2-Acetoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline and acetoxy(methoxy)carbene

Wojciech Czardybon, Arkadiusz Klys, John Warkentin, and Nick Henry Werstiuk

Abstract: 2-Acetoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline undergoes two competitive 1,3-dipolar cycloreversions at 110 °C. It loses N_2, presumably to afford a short-lived carbonyl ylide that fragments to acetone and acetoxy(methoxy)carbene. It also forms 2-diazopropane and the appropriate mixed anhydride. It is the only currently known source of acetoxy(methoxy)carbene.

Key words: acetoxy(methoxy)carbene, 2-diazopropane, 1,3-dipolar cycloreversion.

Résumé : À 110 °C, la 2-acétoxy-2-méthoxy-5,5-diméthyl-Δ^3-1,3,4-oxadiazoline subit deux réactions de cycloréversion 1,3-dipolaire compétitives. Elle perd du N_2, probablement pour fournir un ylure de carbonyle de temps de vie très court qui se fragmente en acétone et en acétoxy(méthoxy)carbène. Elle forme aussi du diazopropane et l'anhydride mixte approprié. C'est aussi la seule source actuellement connue d'acétoxy(méthoxy)carbène.

Mots clés : acétoxy(méthoxy)carbène, 2-diazopropane, cycloréversion 1,3-dipolaire.

[Traduit par la Rédaction]

Introduction

Although many alkylacetoxycarbenes have been studied (1–5) and found to rearrange by 1,2-acyl migration in competition with other intramolecular processes, such as 1,2 migration of H, acyloxy(alkoxy)carbenes appear to be unknown. They are interesting intermediates, without the possibility of a 1,2-H migration. They have the potential for rearrangement by migration of the acyl group to the carbenic site, as well as the potential for fragmentation to alkoxycarbonyl and acyl radicals. The 1,2-acyl migration of known acetoxy(alkyl)carbenes and the most likely reactions of acyloxy(alkoxy)carbenes are illustrated in Scheme 1.

We prepared and purified 2-acetoxy-2-methoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**1**) (6), which is a potential precursor of acetoxy(methoxy)carbene (**3**). 2,2-Dialkoxy-5,5-dimethyl-Δ^3-1,3,4-oxadiazolines undergo 1,3-dipolar cycloreversion by loss of N_2 at 110 °C to afford carbonyl ylides that fragment primarily to dialkoxycarbenes and acetone (7). There is a minor competitive 1,3-dipolar cycloreversion, in some cases, to 2-diazopropane (**4**) and dialkyl carbonate (8). Scheme 2 shows such cycloreversions for the case of **1**, which was expected to produce carbene **3**, via carbonyl ylide **2**, and perhaps 2-diazopropane (**4**) and the mixed anhydride **5**. Moreover the carbene might undergo a concerted rearrangement to methyl pyruvate (**6**) or a fragmentation to the methoxycarbonyl–acetyl radical pair that could couple to afford **6** also, Scheme 3.

We now describe the thermolysis of **1**, which does indeed lead to the formation of both carbene **3** and 2-diazopropane (**4**). At 110 °C in benzene, both the carbene and the diazopropane can be intercepted with chemical trapping agents.

Results and discussion

Thermolysis of **1** in benzene was studied in the absence of potential traps, in the presence of phenol (a carbene trap as well as a trap for diazo compounds and a hydrogen donor to radicals), in the presence of benzylidene malononitrile, and in the presence of TEMPO. TEMPO is a trap for radicals, and benzylidene malononitrile also can trap radicals, carbenes, and diazo compounds.

Thermolysis of **1** in benzene-d_6 containing internal standard *tert*-butylbenzene gave a complex mixture of products. Yields of **4** or of acetone azine from **1** are unreliable for estimation of the yield of the former, because diazopropane would react with the mixed anhydride co-product (**5**). The yield of acetone (presumably from the carbenic pathway) was found to be about 55% by integration of the acetone signal against those from the phenyl and *tert*-butyl groups of the internal standard. The two comparisons were in excellent agreement. Thus, the yield of acetoxymethoxycarbene was about 55% and that of 2-diazopropane about 45%. Methyl pyruvate was a major product (ca. 10%, isolated), but biacetyl and dimethyl oxalate, which might also be expected if the pyruvate had arisen by a radical coupling path, could not be detected by GC, with authentic samples in hand. It was also possible to detect (by GC) a trace of acetophenone, in keeping with the expectation that acetyl radicals would at-

