Nitric Oxide Cheletropic Traps (NOCTs) with Improved Thermal Stability and Water Solubility[1]

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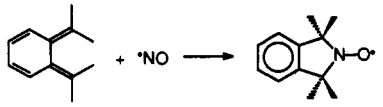
Abstract: The search for nitric oxide cheletropic traps (NOCTs) of the 7,7,8,8-tetraalkyl-*o*-quinodimethane type which would have properties appropriate for monitoring the formation of nitric oxide in cell cultures and *in vivo* by magnetic resonance techniques is described. In addition to the necessary condition that a NOCT reacts rapidly with NO to yield a persistent nitroxide radical, two additional properties were sought: (i) thermal stability at the temperature of interest (37 °C) and (ii) water solubility. To these ends, a number of 1,1,3,3-tetraalkyl-2-indanones (and a related naphthalene derivative) were synthesized and subjected to UV photolysis in solution, a procedure which generally (though not in all cases) caused the elimination of carbon monoxide and formation of the corresponding *o*-quinodimethane. The thermal instability of many of these compounds is due to a 1,5-sigmatropic hydrogen atom transfer which, for example, converts 7,7,8,8-tetramethyl-*o*-quinodimethane (**1**) to *o*-isopropyl-α-methylstyrene (**1*P***) with a half-life of only ca. 140 s at 37 °C. Several *o*-quinodimethanes were discovered which were, for all practical purposes, completely stable at 37 °C. The most suitable lipid-soluble NOCT discovered was 7-(2-indenyl)-7,8,8-trimethyl-*o*-quinodimethane (**5**), which is stable and reacts very rapidly with NO to form a persistent nitroxide. Various derivatives of **5** were also examined and found to be equally, or almost equally, effective NOCTs. Water solubility was explored by addition of water-solubilizing groups to the ring of **1**. The carboxylic acid group, **13**, was found to be particularly suitable, since the carboxylate anion **14** conferred excellent water solubility without interfering with either the nitric oxide trapping reaction or the necessary photoelimination of carbon monoxide from the starting indanone. Of even greater importance, the carboxylate group had no apparent effect on the rate of the thermal 1,5-sigmatropic rearrangement; i.e., the rates of decay of **14** and **1** were equal within experimental error. It is concluded that NOCTs of the *o*-quinodimethane class having long lifetimes and a high reactivity toward NO can now be prepared with appropriate lipophilic, hydrophilic, or amphiphilic properties. These NOCTs should prove suitable for exploratory use in biological systems.

Nitric oxide, ·NO, has been shown to be an intra- and intercellular signal molecule; it regulates vascular tone, is a messenger molecule in the central nervous system, and mediates the cytotoxicity of macrophages.[2-5] In a preliminary communication,[6] we reported that 7,7,8,8-tetramethyl-*o*-quinodimethane (**1**) reacted with nitric oxide to form a persistent nitroxide, **1*NO***, reaction 1. Thus, **1** is the first nitric oxide cheletropic trap or NOCT.

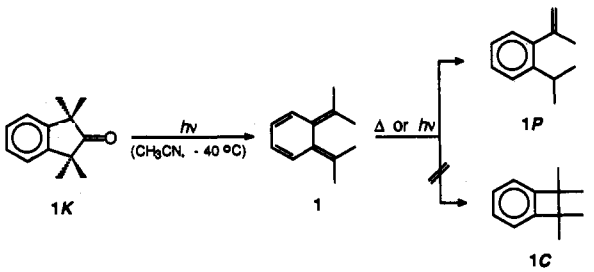


1 (NOCT-1) **1*NO*** (1)

The invention of NOCT-1[6] was driven by the growing need to monitor nitric oxide production continuously, both in time and space, in cell cultures, perfused organs, and living animals.[7] The formation of a persistent nitroxide should permit such monitoring by magnetic resonance imaging (MRI) techniques.[8] Preliminary cell culture experiments using rat liver macrophages (Kupffer cells) and NOCT-1 were successful in that an excellent electron spin resonance (ESR) spectrum of **1*NO*** was obtained.[6]

With the above result to encourage us, we decided to search for a NOCT that would be better suited than **1** for biological and medical use. That is, our first NOCT would not be suitable for such applications for two main reasons: (i) **1** undergoes a fairly rapid, thermal 1,5-sigmatropic hydrogen shift (half life = 140 s at 37 °C) to form *o*-isopropyl-α-methylstyrene (**1*P***) reaction 2. (ii) **1** is almost completely insoluble in water.

