Host–Guest Systems

Fluorophenoxycarbene inside a Hemicarcerand: A Bottled Singlet Carbene[**]

Xuejun Liu, Gaosheng Chu, Robert A. Moss, Ronald R. Sauers,* and Ralf Warmuth**

The reactivity, selectivity, and stability of singlet carbenes are strongly dependent on the carbenes' substituents.[1] Indeed, the intrinsic stabilization of carbenes by electron donation from their substituents and steric crowding permits "tuning" of the carbenes' chemical properties and life-times. This stabilization enables the generation of the fleeting and voraciously electrophilic singlet methylene (CH_2) species,[2] through the long-lived triplet bis[9-(10-phenyl)anthryl]carbene[3] to such stable and isolable species as the phosphorus-stabilized singlet carbene $(i\mathrm{Pr})_2\mathrm{PCSiMe}_3$[4] and the amine-stabilized Arduengo carbene 1,3-di-(1-adamantyl)imidazol-2-ylidene[5a] or $(i\mathrm{Pr})_2\mathrm{NCN}(i\mathrm{Pr})_2$.[5b] Extrinsic stabilization through confinement inside a molecular container should provide additional stabilization to carbenes.[6] In fact, incarceration in the inner phase of a hemicarcerand is one of the most powerful approaches for the room-temperature stabilization of highly reactive intermediates.[7] The surrounding host protects the guest from dimerization or reaction with bulk-phase species that are too large to enter the inner phase. We report herein the first example of a normally nonisolable, fleeting singlet carbene that is rendered persistent by incarceration. We selected fluorophenoxycarbene (**1**) as our target for three reasons: it is sufficiently stabilized by its substituents (calculated stabilization energy = 60 kcal mol^{-1} relative to the singlet methylene species[1c]) that C–H insertion or C=C addition reactions with a hemicarcerand host are unlikely, its size should result in a good fit within host **2**, and it carries a NMR-sensitive fluorine "label".

Treating diol **3**[7c] with $\mathrm{MsO(CH_2)_4OMs}$ (Ms = SO_2Me), Cs_2CO_3, and excess 3-fluoro-3-phenoxydiazirine (**4**)[8] in hexamethylphosphoramide gave the hemicarceplex **2·4** in 23 % yield. Photolysis of **2·4** in degassed CD_2Cl_2 ($\lambda > 320$ nm, 77 K) produced a new hemicarceplex in 93 % yield on the basis of integration of the ^{1}H NMR spectrum (Figure 1 a,b).[9]

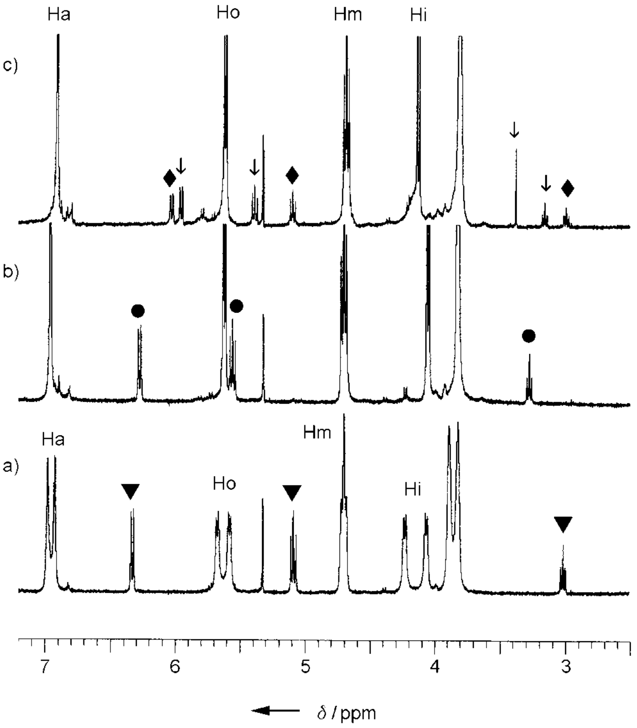
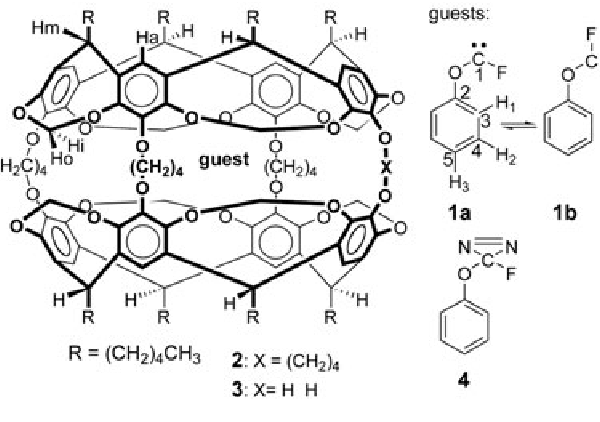


