The gas phase cyclization of deprotonated *N*-aryl-2-cyano-2-diazoacetamides

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Dedicated to Professor Nikolai Zefirov on his 70th birthday

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Abstract

1-Aryl-4-cyano-5-hydroxy-1,2,3-triazoles can be obtained in solution by base-catalysed cyclization of N-aryl-2-cyano-2-diazoacetamides. A similar reaction was shown to take place under conditions of negative ion chemical ionization in the ion source of a mass spectrometer. High resolution mass spectrometry, tandem mass spectrometry, charge reversal spectra, synthesis of the ions with known structures and quantum chemical calculations were used to prove the latter statement. The fact of the observed cyclization demonstrates once again the ability of mass spectrometry to study the gas phase chemical reactions that take place in solution.

Keywords: Cyclization, diazoamides, triazoles, gas phase, negative ion mass spectrometry

Introduction

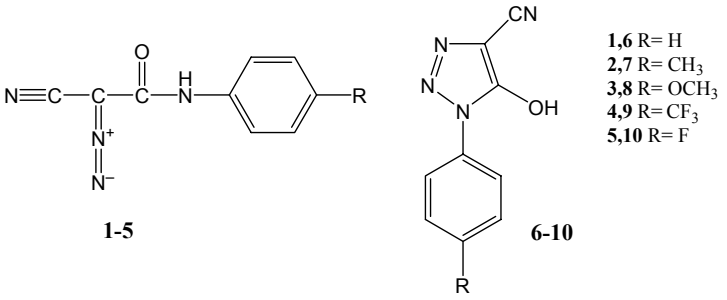
1-Aryl-4-cyano-5-hydroxy-1,2,3-triazoles can be obtained in solution by the base-catalyzed cyclization of N-aryl-2-cyano-2-diazoacetamides.[1] Since the reverse reaction is also possible, these isomers exist in solution in chemical equilibrium. The nature of the solvent is a key factor of this equilibrium. Polar solvents (water, DMSO, alcohols, acetone, acetonitrile) favor the cyclic structures, while aprotic nonpolar solvents (benzene) favor linear isomers. Electronic and steric properties of a substituent at the carboxamide nitrogen atom do not influence the ratio of the isomers notably, although electron withdrawing substituents slightly destabilize the cyclic structure.

Kinetic studies in solution showed that the rate constant of cyclization of N-aryl diazoamides is an order of magnitude greater than that of N-alkyl derivatives, while cyclization of the latter involves a one stage process (monorotatory mechanism). Cyclization of N-arylamides proceeds in two stages with similar activation barriers. The first stage involves deprotonation and the second – heteroelectrocyclization.[1]

Earlier, we have reported that 1-aryl-4-cyano-5-hydroxy-1,2,3-triazoles and N-aryl-2-cyano-2-diazoacetamides isomerise into each other (or into a common structure) in the gas phase under electron ionization conditions.[2] Unfortunately, EI spectra did not allow us to prove that triazole formation in the gas phase occurs. Taking into account that this cyclization requires base-catalysis in solution and starts with deprotonation conditions, negative ion chemical ionization (NICI) was selected to carry out the process of interest in the gas phase. Earlier, a similar NICI reaction was reported for unsubstituted 2-cyano-2-diazoacetamide and its N-methyl derivative.[3]

Results and Discussion

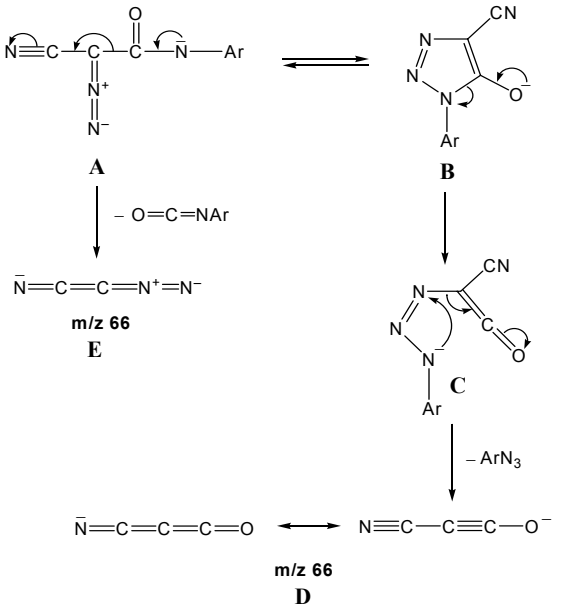
MS/MS spectra (MIKE) were recorded for deprotonated (gas-reagent - water) N-aryl-2-cyano-2-diazoacetamides (**1-5**) and corresponding 1-aryl-4-cyano-5-hydroxy-1,2,3-triazoles (**6-10**). Deprotonation of these neutral compounds yield ions **A** and **B** (Scheme 1) respectively, and, as noted above, **A** cyclizes to **B** in solution.