An additional problem with **1** relates to its method of synthesis, which was by UV photolysis of the ketone 1,1,3,3-tetramethylindan-2-one (**1*K***), reaction 2. Unfortunately, **1** is itself very



(2)

efficiently photolyzed to *o*-isopropyl-α-methylstyrene at the

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‡ Institut für Physiologische Chemie der Universität Essen.
§ National Research Council of Canada.
• Abstract published in *Advance ACS Abstracts*, March 1, 1994.
(1) Issued as NRCC No. 37232.
(2) Furchgott, R. F.; Vanhoutte, P. M. *FASEB J.* **1989**, *3*, 2007–2018.
(3) Moncada, S.; Palmer, R. M. J.; Higgs, E. A. *Biochem. Pharmacol.* **1989**, *38*, 1709–1715; *Pharmacol. Rev.* **1991**, *43*, 109–142.
(4) Ignarro, L. J. *Biochem. Pharmacol.* **1991**, *41*, 485–490.
(5) Noack, E.; Murphy, M. E. in *Oxidative Stress: Oxidants and Antioxidants;* Sies, H., Ed.; Academic: New York, 1991; pp 445–489.
(6) Korth, H.-G.; Ingold, K. U.; Sustmann, R.; de Groot, H.; Sies, H. *Angew. Chem.* **1992**, *104*, 915–917; *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 891–893.
(7) For a recent review see: Archer, S. *FASEB J.* **1993**, *7*, 349–360.
(8) The potential for NOCTs to be used as nitric oxide antagonists *in vivo* has not escaped us.

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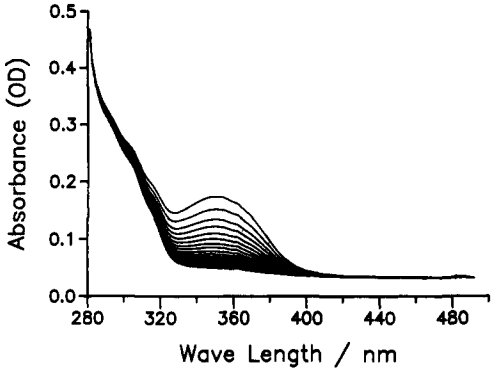


Figure 1. UV/vis absorption spectrum of **1** in CH_3CN at 298 K. Individual traces were recorded at 145-s intervals.

wavelengths required to convert **1*K*** to **1**.[9,10] As a consequence, the maximum concentration of **1** which we could obtain was ca. 7×10^{-4} M (as determined by ^1H NMR on samples prepared in CD_3CN). Fortunately, this concentration of **1** proved adequate for trapping NO in solution both *in vitro* and in the Kupffer cell experiments.

Our overall objective is the efficient synthesis of NOCTs having properties which would allow the formation of nitric oxide *in vivo* to be efficiently monitored by MRI. To this end, our initial priority has been to increase the thermal stability of *o*-quinodimethanes (and other compounds capable of acting as NOCTs) without reducing their ability to react with nitric oxide to form persistent nitroxides. It has also been a priority to make *o*-quinodimethanes which are water soluble and to check whether the water or the water-solubilizing group had an adverse effect on the compound's thermal stability and ability to trap nitric oxide. We describe herein the preparation of a number of thermally stable compounds with excellent NOCT activities. We also demonstrate that neither water nor a water-solubilizing group attached to **1** has any measurable effect on the lifetime of this basic NOCT structure.

