N-Methoxy-1,2,4-Dioxazolidines by Ozonolysis Reactions

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Ozonolysis of ethyl vinyl ether (**7a**) in the presence of the *O*-methylated oxime of cyclohexanone (**8**) afforded *N*-methoxy-1,2-dioxa-4-azaspiro[4.5]decane (**9a**), and ozonolyses of the *O*-methylated dioximes of 1,4- and 1,5-dicarbonyl compounds (**10a−e**) afforded *N*-methoxylated bicyclic 1,2,4-dioxazolidines (**12a−e**).

Introduction

It has been reported that ozonolyses of a large variety of vinyl ethers (**1**) in the presence of a number of imines (**3a**) afford the corresponding monocyclic 1,2,4-dioxazolidines (**4a**) by [3 + 2]-cycloadditions of the carbonyl oxides **2** derived from **1** and the C=N moieties in the imines **3a**.[2,3] Competitive reactions showed that the unsubstituted carbonyl oxide reacts faster with imines **3a** to give **4a** than with ketones **5** to give ozonides **6**, whereas disubstituted carbonyl oxides did not react with imines.[2,3]
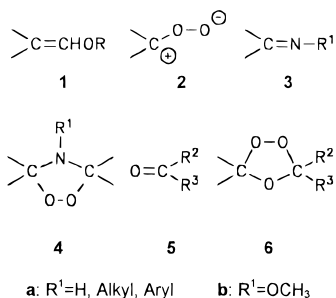
O-methyl oximes (**3b**) are also cleaved by ozone to give carbonyl oxides **2**.[4] Recently, we have made use of this by ozonizing a variety of *O*-methylated ketooximes (**3b**) in the presence of a large number of ketones (**5**) to prepare otherwise inaccessible tetrasubstituted ozonides (**6**).[5] In none of these reactions could we find evidence for the formation of *O*-methoxy substituted 1,2,4-dioxazolidines (**4b**), i.e., in the presence of ketones, disubstituted carbonyl oxides apparently do not undergo cycloadditions with disubstituted *O*-methyl oximes. In the present work, we have examined whether carbonyl oxides can undergo cycloadditions with *O*-methyl oximes in the absence of added ketones.

Results

Ozonolysis of ethyl vinyl ether (**7a**) in the presence of one mol equiv of *O*-methyl cyclohexanoneoxime (**8**) in

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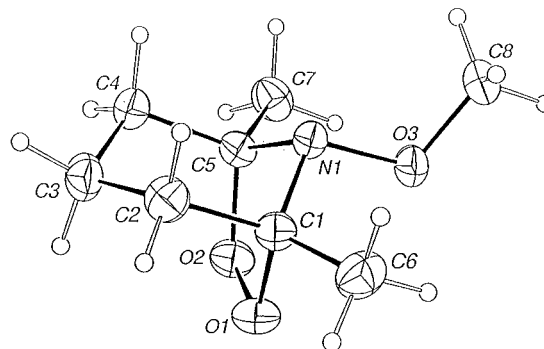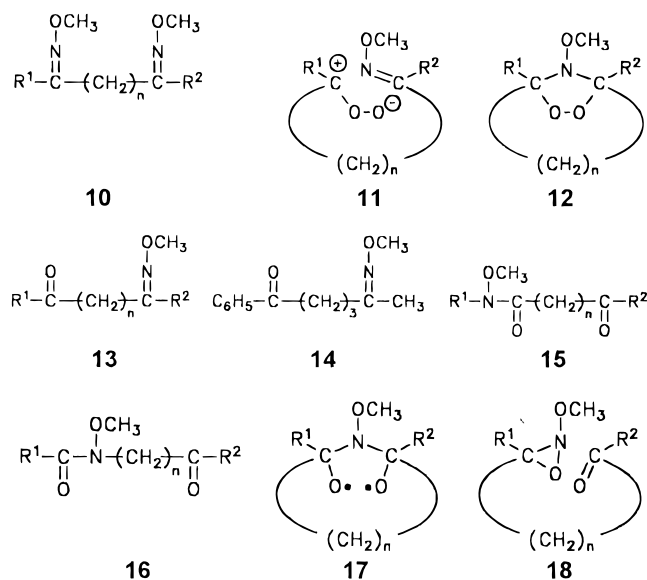(5) Griesbaum, K.; Liu, X.; Kassiaris, A.; Scherer, M. *Liebigs Ann.* **1997,** 1381.