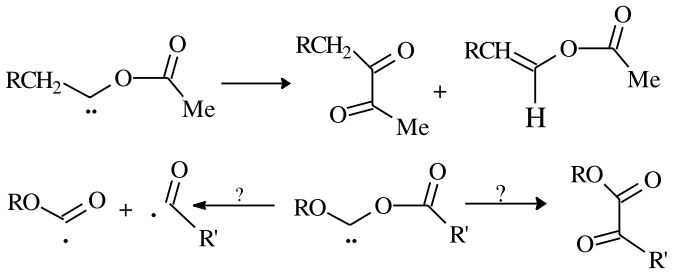
Received 23 May 2003. Published on the NRC Research Press Web site at http://canjchem.nrc.ca on 13 October 2003.

W. Czardybon, A. Klys, J. Warkentin,[1] and N.H. Werstiuk. Department of Chemistry, McMaster University, 1280 Main St. West, Hamilton, ON L8S 4M1, Canada.

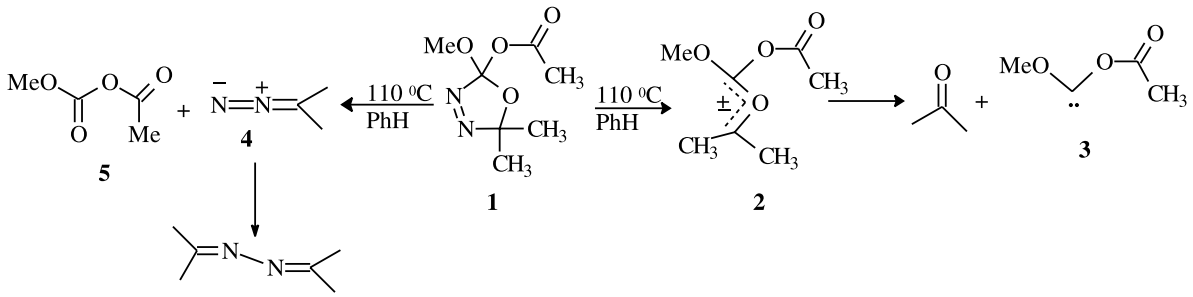
[1]Corresponding author (e-mail: warkent@mcmaster.ca).

 doi: 10.1139/V03-126

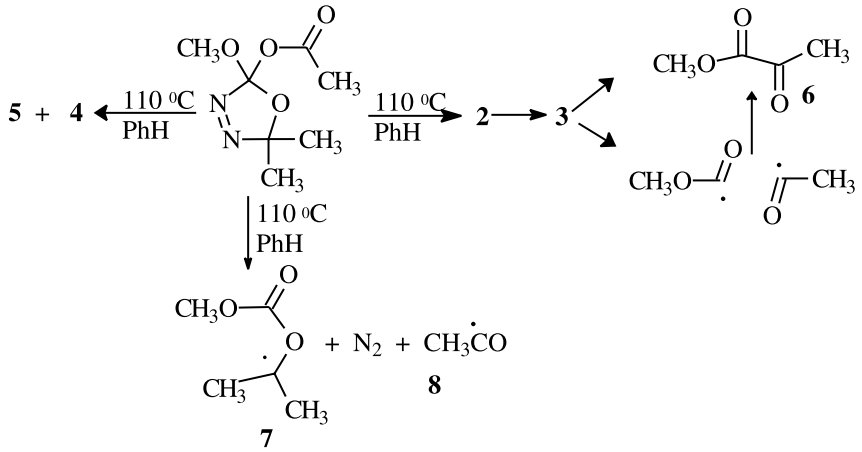
Scheme 1.



Scheme 2.



Scheme 3.