Figure 1. Partial ^{1}H NMR spectra (399.969 MHz, CD_2Cl_2, 25 °C) of the hemicarceplex **2·4**: a) before and b) after photolysis ($\lambda > 320$ nm, 77 K, 4 h). c) Same solution as (b) after complete decomposition. The signals assigned to the protons of the incarcerated **4** (▼), **1** (●), **5** (↓), and **6** (◆) are marked.



The UV absorption of **2** decreases sharply above 275 nm. Thus, it must be the guest **4** that absorbs light at the wavelengths used in the photolysis experiments ($\lambda >$ 320 nm). We assigned the newly formed hemicarceplex as the fluorophenoxycarbene hemicarceplex **2·1** on the basis of: the photochemistry of free **4**, which quantitatively produces **1**;[8] the ^{1}H NMR spectroscopic properties of this hemicarceplex (see below); and trapping experiments. Trapping experiments at 25 °C in CD_2Cl_2 (containing small amounts of water) showed **2·1** reacted very slowly over several days to form the phenyl formate hemicarceplex **2·5** and the phenyl-(difluoromethyl) ether hemicarceplex **2·6** (Figure 1 b,c). The

---

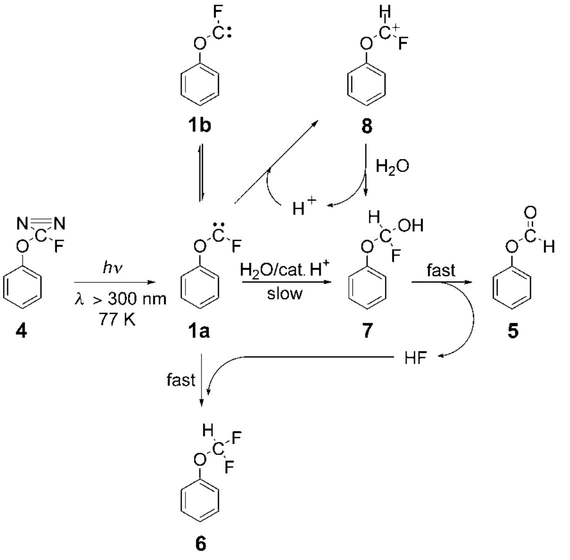
[*] X. Liu, Dr. G. Chu, Prof. R. A. Moss, Prof. R. R. Sauers, Prof. R. Warmuth
Department of Chemistry and Chemical Biology
Rutgers, The State University of New Jersey
610 Taylor Road, Piscataway, NJ 08854 (USA)
Fax: (+1) 732-445-5312
E-mail: moss@rutchem.rutgers.edu
sauers@rutchem.rutgers.edu
warmuth@rutchem.rutgers.edu

[**] This research was supported by the NSF (Grants CHE-0431749 to R.W. and CHE-0345240 to R.A.M.) and Rutgers University. We thank Dr. Seho Kim for assistance with NMR spectroscopic experiments and Prof. Karsten Krogh-Jespersen for helpful suggestions.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