Figure 1. Graphical representation of **12c** by ORTEP with thermal ellipsoids at the 50% probability density level. Hydrogen atoms are drawn as open circles of arbitrary size.

CH$_2$Cl$_2$ afforded 13% of the stable compound **9a**. By contrast, ozonolyses of **7b** and of **7c** in the presence of **8** under the same conditions did not provide **9b** and **9c**, respectively. The structural assignment of **9a** is based on the appearance of ^{13}C NMR signals at δ 89 and 102.68 for the C-atoms in the heterocyclic ring and of ^{17}O NMR signals at δ 269 and 308 for the peroxide group. Reduction of **9a** with triphenyl phosphine (TPP) gave cyclohexanone and the *O*-methyl oxime of formaldehyde in a molar ratio of ca. 1:1.
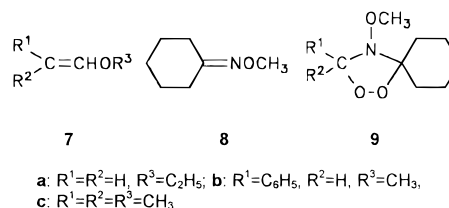
On the basis of the above experience, monoozonolyses of *O*-methylated dioximes (**10**) of dicarbonyl compounds would not be expected to give the corresponding bicyclic products **12** since such ozonolyses generate the mono- or disubstituted carbonyl oxides **11**. However, ozonolyses of **10a−e** did provide the corresponding bicyclic dioxazolidines **12** in yields of 24−50%. As neat samples, **12a−c** were stable, whereas **12d,e** decomposed slowly at room temperature. In CDCl$_3$ or upon prolonged contact with silica gel, **12a** also underwent gradual transformation into a product of unknown identity. Ozonolysis of **10f** gave a peroxidic crude product which decomposed with detonation immediately after the solvent was distilled off.

	a	b	c	d	e	f
n	3	3	3	3	2	1
R^1	H	CH_3	CH_3	CH_3	CH_3	CH_3
R^2	H	H	CH_3	C_6H_5	CH_3	CH_3
Yield of **12** (%)	24	28	50	24	34	0

The structural assignments of compounds **12a**–**e** are based on the appearance of ^{13}C NMR signals in the range of δ 95–105 for the carbon atoms in the heterocyclic rings. The assignments of **12a**–**c** were further supported by ^{15}N NMR signals in the range of δ 203–210 and by ^{17}O NMR signals in the range of δ 304–311 for the peroxide groups. The structure of **12c** was additionally proven by X-ray diffraction (Figure 1). Atoms C(3), H(3a), H(3b), N(1), O(3), C(8), and H(8c) lie on a local mirror plane that is not necessitated by space group requirements, while all other atoms have a mirror-related counterpart in accordance with the NMR spectra; for instance, C(1) is equivalent to C(5). This intrinsic symmetry is further reflected by the observed pattern of interatomic distances and angles (see Supporting Information) and by the envelope conformation of the dioxazolidine ring. Atom N(1) deviates by 63 pm from the least-squares plane through the atoms C(1), O(1), O(2), and C(5). With a length of 148.2(1) pm the peroxide bond is at the upper limit of the expected range,[6] which may be due to the unfavorable ecliptic orientation of the electron lone pairs at O(1) and O(2).[7]

Reductions of **12a**–**c** and **12e** with TPP gave the corresponding monooximes **13**, whereas reduction of **12d** afforded both of the two possible monooximes **13d** and **14**. Decomposition of the labile **12e** in CDCl₃ at room temperature also produced monooxime **13e**, but decomposition of the labile **12d** in CDCl₃ gave the substituted amides **15d** and **16d** in a ratio of 7:3. Their formation may be explained by cleavage of the peroxide bond of **12d**

to give diradical **17d**, by analogy with the postulated course of decomposition of compounds **4a**.[3] Further reaction of diradical **17d** may produce the oxaziridine **18d**, which—in line with previously postulated reactions of oxaziridines[4]—may be converted into **15d** and **16d**. The fact that the isomeric amides **15** and **16** with $R^1 = C_6H_5$ and $R^2 = CH_3$ were not formed may be due to resonance stabilization of the incipient ketone moiety by the phenyl group.