Results

Exploratory Studies on 1. This compound, our first NOCT,[6] was generated from **1*K*** ($\sim 5 \times 10^{-2}$ M) by continuous photolysis (Rayonet reactor, 1 h, λ = 254 and 300 nm) and by laser flash photolysis (LFP, λ = 308 and 337 nm) in a variety of deoxygenated solvents (CH_3CN, CH_3OH and various alkanes) at subambient temperatures (generally ca. –40 °C). The formation of **1** could be demonstrated in three ways, first, by mixing with a deoxygenated solution of nitric oxide and observing **1*NO*** by ESR spectroscopy (reaction 1). This ESR spectrum was identical to that obtained from authentic **1*NO*** under the same experimental conditions (solvent, temperature, etc). The second way to demonstrate formation of **1** was by its absorption in the near UV ($\lambda_{max} \sim 352$ nm), and the third way was (when generated in CD_3CN, maximum concentration 7×10^{-4} M) by its ^1H NMR spectrum with its characteristic[11] vinylic ring protons: δ (ppm) 6.86 (dd, J = 7.85, 3.1 Hz, AA'XX', 2H), 6.01 (dd, J = 7.85, 3.1 Hz, AA'XX', 2H) (see Experimental Section). The potential ring-closed product of **1**, 7,7,8,8-tetramethylbenzocyclobutene (**1*C***) could not be detected by ^1H NMR.

Measurements were made on the rate of thermal conversion of **1** to *o*-isopropyl-α-methylstyrene (**1*P***) (reaction 2) in CH_3CN, CH_3CN/H_2O (9:1, v/v), CH_3OH, and *n*-hexane at temperatures from 278 to 310 K. The solutions of **1** were prepared by 308-nm laser flash photolysis (1800 pulses, 80 mJ/pulse) of 5 x 10^{-2} M solutions of **1*K*** in the deoxygenated solvents at –40 °C. Relative concentrations of **1** were monitored in a thermostated, regular 1-cm UV cell using a diode array spectrophotometer (see Figure 1 for a typical set of traces). Decay of the absorption (measured at $\lambda_{max} \sim 352$ nm) followed clean first-order kinetics under all conditions, as would be expected. The decay of **1** in CD_3CN was also monitored by 300-MHz ^1H NMR at 278 K using the 1.53 and 1.88 ppm signals. The derived first-order rate constants, k_2(**1**), are listed in Table 1.

Table 1. Rate Constants for Decay of **1** and **2**

T/K		solvent	$10^4 k_2/s^{-1}$ [a]
278	1	CH_3CN	1.5, 1.8
		CH_3CN/H_2O, 9:1 (v/v)	1.7, 1.3,[b] 1.1[c]
		CH_3OH	1.7
		n-C_6H_{14}	1.7
		CD_3CN	1.4[d]
280	1	CH_3CN	2.0
288	1	CH_3CN	4.9, 5.5
		n-C_6H_{14}	6.1, 6.1
298	1	CH_3CN	13, 17, 17[e]
		CH_3CN/H_2O, 9:1 (v/v)	17, 13,[b] 17[c]
		CH_3OH	12
		n-C_6H_{14}	17
310	1	CH_3CN	39
		CH_3OH	44
		n-C_6H_{14}	48
287	2	CH_3CN	0.5
293	2	CD_3CN	1.5[d]
300	2	CH_3CN	2.0, 2.0, 2.0, 2.0[f]
308	2	CH_3CN	3.9, 3.8, 5.3
323	2	CH_3CN	18, 19, 21

[a] Multiple values correspond to individual experiments and are given in the order the experiments were carried out. [b] Acidified. [c] Made basic. [d] By 300-MHz ^1H NMR. [e] Oxygen-saturated (all other measurements in nitrogen-saturated solutions including the carefully matched experiment preceding this data point). [f] Exposure of the sample to the UV/vis monitoring light for only 2% of the duration of the experiment (5000 s) rather than the normal 100% (which was used in the carefully matched experiment preceding this data point).

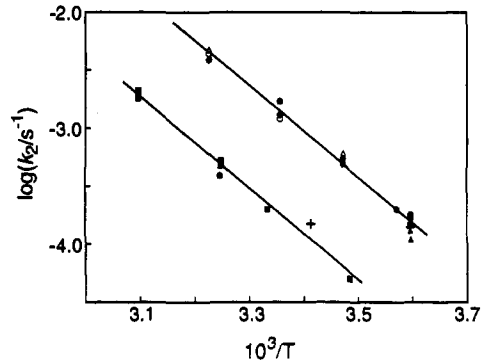


Figure 2. Plots of $\log(k_2/s^{-1})$ vs $1/T$ for the thermally induced 1,5-sigmatropic rearrangements of **1** (upper line) and **2** (lower line). Key: for **1** the solvents are CH_3CN (●), CD_3CN (+), CH_3OH (○), *n*-C_6H_{14} (△), and CH_3CN/H_2O (10:1 v/v) (▲); for **2** the solvents are CH_3CN (■) and CD_3CN (+).