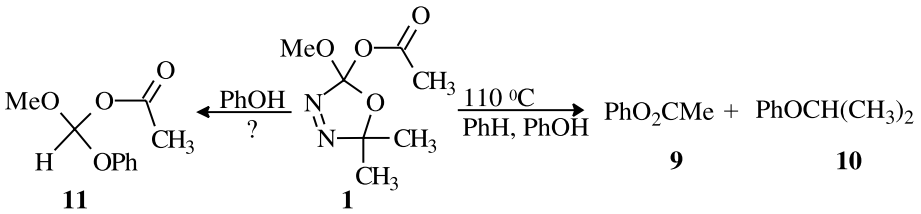
tack the benzene solvent. Thermolysis of **1** in the presence of TEMPO led to the isolation of enough of the known (9) TEMPO adduct of the acetyl radical (1-acetoxy-2,2,6,6-tetramethylpiperidine) for an NMR spectrum. However, the known adduct (10) of TEMPO with the methoxycarbonyl radical could not be found.

The results listed thus far are accounted for in terms of Scheme 3, which shows not only parallel 1,3-dipolar cycloreversions but also a radical decomposition of **1**. That minor radical decomposition is assumed to be concerted, leading to **7** and **8**. TEMPO would have trapped both **7** and **8** but the product expected from **7** was not identified. The failure to find any evidence for the methoxycarbonyl radical indicates that acetyl and methoxycarbonyl radicals are probably not formed by fragmentation of carbene **3**.

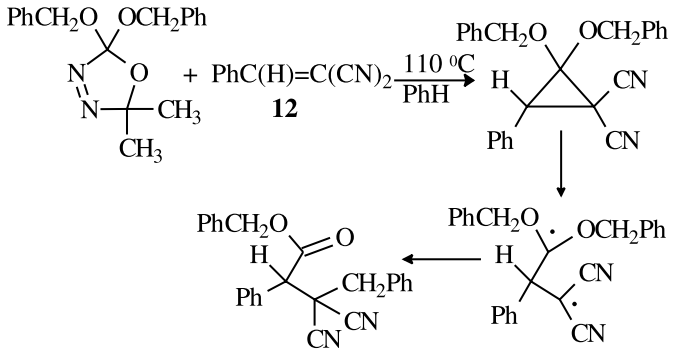
Thermolysis of **1** in benzene containing phenol gave **9** (31%) and **10** (5%) but not **11**. Compound **9** probably arises from a transesterification reaction with **1**, while **10** and **11** are expected products from reactions of **4** and **3**, respectively, with phenol, Scheme 4. Protonation of **3** and ion-pair collapse would generate **11**, which has never been reported. Such compounds may be unstable at 110 °C.

Benzylidene malononitrile (**12**) was very successful in trapping intermediates from the thermolysis of **1**. Dinitrile **12** had been useful in helping to sort out the chemistry of dibenzyloxycarbene and benzyloxy(methoxy)carbene (11) because it reacts fast with nucleophilic carbenes, making it possible to trap some of them before they can fragment to radical pairs, Scheme 5. Thermolysis of **1** in the presence of **12** did not furnish a carbene adduct. Instead, the methoxy-

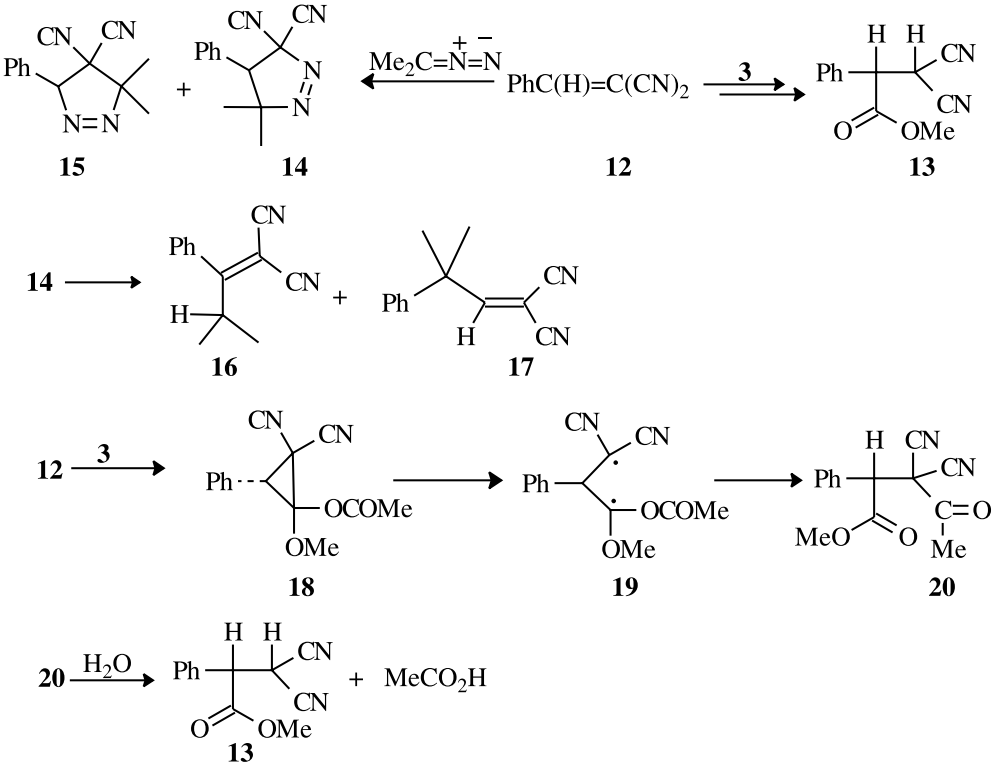
Scheme 4.