DOI: 10.1002/ange.200462633

hemicarceplex **2·5** was identified by comparison with an authentic sample prepared by heating empty **2** in neat **5**, whereupon **5** enters **2** (150 °C, 48 h, 58 % yield).[7b] The hemicarceplex **2·6** gave FAB-MS, ^{1}H NMR, and ^{19}F NMR spectra that are fully consistent with its structure. For example, the ^{19}F NMR spectrum shows a doublet at $\delta_F = -82.9$ ppm ($^2J_{HF} = 73.3$ Hz) which is almost identical to that of free **6** ($\delta_F = -81.39$ ppm, $^2J_{HF} = 74$ Hz).[10] We rationalize the formation of **2·5** and **2·6** in almost equal amounts as follows: bulk phase water enters the inner phase and reacts with **1** to give the hemiacetal **7**, which subsequently loses HF. The HF is extruded from the inner phase and rapidly enters another hemicarceplex **2·1**, where it reacts with **1** to yield **6** (Scheme 1). The concentrations of HF and **2·7** were below the NMR detection limit, which shows that fragmentation of **7** and addition of HF to **1** are much faster than the acid-catalyzed addition of water to encapsulated **1**.



Scheme 1. Photolysis of **4** and reactions of **1** in the inner phase of **2**.

If [D$_5$]pyridine is added to the sample before photolysis, **2·1** persists for days without any decomposition (Figure 2). This shows that the addition of water is acid-catalyzed (Scheme 1, **1a**→**8**→**7**) and that water is not acidic enough in the hydrophobic inner phase of **2** to trap **1**, presumably because of the high energetic cost of charge separation to form [**8**]$^+$OH$^-$.[7e] It also suggests that **7** does not form from **1** by an ylide pathway, which would not be inhibited by pyridine. Thus, the following factors lead to the remarkable stability of **2·1**: 1) the incarceration of **1** which inhibites dimerization;[11] 2) the hydrophobicity of the inner phase; and, possibly, 3) the stabilization effect of the carbene–π interactions.[6,12] In the absence of a base, trace amounts of DCl in CD$_2$Cl$_2$ initiate the catalytic cycle shown in Scheme 1 (**1a**→**8**→**7**). After the H$^+$ concentration reaches a certain level, the reaction proceeds to completion at a constant rate, which depends on the concentration of bulk water (Figure 2).

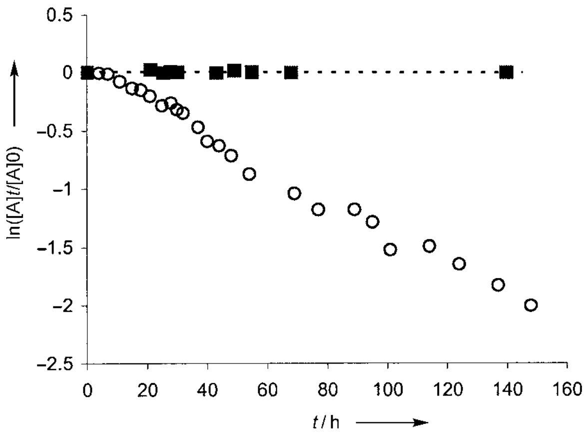


Figure 2. Concentration change of **2·1** versus time (CD$_2$Cl$_2$, 25 °C) in the presence (■) and absence (○) of [D$_5$]pyridine. The amount of **2·1** was estimated from the integral of the guest proton H1.

Table 1: ^{1}H, ^{19}F, and ^{13}C NMR chemical shifts of **1** referenced to trimethylsilane (TMS) or CFCl$_3$.

Nucleus	δ_{exp} [ppm]	δ_{calcd}[a] [ppm]	
		cis	*trans*
H1	6.28	7.13	7.70
H2	5.56	7.57	7.62
H3	3.28	7.47	7.56
F	149.8	179.1	159.4
C1	285.7	297.1	309.0
C2	148.0	158.3	159.6
C3	117.4	125.8	122.6
C4	129.9	133.1	134.1
C5	124.7	131.4	131.6

[a] GIAO chemical shift tensors (PBE1PBE/6-311++G(2d,p) relative to TMS (^{1}H, ^{13}C) or CFCl$_3$ (^{19}F).