Inspection of Table 1 reveals that the rate of decay of **1** is essentially independent of the nature (polarity, etc.) of the solvent. Furthermore, the decay rate was unaffected by the addition of acid or base (as previously reported by McCullough and co-workers[9]) and was insensitive to the presence or absence of oxygen[12] (as previously reported by Scaiano and co-workers[10]). An Arrhenius plot of the kinetic data (Figure 2) yields

$$\log(k_2(\mathbf{1})/s^{-1}) = (10.6 \pm 0.4) - (18.3 \pm 0.5)/\theta \quad (I)$$

where $\theta = 2.3RT$ kcal/mol and the errors correspond to one σ.

(9) de Fonseka, K. K.; McCullough, J. J.; Yarwood, A. J. *J. Am. Chem. Soc.* **1979**, *101*, 3277–3282. McCullough, J. J. *Acc. Chem. Res.* **1980**, *13*, 270–276.

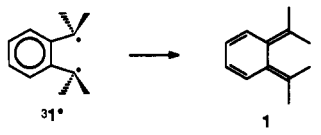
(10) Wintgens, V.; Netto-Ferreira, J. C.; Casal, H. L.; Scaiano, J. C. *J. Am. Chem. Soc.* **1990**, *112*, 2363–2367.

(11) Trahanovsky, W. S.; Chou, C.-H.; Fischer, D. R.; Gerstein, B. C. *J. Am. Chem. Soc.* **1988**, *110*, 6579–6581.

(12) Note, however, that oxygen must be rigorously eliminated from the solutions employed during the photosynthesis of **1** from **1*K***.

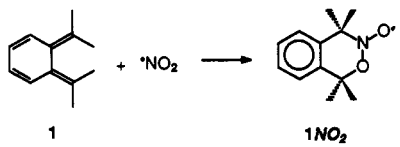
These Arrhenius parameters are in reasonable agreement with those given by McCullough and co-workers[9] from their measurements which were made at temperatures from 293 to 323 K, viz., $\log(A/s^{-1}) = 11.5$ and $E_a = 19.0$ kcal / mol. At 37 °C, the temperature of physiological interest, $k_2(\mathbf{1}) = 4.9 \times 10^{-3}$ s^{-1}, corresponding to a half-life of 141 s and a lifetime ($=1/k_2(\mathbf{1})$) of 204 s.

Scaiano and co-workers[10,13] have shown that LFP of **1*K*** does not yield **1** "instantaneously". After an essentially instantaneous ring opening of triplet **1*K*** and loss of carbon monoxide comes a "slow" conversion of the triplet of **1** (^{3}**1***, which can also be considered as a biradical) into **1**, reaction 3, with $k_3 = 1.7 \times 10^6$ s^{-1} in benzene at room temperature.[10,13] We have confirmed the findings of Scaiano and co-workers and have obtained $k_3 = 1.6 \times 10^6$ s^{-1} in CH_3CN at 293 K.



(3)

Addition of deoxygenated solutions of **1** via a hypodermic syringe to a septum-capped ESR tube containing freshly prepared solutions of nitric oxide in deoxygenated acetonitrile or *n*-hexane (typically ca. 1.5×10^{-2} M NO[14]) yielded the spectra of two different nitroxide radicals with intensity ratios ranging from 1:10 to 1:20. Both signals were present as soon as they could be recorded (ca. 1 min) and did not increase further in intensity. The more intense spectrum had a large nitrogen hyperfine splitting, $a_N \sim 28$ G, which is clearly due to an alkoxy alkyl nitroxide.[15] We assign this spectrum to **1*NO*$_2$**, reaction 4. (The ESR parameters for all the nitroxides prepared in this work have been collected together in Table 2.)