Scheme 5.



Scheme 6.



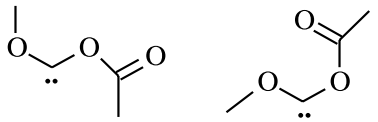
carbonyl radical, *apparently* resulting from carbene fragmentation to a radical pair, *appeared* to be trapped as **13** (30%), Scheme 6. Adduct **20**, expected on the basis of precedent (11) was not found, but **16** (17%) and **17** (12%) were also isolated.

The finding that **13** was formed from thermolysis of **1** in the presence of **12** but that **20** could not be found led us to search the literature for analogues of **20**. Such compounds hydrolyze spontaneously when exposed to the atmosphere (12), Scheme 6. Thus, the most likely explanation for the formation of **13** is trapping of a carbene intermediate with **12** to form diastereomers **18** and subsequent ring-opening fragmentation to diradical **19**, followed by fragmentation and coupling to **20**, according to Scheme 6. Subsequent

deacylation of **20** (12), once the sample is exposed to the atmosphere, leads to **13**.

The concentration of **12** was increased from 0.455 to 2.127 mol·L^{-1} to improve the chances of trapping carbene **3**. There was little change, suggesting that the lower concentration was sufficient to trap essentially all of **3**. Compounds **16** and **17** can be attributed to reaction of **4** in the expected sense with **12** to afford **14**, which then loses N_2, Scheme 6. The higher concentration of **12** did lead to two very minor products (not identified) that were detected by GC–MS. Those compounds, which gave essentially the same mass spectrum as **16** and **17**, might be derived from cycloaddition of **4** in the alternative sense to form **15**, Scheme 6. Alkylidene malononitriles are known to react with diazo compounds by cycloaddition, and the resulting 3*H*-pyrazoles, not surprisingly (13), lose N_2 at 110 °C to afford diradicals that rearrange. Both regiochemistries of addition of diazomethane to a β-phenyl-α,β-unsaturated sulfone have been reported (14). Although **16** and **17**, as well as the minor products with the same MS, can be accounted for on the basis of **14** alone, formation and decomposition of some of compound **15** cannot be excluded.

The concerted rearrangement of the carbene and its fragmentation to a radical pair were modeled computationally with Gaussian 98 at the Becke3PW91/6-31+G(d, p) level (15). Concerted carbene rearrangement from one of the pos-



21 **22**

sible sickle conformations (**21**) has the lowest barrier (14.6 kcal·mol^{-1}), whereas the lowest barrier to fragmentation (28.8 kcal·mol^{-1}) is that from a second sickle conformation (**22**). Details of the computational work, which includes the examination of a number of other conceivable pathways, will be published separately.[2]

In summary, oxadiazoline **1** undergoes two competing cycloreversions at 110 °C in benzene, leading to both carbene **3** and diazopropane **4**. A minor, third thermolysis mechanism, currently regarded as tentative, is a radical process that generates the acetyl radical and **7**. Carbene **3** does not fragment to radicals but rearranges to methyl pyruvate by a 1,2-acyl migration, like other acetoxycarbenes (1–5).