In conclusion, the present investigation has revealed that the known principle of cycloadditions of carbonyl oxides (**2**) with imines (**3**) to give dioxazolidines (**4**)[2,3] can be extended to the cycloaddition of the unsubstituted carbonyl oxide **7a**, yet not of the substituted carbonyl oxides **7b** and **7c** with the *O*-methylated oxime **8** to give a *N*-methoxy-substituted dioxazolidine (**9a**). This, together with the fact that no *N*-methoxydioxazolidines (**4b**) had been obtained in ozonolysis reactions of *O*-methylated oximes (**3b**) in the presence of ketones (**5**),[4] indicates that, in contrast to alkyl or aryl imines,[2,3] *O*-methylated oximes are poorer dipolarophiles than ketones. Furthermore, ozonolyses of *O*-methylated dioximes (**10**) opened for the first time a one-step synthesis for bicyclic *N*-methoxy-substituted 1,2,4-dioxazolidines. Compounds **9a** and **12a**–**f** are the first examples of *N*-methoxy substituted 1,2,4-dioxazolidines.

Experimental Section

General. ^1H,[5] ^{13}C,[5] and ^{17}O[8] NMR spectra were recorded on a Bruker AC 250, as reported previously. ^{15}N NMR spectra (CDCl₃, NH₄NO₃ external) were collected with a Bruker DRX-500. Chromatographic separations were done with flash chromatography on silica gel.

Substrates **7a**–**c** are commercially available. Substrates **8** and **10a**–**f** were prepared according to a published procedure[9] by reactions of the corresponding carbonyl compounds with an excess of *O*-methyl hydroxylamine hydrochloride, and isolated by flash chromatography. As shown by GLC analysis, compounds **10a**–**c**,**e**,**f** were obtained as mixtures of three isomers, each, whereas only two isomers of **10d** were obtained. In each case, the isomer with the shorter elution time was the predominant one and has been isolated and characterized: **10a** [^1H NMR: δ 1.70 (m), 2.20 (q), 3.81 (s), 7.36 (t). ^{13}C NMR: δ 23.77, 28.90, 61.54, 149.74.]; **10b** [^1H NMR: δ 1.70 (m), 1.83 (s), 2.21 (m), 3.81 (s), 3.82 (s), 7.36 (t). ^{13}C NMR: δ 13.87, 23.50, 25.11, 35.16, 61.10, 61.54, 150.05, 156.20.]; **10c** [^1H NMR: δ 1.73 (m), 1.82 (s), 2.18 (t), 3.82 (s). ^{13}C NMR: δ 13.78, 23.78, 35.24, 60.95, 156.71.]; **10d** [^1H NMR: δ 1.78 (m), 2.22 (t), 2.75 (t), 3.82 (s), 3.96 (s), 7.30–7.40 (m), 7.60–7.70 (m). ^{13}C NMR: δ 13.77, 23.19, 26.06, 35.78, 61.06, 61.80, 126.24, 128.40, 128.99, 135.68, 156.73, 157.95.]; **10e** [^1H NMR: δ 1.84 (s), 2.38 (s), 3.82 (s). ^{13}C NMR: δ 13.98, 32.68, 61.12, 156.25; identical with lit. data.[10]]; **10f** [^1H NMR: δ 1.80 (s), 3.01 (s), 3.86 (s). ^{13}C NMR: δ 13.42, 42.30, 61.41, 153.76.].

Ozonolysis Procedure. A solution of the respective substrate(s) in pentane and/or in dichloromethane was treated with ozone until the solution turned blue. Residual ozone was flushed off with nitrogen, the solvent was distilled off at room temperature and reduced pressure, and from the remaining residue, the products were isolated by flash chromatography.

Reduction Reactions. A solution of a dioxazolidine in 1 mL of CDCl₃ was admixed with excess TPP in a NMR tube and kept at room temperature until ^1H NMR analysis showed the disappearance of the substrate. The products were as-

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signed on the basis of comparison of their ^{1}H and ^{13}C NMR data with those of authentic samples.