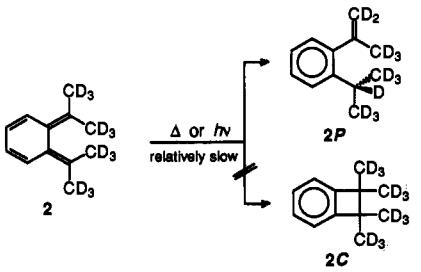


(4)

The less intense spectrum had $a_N \sim 14.5$ G and is readily assigned to **1*NO***, reaction 1. Over the course of time the intensity of the **1*NO*$_2$** spectrum declines until it can no longer be observed (half-life ca. 9 h at room temperature) while the intensity of the spectrum due to **1*NO*** remains almost unchanged. The lower thermal stability of the ·NO_2 adduct relative to the ·NO adduct is consistent with the known instability of *tert*-butoxy *tert*-butyl nitroxide relative to di-*tert*-butyl nitroxide.[16]

Interestingly, if the solutions containing nitric oxide were allowed to "age" for 40 min or more prior to the addition of the solution containing **1**, *only* **1*NO*** was formed. We assume that the formation of **1*NO*$_2$** with fresh nitric oxide solutions is due either to NO_2 formation from residual oxygen in our "deoxygenated" solvents or to traces of NO_2 being present in the cylinders of nitric oxide we employed.[17] We further assume that because of its high reactivity the NO_2 is completely destroyed after some time in acetonitrile.[19] As measured by the UV/vis absorption of nitrous acid[20,21] at 355 nm, the average NO_2 content of our fresh acetonitrile solutions of NO was calculated to be ≤5%. From the initial relative ratios of the **1*NO*$_2$** /**1*NO*** ESR signals, we can therefore estimate that NO_2 reacts with **1** at least 200 times as rapidly as NO.

Studies on Two o-Quinodimethanes Known To Be Longer Lived than 1. McCullough and co-workers[9] have shown that the hydrogen-transfer reaction **1** → **1*P*** has a substantial deuterium kinetic isotope effect when all four CH_3 groups in **1** are replaced by CD_3 groups, **2**, reaction 5.



(5)

Irradiation (254 nm) of 5×10^{-2} M tetra(trideuteriomethyl)-2-indanone (**2*K***) in CD_3CN at –40 °C yielded **2** at a steady-state concentration of ca. 1.4×10^{-3} M (for NMR parameters and details see Experimental Section). Rate constants for decay of **2** in CH_3CN were measured at temperatures from 278 to 323 K as described for **1** (and in CD_3CN by 300-MHz ^{1}H NMR at 293 K using the δ 6.01 and 6.84 ppm signals). These kinetic data, which are given in Table 1 and have been plotted in Figure 2, yield the Arrhenius expression

$$\log(k_2(\mathbf{2})/s^{-1}) = (9.5 \pm 0.5) - (18.1 \pm 0.7)/\theta \quad \text{(II)}$$

At 37 °C, $k_2(\mathbf{2}) = 5.4 \times 10^{-4}$ s^{-1}, corresponding to a half-life of 1283 s and a lifetime of 1852 s. The deuterium kinetic isotope effect is 9.1, a value which is somewhat larger than that found by McCullough and co-workers, viz.,[9] $k_2(\mathbf{1})/k_2(\mathbf{2}) = 5.4$ at 38.5 °C.

The increased lifetime of **2** allowed the photolysate to be analyzed by reversed-phase HPLC, under which conditions **2** could be separated from **2*P*** and detected by its UV/vis absorption at 350 nm. The HPLC analysis (as well as the ^{2}H NMR spectra) gave no indication for the presence of significant amounts of 7,7,8,8-tetra[D_3]methylbenzocyclobutene (**2*C***) (see Experimental Section).

McCullough and co-workers reported that one *o*-quinodimethane, **3** (*vide infra*), "was rapidly destroyed by light from the monitoring beam in the kinetic spectroscopy system".[9] Fortunately for our kinetic studies, deuterium atom migration in **2** (reaction 5) is a process which is not photoaccelerated to any measurable extent by the monitoring beam used in the present work. This was demonstrated by showing that the rate of decay of a sample which was monitored continuously was identical with

(13) Scaiano, J. C.; Wintgens, V.; Netto-Ferreira, J. C. *Pure Appl. Chem.* **1990**, *62*, 1557–1564.

