thermodynamically facilitated (the total reaction heat was

[3]) The total reaction heat for this process is – 0.46 kcal/mol, as calculated from the difference between the C–H *BDE* value for the radical derived from **4** (22.99 kcal/mol; *Table*) and that of the O–H bond of HOO$^{\bullet}$ (23.45 kcal/mol; calculated by (RO)B3LYP/6-311 + G(2d,2p)//AM1/AM1).

+6.67 kcal/mol)[4]). Therefore, the subsequent reactions of the radicals of type **5** (derived from **1**) are likely to be H-atom abstraction or addition to peroxide radicals (*Scheme 1*), which is supported by the extremely negative reaction heats[5]). On the other hand, an *IP* value *ca.* 8 kcal/mol higher than that of α-T, but *ca.* 20 kcal/mol lower than that of **4** (*Table*), indicates that **1** is less potent than α-T, but more potent than **4** as a pro-oxidant. And indeed, **4** has been shown to have no pro-oxidant activity [27]. Therefore, 1,4-dihydropyridine (**1**) seems to be a promising lead antioxidant, combining the features of a strong H-atom donor with those of a relatively poor pro-oxidant.

Scheme 1. *Possible Reaction Pathways for Radicals Derived from 1,4-Dihydropyridine* (**1**)



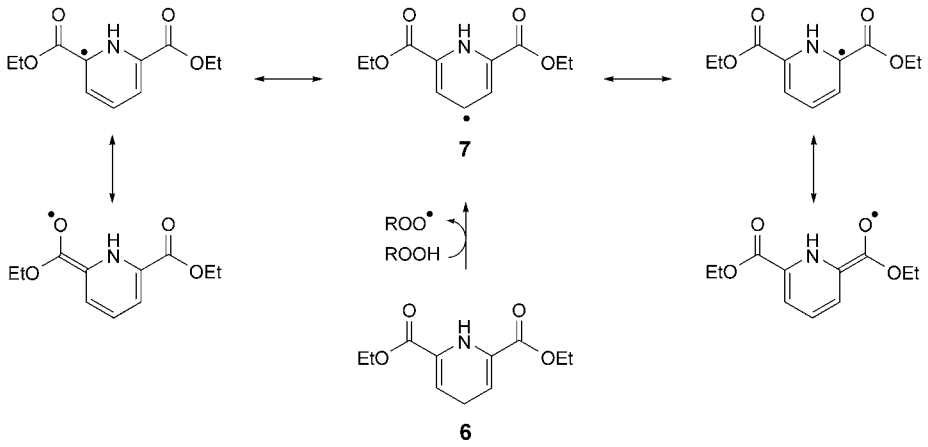
Interestingly, for compound **6**, containing two EtOCO groups at C(2) and C(6), the C(4)–H *BDE* value becomes as low as 59.86 kcal/mol, and the subsequent N–H *BDE* value is relatively low (*Table*)[6]). This contrasts with **2** and **3**, where the two ester groups have no positive effect in lowering the *BDE* value of the C(4)–H bond. This large difference can be rationalized by resonance effects. The C(4)-radical **7** is resonance-

[4]) The total reaction heat is calculated from the difference between the *BDE* value of the N–H bond of the radical derived from **1** (30.12 kcal/mol; *Table*) and that of the O–H bond of HOO• (23.45 kcal/mol).

[5]) The total reaction heat for the H-atom abstraction by MeOO• is −58.10 kcal/mol, as calculated from the difference between the *BDE* of the N–H bond of the radical derived from **1** (30.12 kcal/mol; *Table*) and that of the O–H bond of MeOOH (88.22 kcal/mol; calculated by (RO)B3LYP/6-311+G(2d,2p)//AM1/AM1). The (RO)B3LYP/6-311+G(2d,2p)//AM1/AM1-calculated reaction heats for the addition reaction with MeOO• are *ca.* −38 kcal/mol.

[6]) The first *BDE* value of the N–H bond in **6** is much higher than that of **1**, which results from the electron-withdrawing effect of the two ester groups.

Scheme 2. *Resonance Modes for the Radical Species* **7** *Derived from Diethyl 1,4-Dihydropyridine-2,6-dicarboxylate* (**6**)



stabilized by the EtOCO groups at C(2) and C(6) (*Scheme 2*), but not at C(3) and C(5).

Although electron-withdrawing and -donating groups tend to lower the *BDE* values of C–H bonds in *para*-substituted toluenes, the substituent effects amount to only *ca.* 1 kcal/mol [35][36]. The present study reveals that two EtOCO groups reduce the *BDE* value of C–H bonds by as much as 10 kcal/mol, indicating that resonance effects are much stronger in this case than electronic effects in lowering the dissociation enthalpy. This rationale may be used in the design of novel nonphenolic antioxidants. The *IP* value of **6** is little influenced by the EtOCO groups at C(2) and C(6) (*Table*), which implies that **6** is superior to α-T with respect to pro-oxidant danger. Furthermore, if a phenyl group is present at C(4), as in compound **8**, the *BDE* and *IP* values are only slightly influenced, which offers the opportunity to improve the lipid solubility of DHDs without affecting the antioxidant and pro-oxidant ability.