Although thermolysis of **1** is far from ideal, in that it generates **3** in only about 50% yield and the co-products complicate the thermolysis, it is the only reaction available today to generate acetoxy(methoxy)carbene.

Experimental

General

A Bruker AC-200 spectrometer was used to obtain ^{1}H and ^{13}C NMR spectra, with $CDCl_3$ as solvent and with the signal from residual $CHCl_3$ in $CDCl_3$ set at δ = 7.25. GC–MS mass spectra were recorded with a Hewlett-Packard 5890 gas chromatograph equipped with an HP-5971A mass selective detector and a DB-1 capillary column (12 m × 0.2 mm). Other mass spectra were obtained with a VG Analytical ZAB-E double focusing mass spectrometer.

Synthesis of 1

A solution of the carbomethoxy hydrazone of acetone (30 g, 0.23 mol) was added slowly to an ice-cooled heterogeneous mixture of $Pb(OAc)_4$ (115.3 g, 0.26 mol), acetic acid (1 mL), and CH_2Cl_2 (114 mL). The yellow mixture was stirred under N_2, warmed to 25 °C after addition was complete, and stirred for an additional 3 h. The mixture was then filtered through Celite and washed with 5% Na_2CO_3 solution. The water fraction was back-extracted twice with 20 mL of CH_2Cl_2, and the combined organic fraction was dried over Na_2SO_4 before the solvent was evaporated. The yellow oil that remained weighed 39 g (90%) and consisted of **1** (ca. 72%) and an acyclic isomer (Me_2C-(OAc)N=NCO_2Me) (ca. 28%).

Purification of 1

A yellow mixture of **1** and its acyclic isomer (5 g) was chromatographed as rapidly as possible on neutral alumina (35 g) with hexane – ethyl acetate (9:1). The solvents were evaporated from the combined colourless fractions, and the residue was distilled under vacuum (2–5 mmHg (1 mmHg = 133.322 Pa)) to afford 2.2 g of pure **1** (61%). IR (neat) (cm^{-1}): 1771. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.52 (s, 3H), 1.63 (s, 3H), 2.11 (s, 3H), 3.59 (s, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ: 21.44, 22.59, 24.49, 52.49, 122.15, 133.80, 161.67.

Thermolysis of 1 in benzene-d_6

A solution of **1** (0.157 mmol) and *tert*-butylbenzene (0.127 mmol) in C_6D_6 (0.7 mL) in an NMR tube fitted with a ground glass joint was degassed by means of three freeze–pump–thaw cycles before the tube was sealed and heated for 72 h at 110 °C. The ^{1}H NMR spectrum was acquired with the tube still sealed and with a pulse delay of 6 s to ensure complete relaxation of the acetone signal. Integrations of the acetone signal against those of the *tert*-butyl and aryl signals of *tert*-butyl benzene were in good agreement and gave the yield of acetone as 55%. Analysis by GC, with the column compartment cooled alternately to 7, 15, 21, and 32 °C, showed that methyl pyruvate (ca. 10%) and acetophenone (trace), both confirmed with authentic samples, were present. Biacetyl, dimethyl oxalate, acetaldehyde, and methyl formate were not detectable, as determined by injection of authentic samples under the same conditions, but there were peaks from unidentified volatile components.

Thermolysis of 1 in the presence of phenol

Thermolysis of **1** (1.596 mmol) in C_6H_6 (7 mL) containing phenol (3.191 mmol) gave a product mixture that was analyzed by GC. Major and minor products were phenylacetate (**9**) (ca. 30%) and isopropyl phenyl ether (**10**) (ca. 5%). The identities of those products were confirmed by GC of authentic samples prepared by standard methods. Acetaldehyde and methyl formate were not detectable.

[2] W. Czardybon, J. Warkentin, and N.H. Werstiuk. Unpublished results.

Thermolysis of 1 in the presence of 12

A solution of **1** (1.596 mmol) and **12** (3.188 mmol) in dry benzene (7 mL) was degassed by means of three freeze–pump–thaw cycles before it was sealed into a glass tube and heated for 72 h at 110 °C. The product mixture was analyzed by GC and separated by centrifugal chromatography on a 2 mm silica gel plate (Chromatotron apparatus, hexane: ethyl acetate = 4:1).