The aryl protons H1, H2, and H3 of **2·1** are assigned to a doublet at $\delta = 6.28$ ppm and triplets at $\delta = 5.56$ and 3.28 ppm in the ^{1}H NMR spectrum (Table 1, Figure 1b). The observation of single multiplets for host protons Ha, Ho, Hm, and Hi indicates fast tumbling of **1** relative to **4**, whose rotation around the equatorially located axis of **2** is frozen. This observation is consistent with the difference in size between **1** and **4**. The ^{19}F and ^{13}C NMR spectra of **2·1** provided further interesting insights into the properties of **1**. The ^{19}F atom of **1** resonates at $\delta = 149.8$ ppm, which indicates a fairly electropositive fluorine center (Figure 3).[13] Furthermore, the multiplicity and chemical shift of the ^{19}F signal clearly rules out **7** as the guest.

The guest's aryl carbon atoms are assigned to singlets at $\delta = 148$ (C2), 129.9 (C4), 124.7 (C5), and 117.4 ppm (C3) in the ^{13}C NMR spectrum. The highly electron-deficient carbene C1 resonates at $\delta_C = 285.7$ ppm (d, $^1J_{CF} = 569$ Hz), which is comparable to the δ_C value of other persistent heteroatom-substituted singlet carbenes.[4b] The strongly downfield-shifted fluorine atom, the unusually large C–F coupling constant,[13] and the C2 signal, which is shifted upfield by $\Delta\delta_C = 3.2$ ppm relative to C2 of **4**, are consistent with strong participation of both oxygen and fluorine atoms in carbene stabilization through delocalization of a lone pair into the vacant carbene p orbital (Scheme 2).

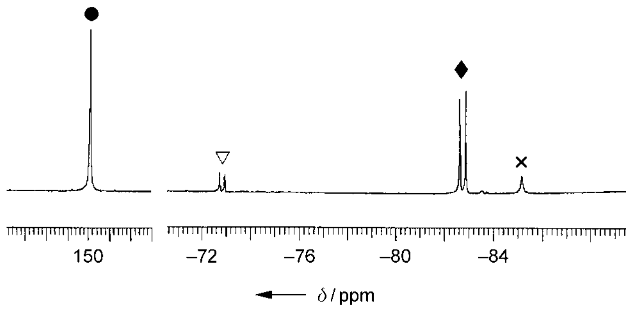
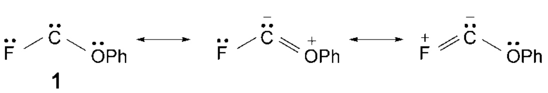


Figure 3. ^{19}F NMR spectrum (282.232 MHz, CD_2Cl_2, 25 °C) of partially decomposed **2·1** referenced to $CFCl_3$. Signals assigned to ^{19}F atoms of incarcerated **1** (●), **6** (◆), and two further photoproducts of **2·4** (▽,×) are marked.



1

Scheme 2. Resonance stabilization of **1**.