Conclusions. – Density-functional-theory (DFT) calculations indicate that 1,4-dihydropyridine (**1**) is a very promising lead antioxidant. By introducing ester (ethoxycarbonyl) functions at C(2) and C(6), as in compounds **6** and **8**, the antioxidant power of **1** can be even enhanced. However, dihydropyridines should be used in nonpolar rather than in polar solvents since, in the latter, not H-atom-, but electron-transfer, is preferred in the radical-scavenging process.

Experimental Part

Bond-dissociation enthalpies (*BDE*s) and adiabatic ionization potentials (*IP*s) were calculated by a combined density-functional-theory (DFT) method, designated as B3LYP/6-311 + G(2d,2p)//AM1/AM1, which takes advantage of accuracy and economy [16][37–39]. For calculating *BDE*, the open shells were treated with ROHF, while, for *IP*, the open shells were treated with UHF [16]. In a typical calculation of *IP*, designated as B3LYP/6-31G(d)//AM1/AM1, the open shells were also treated with UHF [38][39]. Employing this method, the *IP* values of compounds **1**–**3**, **6**, and **8**, as well as of α-tocopherol (α-T), were calculated as 156.40, 154.92,

153.92, 155.48, 153.06 and 147.73 kcal/mol, respectively. These values are, in a relative sense, comparable to those calculated by the B3LYP/6-311 + G(2d,2p)//AM1/AM1 approach.

The detailed calculation procedures are as follows. The geometry optimization and the determination of vibrational frequencies were performed by means of the semiempirical AM1 method [40]. Then, single-point electronic energies (*SPE*s) were obtained by the DFT method, using the B3LYP functional on the 6-311 + G(2d,2p) level. Employing the molecular enthalpy in the gas-phase at 298.15 K, which consists of B3LYP/6-311 + G(2d,2p)-calculated *SPE* values, AM1-calculated zero-point vibrational energy (*ZPVE*; scaled by a factor of 0.973), vibrational contribution to energy (scaled by a factor of 0.973), translational, rotational and *PV*-work terms, the bond-dissociation enthalpy *BDE* is equal to $H_r + H_h - H_p$, where H_r is the enthalpy of the radical generated by H-abstraction, H_h is the enthalpy of the H-atom (−0.49765 hartree), and H_p is the enthalpy of the parent molecule. The ionization potential *IP* is equal to $[(SPE_c + ZPVE_c \times 0.973) - (SPE_p + ZPVE_p \times 0.973)]$, where the subscripts 'p' and 'c' indicate the *parent* molecule and the corresponding radical *cation* generated after electron transfer, respectively. The accuracy of the combined method is attributed to the fact that the AM1-optimized molecular structures were in good agreement with those derived from a pure DFT optimization with an error of 0.01 Å [41][42]. All of the calculations were performed with the GAUSSIAN-98 program package [43].