Ozonolysis of 7a in the Presence of 8. A solution of 0.88 g (12.2 mmol) of **7a** and 1.55 g (12.2 mmol) of **8** in 60 mL of dichloromethane was ozonized at −78 °C. From the liquid residue of 1.77 g, we isolated 0.27 g (13%) of **9a** [solvent: petroleum ether/ether, 19:1 (1000 mL), 1:1 (500 mL), acetone (500 mL)].

N-Methoxy-1,2-dioxa-4-azaspiro[4.5]decane (9a): colorless liquid. ^{1}H NMR: δ 1.40−1.55 (m, 2 H), 1.55−1.75 (m, 6 H), 1.85−2.15 (m, 2 H), 3.62 (s, 3 H), AB-system δ$_A$ 4.86, δ$_B$ 4.95 (J = 7.0 Hz, 2 H). ^{13}C NMR: δ 23.29, 23.83, 25.15, 28.73, 35.15, 62.07, 89.00, 102.68. ^{17}O NMR: δ 109 (s), 269 (s), 308 (s). Anal. Calcd for C$_8$H$_{15}$NO$_3$ (173.2): C, 55.47; H, 8.73; N, 8.09. Found: C, 55.58; H, 8.60; N, 8.08.

Reduction of **9a** for 24 h gave cyclohexanone [^{1}H NMR: δ 2.28−2.38 (m)] and the *O*-methylated oxime of formaldehyde[11] [^{1}H NMR: δ 3.89 (s, 3 H), AB-system δ$_A$ 6.41, δ$_B$ 7.00 (J = 8.3 Hz, 2 H). ^{13}C NMR: δ 61.71, 136.86.], as evidenced with the help of authentic samples.

Ozonolysis of 7b in the Presence of 8. A solution of 0.90 g (6.7 mmol) of **7b** and 0.85 g (6.7 mmol) of **8** in 60 mL of dichloromethane was ozonized at −78 °C. From the liquid residue of 1.93 g we isolated 0.44 g (49%) of **7b** and 0.70 g (82%) of **8** (solvents as above).

Ozonolysis of 7c in the Presence of 8. A solution of 0.60 g (7.0 mmol) of **7c** and 0.89 g (7.0 mmol) of **8** in 60 mL of dichloromethane was ozonized at −78 °C. The viscous residue of 1.25 g was treated with pentane to give 0.30 g of a peroxidic precipitate. From the pentane solution the solvent was distilled off at room temperature and reduced pressure, and from the liquid residue of 0.91 g, we isolated 0.72 g (81%) of **8** (solvents as above).

Ozonolysis of 10a. Ozonolysis of 0.67 g (4.2 mmol) of **10a** in 50 mL of pentane and 10 mL of dichloromethane gave 0.80 g of a viscous residue, from which 0.15 g (24%) of **12a** and 0.04 g of an unassigned byproduct were isolated (petroleum ether/ether, 6:1).

N-Methoxy-6,7,8-dioxazo-bicyclo[3.2.1]octane (12a): colorless liquid. ^{1}H NMR: δ 1.30−1.60 (m, 1 H), 1.60−2.00 (m, 5 H), 3.64 (s, 3 H), 5.36 (d, J = 4.6 Hz, 2 H). ^{13}C NMR: δ 14.34, 30.82, 60.74, 95.45. ^{17}O NMR: δ 117 (s), 304 (s). ^{15}N NMR: δ 203 (s). Anal. Calcd for C$_6$H$_{11}$NO$_3$ (145.2): C, 49.65; H, 7.64; N, 9.65. Found: C, 49.60; H, 7.67; N, 9.60.

Unassigned byproduct: colorless liquid. ^{1}H NMR: δ 1.70 (m, 2 H), 2.02 (m, 2 H), 2.45 (m, 2 H), 3.80 (s, 3 H), 5.28 (t, J = 5.4 Hz, 1 H). ^{13}C NMR: δ 16.33, 30.85, 33.28, 62.60, 81.20, 168.73.

Reduction of 12a. After 5 d, **12a** had disappeared and two isomers of **13a** as well as the unassigned byproduct were present in relative amounts of 54%, 18%, and 28%, respectively, as evidenced by ^{1}H NMR analysis with the help of authentic samples [**13a**, isomer 1:[5] δ 3.81 (OCH$_3$), 7.35 (HC=N). **13a**, isomer 2:[5] δ 3.86 (OCH$_3$), 6.63 (H−C=N). Unassigned product: δ 3.80 (OCH$_3$).].