1-5 **6-10**

1,6 R= H
2,7 R= CH_3
3,8 R= OCH_3
4,9 R= CF_3
5,10 R= F

The present study seeks to determine whether there is any interconversion between **A** and **B** in the gas phase. In principle, the fragmentation of **A** and **B** should settle this question, since the cleavage of **A** should lead to ion **E**, while the corresponding fragmentation of **B** should yield product ion **D** (Scheme 1). Although both key fragments **E** and **D** have the m/z value 66, their composition is different.



Scheme 1

The collision-induced dissociation (CID) spectra of five isomeric pairs of ions are listed in Table 1. Representative spectra of compounds **1** and **6** are illustrated in Figure 1.

It is obvious that MIKE spectra are identical for each pair of isomers (Table 1). All the spectra show ions $[M\text{-}H,\text{-}N_2]^-$ and m/z 66 as base peaks. Other peaks are less abundant. They are due to ions $[M\text{-}H,\text{-}Ar]^{-\bullet}$ (m/z 108), $[CCN]^-$ (m/z 38), CN^- (m/z 26). Another group of fragment ions arises due to elimination of substituent R (or its portions): for example, ions $[M\text{-}H,\text{-}R]^{-\bullet}$ (m/z 184) in case of **2**, **4**, **5**, **7, 9**, **10** and $[M\text{-}H,\text{-}CH_4]^-$ (m/z 199) in case of **3**, **8**.

Table 1. MIKE-spectra of $[M\text{-}H]^-$ ions of compounds **1-10**

№	m/z (%, to the base peak)[a]
1	157(23) 143(2) 129(3) 108(3) 66(100) 38(1) 26(3)
2	184(17) 171(46) 157(9) 143 (10) 108(4) 66(100) 38(3) 26(7)
3	199(71) 187(71) 171(32) 156 (6) 143(16) 108(1) 66(100) 38(1) 26(3)
4	225(100) 209(16) 184(10) 108(6) 66(44) 38(1) 26(2)
5	184(8) 175 (65) 161(2) 127 (2) 108(2) 66(100) 38(4) 26(8)
6	157(24) 143(3) 129(3) 108(2) 66(100) 38(1) 26(4)
7	184(17) 171(47) 157(11) 143 (10) 108(4) 66(100) 38(3) 26(8)
8	199(73) 187(72) 171(33) 156 (5) 143(16) 108(1) 66(100) 38(1) 26(3)
9	225(100) 209(15) 184(9) 108(5) 66(45) 38(1) 26(2)
10	184(9) 175 (67) 161(3) 127 (2) 108(3) 66(100) 38(4) 26(7)

[a] The value in brackets corresponds to the peak height.

It is worth mentioning that the peak at m/z 66 dominates in the spectra of analogous N-alkyl-2-cyano-2-diazoacetamides and 1-alkyl-4-cyano-5-hydroxy-1,2,3-triazoles.[3] The peak widths at half height of $[M\text{-}H,\text{-}N_2]^-$ (m/z 157) and m/z 66 for compounds **1** and **6** are the same within the experimental error (Table 2). This fact proves the same mechanism of formation of these ions from initial $[M\text{-}H]^-$ ions, which should isomerize before the fragmentation starts into one or several common structures.

Table 2. Peak width at half height (in volts)

№\ion	m/z 157	m/z 66
1	111.0[a]	29.6[a]
6	110.8[a]	29.5[a]

[a] An average of ten measurements, error ±0.5 V.