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REFERENCES

[1] L. Packer, E. Cadenas, 'Handbook of Synthetic Antioxidants', Marcel Dekker, New York, 1997, p. 1.
[2] N. Noguchi, E. Niki, *Free Radical Biol. Med.* **2000**, *28*, 1538.
[3] H. Y. Zhang, D. Z. Chen, *Acta Biophys. Sin.* **2000**, *16*, 1.
[4] G. W. Burton, Y. Le Page, E. J. Gabe, K. U. Ingold, *J. Am. Chem. Soc.* **1980**, *102*, 7791.
[5] G. W. Burton, T. Doba, E. J. Gabe, L. Hughes, F. L. Lee, L. Prasad, K. U. Ingold, *J. Am. Chem. Soc.* **1985**, *107*, 7053.
[6] M. I. de Heer, P. Mulder, H.-G. Korth, K. U. Ingold, J. Lusztyk, *J. Am. Chem. Soc.* **2000**, *122*, 2355.
[7] M. C. Foti, E. R. Johnson, M. R. Vinqvist, J. S. Wright, L. R. C. Barclay, K. U. Ingold, *J. Org. Chem.* **2002**, *67*, 5190.
[8] H. Y. Zhang, L. F. Wang, *J. Phys. Chem. A* **2003**, *107*, 11258.
[9] S. V. Jovanovic, S. Steenken, M. Tosic, B. Marjanovic, M. G. Simic, *J. Am. Chem. Soc.* **1994**, *116*, 4846.
[10] S. V. Jovanovic, S. Steenken, Y. Hara, M. G. Simic, *J. Chem. Soc., Perkin Trans. 2* **1996**, *11*, 2497.
[11] I. Nakanishi, K. Miyazaki, T. Shimada, K. Ohkubo, S. Urano, N. Ikota, T. Ozawa, S. Fukuzumi, K. Fukuhara, *J. Phys. Chem. A* **2002**, *106*, 11123.
[12] S. A. B. E. van Acker, L. M. H. Koymans, A. Bast, *Free Radical Biol. Med.* **1993**, *15*, 311.
[13] E. Migliavacca, P. A. Carrupt, B. Testa, *Helv. Chim. Acta* **1997**, *80*, 1613.
[14] H. Y. Zhang, *J. Am. Oil Chem. Soc.* **1998**, *75*, 1705.
[15] H. Y. Zhang, Y. M. Sun, G. Q. Zhang, D. Z. Chen, *Quant. Struct.-Act. Relat.* **2000**, *19*, 375.
[16] J. S. Wright, E. R. Johnson, G. A. DiLabio, *J. Am. Chem. Soc.* **2001**, *123*, 1173.
[17] E. G. Bakalbassis, A. Chatzopoulou, V. S. Melissas, M. Tsimidou, M. Tsolaki, A. Vafiadis, *Lipids* **2001**, *36*, 181.
[18] L. Kong, Z. L. Sun, L. F. Wang, H. Y. Zhang, S. D.Yao, *Helv. Chim. Acta* **2004**, *87*, 511.
[19] D. A. Pratt, G. A. DiLabio, G. Brigati, G. F. Pedulli, L. Valgimigli, *J. Am. Chem. Soc.* **2001**, *123*, 4625.
[20] K. Fukuhara, I. Nakanishi, H. Kansui, E. Sugiyama, M. Kimura, T. Shimada, S. Urano, K. Yamaguchi, N. Miyata, *J. Am. Chem. Soc.* **2002**, *124*, 5952.
[21] H. H. Hussain, G. Babic, T. Durst, J. S. Wright, M. Flueraru, A. Chichirau, L. L. Chepelev, *J. Org. Chem.* **2003**, *68*, 7023.
[22] N. Noguchi, E. Damiani, L. Greci, E. Niki, *Chem. Phys. Lipids* **1999**, *99*, 11.
[23] J. Antosiewicz, E. Bertoli, E. Damiani, L. Greci, J. Popinigis, S. Przybylski, F. Tanfani, M. Wozniak, *Free Radical Biol. Med.* **1993**, *15*, 203.
[24] H. Y. Zhang, L. F. Wang, *Chin. Chem. Lett.* **2003**, *14*, 437.
[25] R. Tabrizchi, *Curr. Opin. Investig. Drugs* **2000**, *1*, 347.
[26] L. F. Wang, H. Y. Zhang, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3789.
[27] M. C. Foti, K. U. Ingold, *J. Agric. Food Chem.* **2003**, *51*, 2758.
[28] C. H. Li, L. Y. Zhu, *Chin. Feed* **2000**, 17.

[29] X. T. Fang, L. L. Shen, J. M. Sun, *Feed Ind.* **2002**, *23*, 14.
[30] G. Tirzitis, I. Kirule, *Czech. J. Food Sci.* **1999**, *17*, 133.
[31] A. G. Sadoyan, V. Yu, Zvyagintseva, *Biol. Zh. Arm.* **1984**, *37*, 748.
[32] S. H. Bai, Y. B. Chen, *Pharm. Prog.* **1999**, *23*, 13.
[33] W. G. Zhang, *Pharmacol. Res.* **1996**, *34*, 187.
[34] 'Handbook of Bond Dissociation Energies in Organic Compounds', Ed. Y.-R. Luo, CRC Press, Boca Raton, FL, 2003, p. 251
[35] Y. D. Wu, C. L. Wong, K. W. K. Chan, G. Z. Ji, X. K. Jiang, *J. Org. Chem.* **1996**, *61*, 746.
[36] G. P. Bean, *Tetrahedron* **2002**, *58*, 9941.
[37] G. A. DiLabio, D. A. Pratt, A. D. LoFaro, J. S. Wright, *J. Phys. Chem. A* **1999**, *103*, 1653.
[38] G. A. DiLabio, D. A. Pratt, J. S. Wright, *Chem. Phys. Lett.* **1999**, *311*, 215.
[39] G. A. DiLabio, D. A. Pratt, J. S. Wright, *J. Org. Chem.* **2000**, *65*, 2195.
[40] M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, J. J. P. Stewart, *J. Am. Chem. Soc.* **1985**, *107*, 3902.
[41] J. S. Wright, D. J. Carpenter, D. J. McKay, K. U. Ingold, *J. Am. Chem. Soc.* **1997**, *119*, 4245.
[42] Y. M. Sun, D. Chen, C. Liu, *THEOCHEM* **2002**, *618*, 181.
[43] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, P. Salvador, J. J. Dannenberg, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaroni, R. Gomperts, 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, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle, J. A. Pople, Gaussian 98, Revision A.11, Gaussian, Inc., Pittsburgh, PA, 2001.

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