Decomposition of 12a in CDCl$_3$. One drop of **12a** in 1 mL of CDCl$_3$ was kept at room temperature for 2 weeks. ^{1}H NMR analysis showed the presence of only the unassigned byproduct.

Ozonolysis of 10b. Ozonolysis of 0.45 g (2.6 mmol) of **10b** in 60 mL of pentane gave 0.47 g of a viscous residue, from which 0.12 g (28%) of **12b** was isolated [petroleum ether/ether, 17:3 (1000 mL), 1:1 (500 mL)].

N-Methoxy-1-methyl-6,7,8-dioxazobicyclo[3.2.1]-octane (12b): colorless liquid. ^{1}H NMR: δ 1.35−1.75 (m, 1 H), 1.56 (s, 3 H), 1.80−2.10 (m, 5 H), 3.66 (s, 3 H), 5.33 (d, J = 4.6 Hz, 1 H). ^{13}C NMR: δ 16.09, 16.66, 31.27, 37.18, 61.78, 97.36, 101.16. ^{17}O NMR: δ 106, 308. ^{15}N NMR: δ 207. Anal. Calcd for C$_7$H$_{13}$NO$_3$ (159.2): C, 52.82; H, 8.23; N, 8.80. Found: C, 52.60; H, 8.27; N, 8.71.

Reduction of 12b. After 12 h, **12b** had disappeared and **13b** was shown to be the sole product of reduction by ^{1}H NMR [δ 1.77 (m), 2.13 (s), 2.17 (q), 2.48 (t), 3.80 (s)][5] and ^{13}C NMR analysis [δ 20.40, 28.62, 29.78, 42.33, 61.07, 207.67].

Ozonolysis of 10c. Ozonolysis of 0.74 g (4.0 mmol) of **10c** in 60 mL of pentane gave 0.73 g of a viscous residue, from which 0.34 g (50%) of **12c** was isolated [petroleum ether/ether, 9:1 (1000 mL), 1:1 (500 mL)].

1,5-Dimethyl-N-methoxy-6,7,8-dioxazobicyclo[3.2.1]-octane (12c): colorless solid, mp 36 °C. ^{1}H NMR: δ 1.55 (s, 3 H), 1.40−1.63 (m, 1 H), 1.80−2.10 (m, 5 H), 3.66 (s, 3 H). ^{13}C NMR: δ 17.23, 17.56, 37.66, 62.79, 102.67. ^{17}O NMR: δ 91 (s), 311 (s). ^{15}N NMR: δ 210 (s). Anal. Calcd for C$_8$H$_{15}$-NO$_3$ (173.2): C, 55.47; H, 8.73; N, 8.09. Found: C, 55.44; H, 8.87; N, 8.07.

Reduction of 12c. After 15 d, **12c** had disappeared and two isomers of **13c** were present as the sole products of reduction as evidenced by ^{1}H NMR [**13c**, isomer 1 (32%): δ 1.85 (s), 3.78 (s). **13c**, isomer 2 (68%): δ 1.81 (s), 3.81 (s).] and ^{13}C NMR analysis [**13c**, isomer 1: δ 157.04 (C=N), 207.55 (C=O). **13c**, isomer 2: δ 156.69 (C=N), 208.10 (C=O).] with the help of authentic samples.[5]

Crystal Structure Determination of 12c. Long prismatic needles are formed if a concentrated petroleum ether solution of **12c** is cooled to −20 °C. A single-crystal of suitable size (0.9 × 0.5 × 0.4 mm^3) was cut from such a needle. Crystal data: C$_8$H$_{15}$NO$_3$, fw = 173.2 g mol^{-1}, monoclinic, C2/c (no. 15), a = 1538.4(3) pm, b = 1000.8(2) pm, c = 1376.6(2) pm, $β$ = 119.87(1)°, Z = 8, D_{calcd} = 1.252 mg mm^{-3}, T = −90(2) °C.