As it was mentioned already in Scheme 1, formation of the ion at m/z 66 may involve two different mechanisms. Corresponding ions (**E** or **D**) possess the same m/z value, but different composition. The formation of ion **E** requires simple heterolytic rupture of the C-C bond in the deprotonated N-aryl-2-cyano-2-diazoacetamides **1-5**, while in case of 1-aryl-4-cyano-5-hydroxy-1,2,3-triazoles **6-10** preliminary opening of the cycle with isomerization to the diazo compound is necessary. Formation of ion **D** proceeds only from the triazole cycle via intermediate **C**. The detection of ion **D** in the spectra of diazoamides **1-5** should prove the realization of preliminary cyclization of the initial compounds to triazoles **6-10**. Therefore, identification of the ion structure (**E** or **D**) should answer the question on the initial structure of $[M\text{-}H]^-$ ions of compounds **1-10**, or in other words does cyclization of diazoamides or opening of triazole cycle takes place under NICI conditions.

High resolution mass measurements of the source-formed ions give 65.9980D and 65.9981D for compounds **1** and **6** respectively. Similar values for the collisionally-formed ions were 65.9981D and 65.9979D correspondingly. The measured values prove C_3NO structure (65.9980D) as the alternative C_2N_3 ion is significantly heavier (66.0092D).

Charge-reversal spectra of ions at m/z 66 arising from isomers **1** and **6** (Figure 2) are identical to each other. Peak at m/z 66 corresponds to the ion $[NCCCO]^+$, m/z 54 $[NC_2O]^+$, m/z 52 $[C_3O]^{+\bullet}$, m/z 50 $[C_3N]^+$, m/z 40 $[C_2O]^{+\bullet}$, m/z 38 $[C_2N]^+$, m/z 36 $[C_3]^{+\bullet}$, m/z 28 $[CO]^{+\bullet}$, m/z 26 $[CN]^+$, m/z 24 $[C_2]^{+\bullet}$, m/z 12 $[C]^{+\bullet}$. Although the majority of the recorded losses could fit either **E** or **D** there are two ions that can only arise from ion **D**: m/z 50 $[C_3N]^+$ and m/z 36 $[C_3]^{+\bullet}$. Besides that, it is easy to correlate the observed m/z values with the losses of trivial neutrals: m/z 54 $[NC_2O]^+$ (the loss of N atom), m/z 50 $[C_3N]^+$ (the loss of O atom), m/z 40 $[C_2O]^{+\bullet}$ (the loss of CN-radical), m/z 38 $[C_2N]^+$ (the loss of CO molecule). Hence, ion **D**, represented in Scheme 1 is the most probable in comparison with ions of alternative structures with the same composition.[4]