DFT calculations (B3LYP/6-31G*) predict that **1** preferentially adopts the *trans-* (**1b**) rather than the *cis* conformation (**1a**; $\Delta H^{\circ} = 2.2\,\text{kcal mol}^{-1}$). Does **1** also adopt the intrinsically more stable *trans* conformation in the inner phase of **2**? This is an interesting question in light of recent work by Rebek and co-workers,[14] who found that linear alkanes prefer higher energy conformations when encapsulated inside self-assembled capsules. We addressed this question by comparing the experimental δ_C and δ_F values of **1** with those predicted by gauge-independent atomic orbital (GIAO) chemical-shift calculations at the PBE1PBE/6-311++G(2d,p) level (Table 1).[15] Olah, Prakash, and co-workers compared experimental and computed chemical shifts for several F-substituted carbocations and showed that GIAO calculations slightly overestimate δ_F and δ_C values.[13] More importantly, they observed excellent linear correlations between measured and computed δ_F and δ_C values. We were delighted to find similar correlations when we compared the experimentally derived chemical shifts of C_6H_5F, CH_3F, 1,3-dimethylimidazolidin-2-ylidene,[4b] 1,3-dimethylimidazol-2-ylidene,[4b] 1-fluoro-1-cyclopentyl cation,[13] 1-fluoro-1-cyclopropyl cation,[16] and 2-fluoro-2-propyl cation[16] with those computed at the PBE1PBE/6-311++G(2d,p) level (see the Supporting Information). These experimentally derived values were then used to correct the δ_F and δ_C values reported in Table 1: $\delta_F^{corr}(\mathbf{1a}) = 159.2$, $\delta_F^{corr}(\mathbf{1b}) = 141.1$, $\delta_C^{corr}(\mathbf{1a}) = 290.0$, and $\delta_C^{corr}(\mathbf{1b}) = 301.4$ ppm. If we also take a complexation-induced upfield shift of $\Delta\delta_F \sim 1\text{–}2$ and $\Delta\delta_C \sim 1\text{–}2$ ppm into consideration, we find that the chemical shifts predicted for **1a** are in better agreement with the experimental values, which suggest that **1a** is the major conformer inside **2**. To further strengthen this conclusion we performed heteronuclear ^{1}H[^{19}F] NOE interaction experiments (Figure 4). The fluorine center in **1** yields positive NOE interactions for H1(s) in **1** and for Hi(m) and Ha(m) in **2** upon irradiation.

A strong NOE interaction between the fluorine atom and H1 is only expected for **1a**. The calculated F–H1 distances are 3.021 and 3.716 Å for **1a** and 3.839 and 4.392 Å for **1b**. The steep distance-dependence of the ^{1}H[^{19}F] NOE interaction renders a NOE interaction in the *trans* conformation unlikely. Also consistent with **1a**, is the intermolecular Hi–F NOE interaction. However, our observation of an almost equally strong intermolecular Ha–F NOE interaction is more difficult to rationalize for **1a** and suggests that **1b** is partially populated. From the temperature insensitivity of δ_F (25 to −70 °C, $\Delta\delta_F = 0.2$ ppm) and the failure to detect a second ^{19}F signal at $\delta_F = 150 \pm 30$ ppm at −70 °C, the *cis–trans* isomerization should be frozen at −70 °C ($\Delta H^{\ddagger}_{calcd} = 13.9\,\text{kcal mol}^{-1}$), which suggests that one conformer is predominately populated at 25 °C and below. On the basis of the NOE interaction experiments and the comparison of the δ_C and δ_F values with the calculated GIAO chemical shifts we conclude that **1a** is the major conformer in the inner phase. The higher population of **1a** must be a consquence of steric interactions between **1b** and **2** (ca. 2–3 kcal mol^{-1}) and is consistent with earlier observations that confinement favors coiled over extended conformations.[14,17]

In summary, free fluorophenoxycarbene is a transient species;[8] however, if incarcerated inside a hemicarcerand, **1** persists for days at room temperature. Incarceration not only prevents dimerization but also slows the reaction of **1** with water by many orders of magnitude and reverses its *cis–trans* equilibrium. We predict that many other singlet carbenes of comparable reactivity will become persistent by this approach.

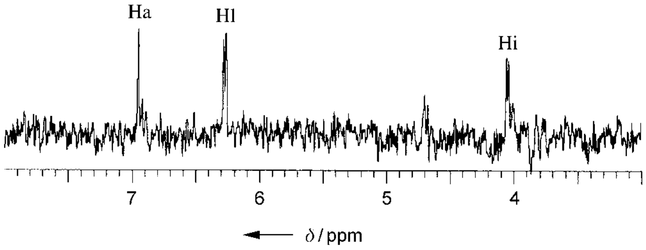


Figure 4. ^{1}H[^{19}F] NOE difference spectrum (399.971 MHz, CD_2Cl_2, 28 °C) of **2·1**.