Intensity data collection was performed with a Stoe four-circle diffractometer equipped with a graphite monochromator (Mo Kα radiation) and a low-temperature attachment LT-1 of Nicolet. Altogether 4374 reflections ±h,k,±l were measured up to the limit of 2θ = 55° applying the method of learnt profiles[12] and ω/θ scans: basic width 34 steps, extra steps for α$_1$/α$_2$ dispersion, counting times between 0.5 and 1.5 s per step depending on intensity I/σ(I). Corrections were made for background rate, Lorentz and polarization factors, and the intensity loss (<1.1%) of three standard reflections recorded every 2 h.

The structure was solved by direct methods (SHELXS-86) and refined on F_o^2 data with anisotropic temperature factors for C, N, and O (SHELXL-93). All hydrogen atoms appeared in a difference Fourier synthesis. Their positions were refined with individual isotropic temperature parameters giving the final residuals R_1 = 0.031 for 1878 reflections, $F_o > 4σ$ (F_o), R_1 = 0.036 for all 2101 independent reflections, wR_2 = 0.084, 169 structure parameters. At this stage a difference density map showed no feature above 0.28e/10^6 pm^3 (see Supporting Information).

Ozonolysis of 10d. Ozonolysis of 0.80 g (3.2 mmol) of **10d** in 40 mL of pentane and 20 mL of CH$_2$Cl$_2$ gave 0.82 g of a viscous residue, from which 0.18 g (24%) of **12d** was isolated [petroleum ether/ether, 9:1 (1000 mL), 1:1 (500 mL)].

N-Methoxy-1-methyl-5-phenyl-6,7,8-dioxazobicyclo-[3.2.1]octane (12d): colorless liquid. ^{1}H NMR: δ 1.60 (s, 3 H), 1.65 (m, 1 H), 1.90−2.50 (m, 5 H), 3.25 (s, 3 H), 7.20−7.50 (m, 3 H), 7.50−7.70 (m, 2 H). ^{13}C NMR: δ 17.56, 17.65, 37.56, 38.65, 62.31, 103.58, 105.10, 126.06, 127.88, 127.94, 136.66.

Reduction of 12d. After 14 h, **12d** had disappeared. ^{1}H NMR analysis showed the presence of **13d** [17%; δ 2.10 (s, CH$_3$C=O)], **14** [26%; δ 1.85 (s, CH$_3$C=N)], **15d** [36%; δ 3.16 (s, CH$_3$N)], and **16d** [21%; δ 2.14 (s, CH$_3$C=O)].

Decomposition of 12d. A solution of one drop of **12d** in 1 mL of CDCl$_3$ was heated to 40 °C in a sealed NMR tube. ^{1}H NMR analysis after 30 h showed the presence of **15d** (69%) and **16d** (31%).

Ozonolysis of 10e. Ozonolysis of 0.71 g (4.1 mmol) of **10e** in 60 mL of pentane gave 0.65 g of a viscous residue, from which 0.22 g (34%) of **12e** was isolated (petroleum ether/ether, 9:1).

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N-Methoxy-1,4-dimethyl-2,3,7-dioxazobicyclo[2.2.1]-heptane (12e): colorless liquid. ^{1}H NMR: δ 1.53 (s, 6 H), 1.80−2.05 (m, 4 H), 3.69 (s, 3 H). ^{13}C NMR: δ 12.99, 30.80, 62.89, 101.68.

Reduction of 12e. After 1 h, **12e** had disappeared and **13e** was shown to be the sole product of reduction by ^{1}H NMR [δ 1.82 (s), 2.19 (s), 2.45 (t, J = 6.9 Hz), 2.68 (t, J = 7.3 Hz), 3.80 (s)] and ^{13}C NMR analysis (δ 14.55, 29.90, 30.01, 39.17, 61.12, 155.51, 207.43) with the help of an authentic sample.[5]

Decomposition of 12e. One drop of **12e** in 1 mL of CDCl$_3$ was kept at room temperature for 7 h to give **13e** as the sole product as shown by ^{1}H and ^{13}C NMR analysis.

Ozonolysis of 10f. Ozonolysis of 0.60 g (3.8 mmol) of **10f** in 60 mL of pentane gave a residue which decomposed with detonation at room temperature. In a second experiment, the solvent was not completely removed to leave 7 mL of a concentrated solution. When this was placed on a chromatographic column, a spontaneous, exothermic decomposition occurred.