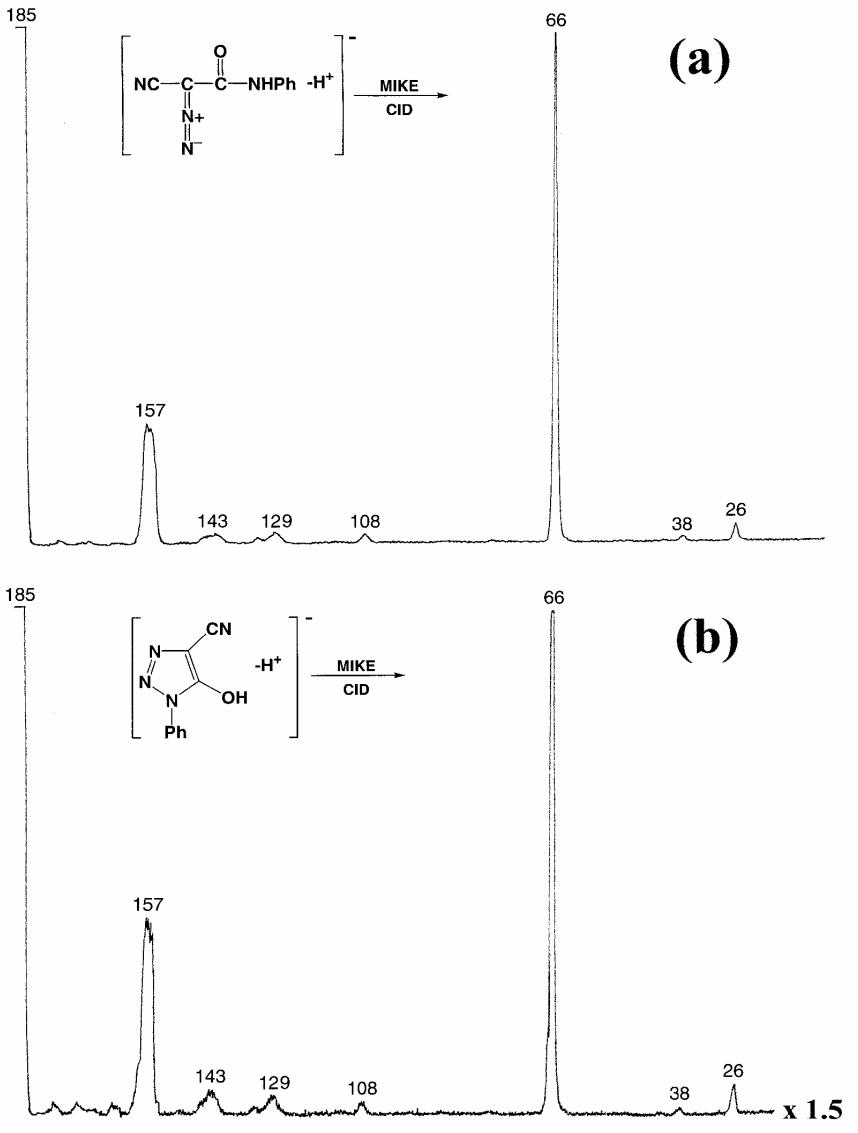


Figure 1. MIKE-spectra (CID) of $[M-H]^-$ ions of compounds **1** (a) and **6** (b).

In order to assign the structure of this ion unambiguously, we have synthesized ion **D** in the mass spectrometer by the standard route using alkyl esters of cyanoacetic acid: [3,4]

$$NCCH_2CO_2R \xrightarrow{HO^-} NC\bar{C}HCO_2R \longrightarrow [(NC{-}CH{=}C{=}O)\ {}^-OR] \xrightarrow[-\ ROH]{} [NCCCO]^-$$

The spectra of m/z 66 ions generated from compounds **1**, **6**, and the methyl and ethyl esters of cyanoacetic acid were indistinguishable, proving the proposed structure $[NCCCO]^-$ of that ion.

Another fragment ion deserving special mention is $[M\text{-}H\text{-}N_2]^-$. In case of analogous alkyltriazoles[3] its abundance was very low. In the case of compounds **1-10** its abundance is much more pronounced, while in the spectra of the trifluoromethyl derivative it becomes the base peak.

The mass spectra presented in Table 1 demonstrate that there is no significant difference in the behavior of the studied compounds depending on the nature of a substituent in the aromatic ring. It is worth mentioning that any substituent brought to an increase of the relative abundance of $[M\text{-}H\text{-}N_2]^-$ ion peak while in the case of the most electron-withdrawing CF_3-group its abundance was higher than that of m/z 66 ion.

Quantum chemical calculations of the studied gas-phase process (Figure 3) showed that cyclization of N-phenyl-2-cyano-2-diazoacetamide **1** (ion **A**) into 1-phenyl-4-cyano-5-hydroxy-1,2,3-triazole **6** (ion **B**) may be characterized by an activation barrier of 8.5 kcal/mol, while formation of deprotonated **6** (ion **B**) is an exothermic process (Δ_rH= -15.8 kcal/mol).

The values of gas phase acidity, obtained by quantum chemical calculations (B3LYP/6-311++G(d,p)//B3LYP/6-31+G(d,p)) for diazo compound **1** is 323.6 kcal/mol. Taking into account that under the conditions of the gas-phase experiment (NICI, H_2O) with OH^- (PA=391 kcal/mol)[5] as an ion reagent, the process of proton transfer from a molecule of compound **1** to the hydroxide anion is an exothermic process (Δ_rH= -67.4 kcal/mol). However as a result of this transfer, the internal energy of ions $[M\text{-}H]^-$ remains at a low level, while the major portion of energy is concentrated on H_2O molecules, arising from ion-reagents OH^-.[5] Nevertheless an increase of internal energy of $[M\text{-}H]^-$ ions over the values of activation energy of cyclization (8.5 kcal/mol), is possible as a result of subsequent ion-molecular interactions. This statement can be supported by the appearance of the ion $[NCCCO]^-$ (m/z 66) in the ion source.