Received: November 17, 2004

Keywords: carbenes · host–guest systems · NMR spectroscopy · photolysis · reactive intermediates

[1] a) R. A. Moss in *Carbene Chemistry: From Fleeting Intermediates to Powerful Reagents* (Ed.: G. Bertrand), FontisMedia–Marcel Dekker, Lausanne, **2002**, p. 57; b) R. A. Moss, *Acc. Chem. Res.* **1980**, *13*, 58; c) N. G. Rondan, K. N. Houk, R. A. Moss, *J. Am. Chem. Soc.* **1980**, *102*, 1770; d) R. A. Moss, *Acc. Chem. Res.* **1989**, *22*, 15.
[2] W. v. E. Doering, R. G. Buttery, R. G. Laughlin, N. Chaudhuri, *J. Am. Chem. Soc.* **1956**, *78*, 3224.
[3] H. Tomioka, E. Iwamoto, H. Itakura, K. Hirai, *Nature* **2001**, *412*, 626.

[4] a) S. Goumri-Magnet, T. Kato, H. Gornitzka, A. Baceiredo, G. Bertrand, *J. Am. Chem. Soc.* **2000**, *122*, 4464; b) D. Bourissou, O. Guerret, F. P. Gabbai, G. Bertrand, *Chem. Rev.* **2000**, *100*, 39.

[5] a) A. J. Arduengo III, R. L. Harlow, M. Kline, *J. Am. Chem. Soc.* **1991**, *113*, 361; b) R. W. Alder, P. R. Allen, M. Murray, A. G. Orpen, *Angew. Chem.* **1996**, *108*, 1211; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1121.

[6] C. Kemmis, R. Warmuth, *J. Supramol. Chem.* **2003**, 253.

[7] a) D. J. Cram, M. E. Tanner, R. Thomas, *Angew. Chem.* **1991**, *103*, 1048; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1024; b) R. Warmuth, *Angew. Chem.* **1997**, *109*, 1406; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1347; c) R. Warmuth, M. A. Marvel, *Angew. Chem.* **2000**, *112*, 1168; *Angew. Chem. Int. Ed.* **2000**, *39*, 1117; d) P. Roach, R. Warmuth, *Angew. Chem.* **2003**, *115*, 3; *Angew. Chem. Int. Ed.* **2003**, *42*, 3039; e) D. A. Makeiff, K. Vishnumurthy, J. C. Sherman, *J. Am. Chem. Soc.* **2003**, *125*, 9558.

[8] R. A. Moss, G. Kmiecik-Lawrynowicz, K. Krogh-Jespersen, *J. Org. Chem.* **1986**, *51*, 2168.

[9] Yields are slightly lower at higher temperature as a result of the formation of by-products, possibly by partial reaction of the photochemically excited **4** with the surrounding host at these temperatures.

[10] S. V. Pasenok, Y. L. Yagupolskii, W. Tyrra, D. Naumann, *Z. Anorg. Allg. Chem.* **1999**, *625*, 831.

[11] Free **1** dimerizes quantitatively in pentane solution (determined by GC–MS analysis).

[12] K. Krogh-Jespersen, S. Yan, R. A. Moss, *J. Am. Chem. Soc.* **1999**, *121*, 6269.

[13] G. A. Olah, G. Liang, Y. K. Mo, *J. Org. Chem.* **1974**, *39*, 2394.

[14] A. Scarso, L. Trembleau, J. Rebek, Jr., *Angew. Chem.* **2003**, *115*, 5657; *Angew. Chem. Int. Ed.* **2003**, *42*, 5499.

[15] Gaussian 03 (Revision B.02), M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, 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, C. Gonzalez, J. A. Pople, Gaussian, Inc., Pittsburgh, PA, **2003**.

[16] G. K. S. Prakash, G. Rasul, A. Burrichter, K. K. Laali, G. A. Olah, *J. Org. Chem.* **1996**, *61*, 9253.

[17] a) A. P. Minton, *Biophys. J.* **1992**, *63*, 1090; b) R. W. Peterson, K. Anbalagan, C. Tommos, A. J. Wand, *J. Am. Chem. Soc.* **2004**, *126*, 9498.