1-(Methoxycarbonyl-1-phenylmethyl)propanedinitrile (13)

Yield: 16%. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.80 (s, 3H), 4.20 (d, J = 8.65 Hz, 1H), 4.39 (d, J = 8.65 Hz, 1H), 7.33–7.34 (m, 2H), 7.43–7.46 (m, 3H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ: 27.09, 51.87, 53.76, 110.96, 111.60, 128.30, 129.87, 130.12, 131.68, 169.25. EI-MS *m*/*z*: 214 (13), 155 (26), 149 (34), 129 (35), 121 (100), 77 (38). HR-MS *m*/*z* calcd. for $C_{12}H_{10}N_2O_2$: 214.0742; found: 214.0736.

2-Methyl-1-(phenylpropylidene)propanedinitrile (16)

Yield: 17%. ^{1}H NMR (200 MHz, $CDCl_3$) δ:1.19 (d, J = 6.9 Hz, 6H), 3.46 (sept. J = 6.9 Hz, 1H), 7.31–7.39 (m, 5H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ: 20.66, 36.40, 86.90, 111.84, 112.13, 126.95, 128.96, 130.58, 134.09, 186.90. EI-MS *m*/*z*: 196 (58), 181 (100), 154 (79), 127 (64), 115 (55), 77 (62). HR-MS *m*/*z* calcd. for $C_{13}H_{12}N_2$: 196.1000; found: 196.0975.

2-(Methyl-2-phenylpropylidene)propanedinitrile (17) (16)

Yield: 12%. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.68 (s, 6H), 7.31–7.39 (m, 6H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ: 28.03, 44.24, 87.01, 110.40, 113.18, 126.39, 128.06, 129.23, 143.65, 176.02. EI-MS *m*/*z*: 196 (44), 181 (100), 154 (99), 127 (58), 115 (50), 78 (39), 77 (67).

Acknowledgements

JW and NHW gratefully acknowledge the financial support of NSERC.

References

1. M. Békhazi and J. Warkentin. J. Org. Chem. **47**, 4870 (1982).
2. R.A. Moss, S. Xue, and W. Liu. J. Am. Chem. Soc. **116**, 1583 (1994).
3. R.A. Moss, S. Xue, W. Liu, and K. Krogh-Jespersen. J. Am. Chem. Soc. **118**, 12 588 (1996).
4. R.A. Moss, S. Xue, W. Ma, and H. Ma. Tetrahedron Lett. **38**, 4379 (1997).
5. R.A. Moss and D.C. Merrer. Tetrahedron Lett. **39**, 8067 (1998).
6. K. Kassam, D.L. Pole, M. El-Saidi, and J. Warkentin. J. Am. Chem. Soc. **116**, 1161 (1994).
7. M. El-Saidi, K. Kassam, D.L. Pole, T. Tadey, and J. Warkentin. J. Am. Chem. Soc. **114**, 8751 (1992).
8. N. Merkley, M. El-Saidi, and J. Warkentin. Can. J. Chem. **78**, 356 (2000).
9. B. Capon and D.McL.A. Grieve. J. Chem. Soc. Perkin Trans. 2, 300 (1980).
10. P.C. Venneri and J. Warkentin. J. Am. Chem. Soc. **120**, 11 182 (1998).
11. N. Merkley, P.C. Venneri, and J. Warkentin. Can. J. Chem. **79**, 312 (2001).
12. R. Sommer, E. Müller, and W.P. Neumann. Liebigs Ann. Chem. **718**, 11 (1968).
13. F.A. da Silva, A.B.B. Ferreira, and M.G. Neumann. J. Braz. Chem. Soc. **10**, 375 (1999).
14. W.E. Parham, F.D. Blake, and D.R. Theissen. J. Org. Chem. **27**, 2415 (1962).
15. 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, 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. Komaromi, 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, and J.A. Pople. Gaussian 98 [computer program]. Gaussian, Inc., Pittsburgh, PA. 1998.
16. J. Bus, H. Steinberg, and Th.J. de Boer. Monatsh. Chem. **98**, 1155 (1967).