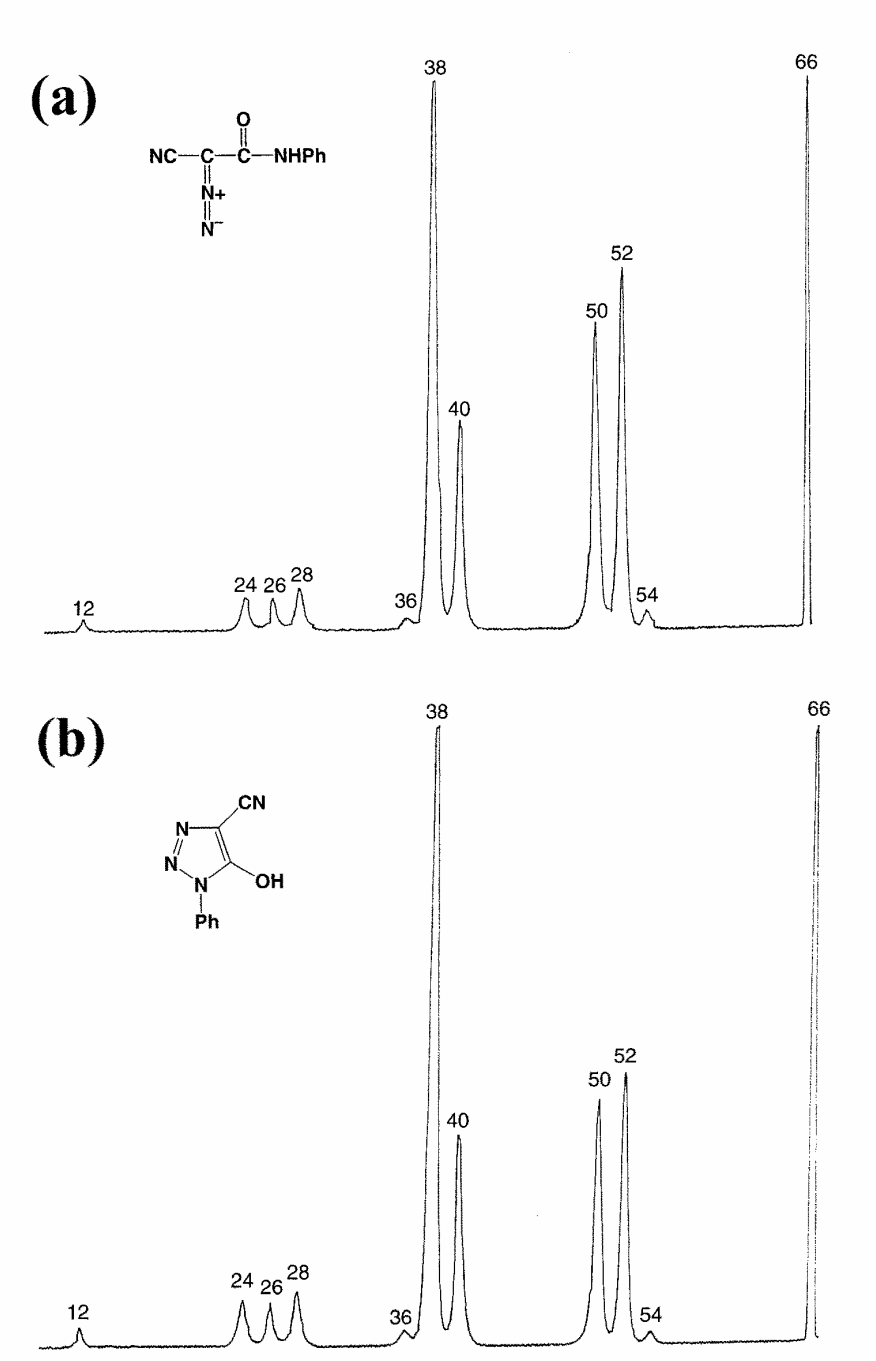


Figure 2. Charge-reversal spectra recorded for ion $[NCCCO]^-$ (m/z 66) for compounds **1** (a) and **6** (b).

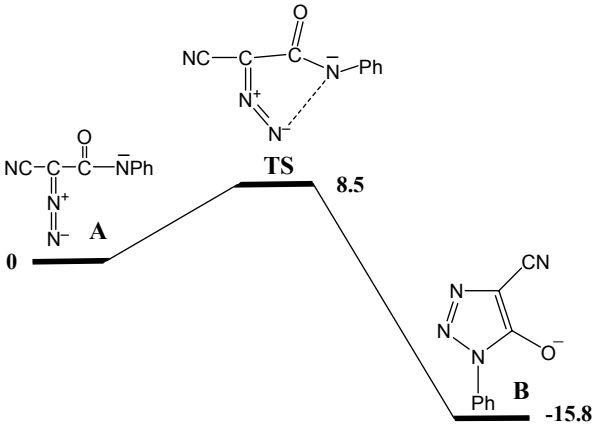


Figure 3. Cyclization of ion $[M-H]^-$ of compound **1** into ion $[M-H]^-$ of compound **6**. Relative values of energies (kcal/mol) in DFT approximation B3LYP/6-311++G(d,p)//B3LYP/6-31+G(d,p).

Conclusions

There is a direct analogy between the behavior of deprotonated diazoamides **1-5** in the gas phase, and that of the neutral precursors under basic conditions in solution.

Mass spectrometry demonstrated its ability to match liquid phase chemical reactions in the ion source.

Experimental Section

Compounds. Compounds **1-10** were synthesized as described in the literature.[1] The purity of the samples was checked by means of TLC and NMR.

Mass spectrometry. Negative ion chemical ionization (NICI) mass spectra were recorded with ZAB 2HF (Micromass, UK) instrument using a direct insertion probe and water as gas-reagent. Source temperature 200°C, accelerating voltage - 7 kV. The parent ions were selected by means of the magnet. For collisional activation experiments the ions were collided in the field free region between B and E with argon at 50% transmission of the incident beam; these conditions approximate single collision conditions.

Charge reversal mass spectra of the anions to cations ($^-CR^+$) were obtained by colliding the ion beam with oxygen (80% transmission) in the field free region preceding E. Under these conditions the CR process can be treated as a vertical two-electron oxidation occurring in a single step at a time scale of a few femtoseconds.

High resolution measurements for ions formed in the source and as a result of collisional activation (NICI spectra, gas-reagent–ammonia) were performed with ZABSpec-oaTOF instrument (Micromass). The resolving power was 10000 (10% valley definition).

Computational methods. Geometry optimizations were carried out with the B3LYP method[6] using the 6-31+G(d,p) basis within the Gaussian 98 program package.[7] Stationary points were characterized as either minima (no imaginary frequencies) or transition structure (one imaginary frequency) by calculation of the frequencies using analytical gradient procedures. The minima connected by a given transition structure were confirmed by intrinsic reaction coordinates (IRC) calculations. The frequencies and zero-point energies (ZPE) were calculated at the B3LYP/6-31G(d) level. The ZPE were scaled by 0.9806.[8] B3LYP single point calculations of energies were carried out using 6-311++G(d,p) basis set.

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References

1. Morzherin, Yu. Yu.; Kolobov, M. Yu.; Mokrushin, V. S.; Braeuer, M.; Anders, E.; Bakulev, V. A. *Khim. Gheterotsikl. Soed*. **2000**, *№ 1*, 26.
2. Lebedev, A. T.; Alekseeva, T. N.; Bakulev, V. A.; Kolobov, M. Yu.; Petrosyan, V. S. *Org. Mass Spectrom.* **1988**, *23*, 825.
3. Lebedev, A. T.; Bakulev, V. A.; Hayes, R. N.; Bowie, J. H. *Rapid Commun. Mass Spectrom.* **1991**, *5*, 234.
4. Dua, S.; Bowie, J. H. *J. Chem. Soc., Perkin Trans. 2* **2001**, 827.
5. Chapman, J. R. *Practical Organic Mass Spectrometry*, John Wiley & Sons: New York, 1985; p197.
6. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.
7. 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.; Rega, N.; Salvador, P.; Dannenberg, J. J.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; 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.; 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.11.3, Gaussian, Inc.: Pittsburgh, PA, 2002.

8. Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502.