(14) (a) *IUPAC Solubility Data Series;* Young, C. L., Ed.; Pergamon: Oxford, U.K., 1981; Vol. 8, pp 260–351. (b) Wisniak, J.; Herskowitz, M. *Solubility of Gases and Solids, Part B, Physical Sciences Data 18;* Elsevier: Amsterdam, The Netherlands, 1984; p 1635.

(15) Forrester, A. R. In *Landolt-Börnstein, New Series, Magnetic Properties of Free Radicals;* Fischer, H., Hellwege, K. H., Eds.; Springer: Berlin, 1979; Vol. 9, Part c1; 1989; Vol. 17, Parts d1, d2.

(16) Mackor, A.; Wajer, T. A. J. W.; DeBoer, T. J.; van Voorst, J. D. W. *Tetrahedron Lett.* **1967**, 385–389. Bowman, D. F.; Brokenshire, J. L.; Gillan, T.; Ingold, K. U. *J. Am. Chem. Soc.* **1971**, *93*, 6551–6555.

(17) Under pressure the thermodynamically favored conversion of NO to N_2O and NO_2 can occur.[18]

(18) Greenwood, N. N.; Earnshaw, A. *Chemistry of the Elements*; Pergamon Press: Oxford, U.K., 1984; p 521. Holleman, A. F. H., Wiberg, E. W. *Lehrbuch der Anorganischen Chemie*, 91–100th ed.; de Gruyter: Berlin 1985; p 580.

(19) The most obvious route for NO_2 destruction is via the reaction sequence

$$NO + NO_2 \rightleftharpoons N_2O_3 \xrightarrow{H_2O} 2\,HNO_2$$ [18,20]

The rate at which NO_2 is lost is therefore dependent upon the water content of the solvent. Thus, there was little or no "aging effect" when hexane was used as the solvent, a moderate aging effect in acetonitrile and THF, and "instantaneous" aging in D_2O (i.e., with D_2O the NO_2 was already destroyed before the NO solution could be added to the photolysate). In agreement, solutions of NO in acetonitrile "aged" for 5 min already showed the characteristic UV/vis spectrum of nitrous acid.[21]

(20) Awad, H. H.; Stanbury, D. M. *Int. J. Chem. Kinet.* **1993**, 25, 375–381.

(21) Turney, T. A.; Wright, G. A. *Chem. Rev.* **1959**, *59*, 497–513. Bongartz, A.; Kames, J.; Welter, F.; Schurath, U. *J. Phys. Chem.* **1991**, *95*, 1076–1082.

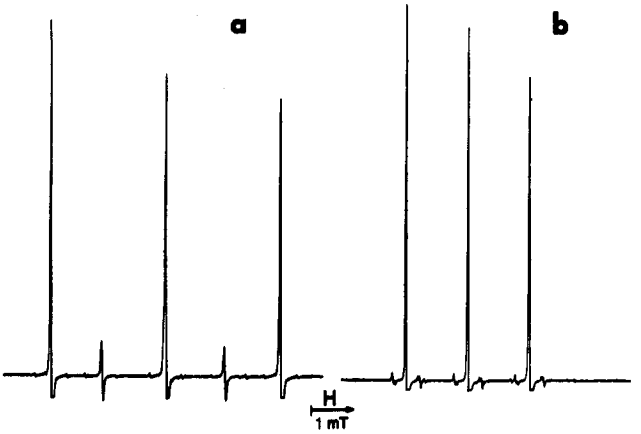
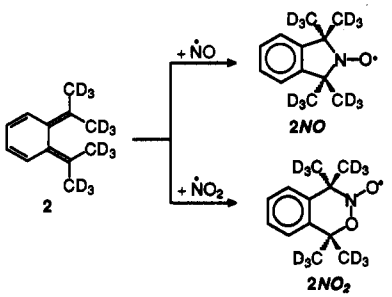


Figure 3. ESR spectra (upper half) of **2*NO*** and **2*NO*$_2$** in CD_3CN at 293 K recorded 2 min after mixing with (a) "fresh" (b) "aged" (1 h) NO solutions in CD_3CN.

the rate of decay of a sample monitored for only 2% of the total duration of the experiment (see 300 K data and footnote f in Table 1).

Since the thermal 1,5-sigmatropic shifts of hydrogen and deuterium show such a pronounced kinetic isotope effect, we must conclude that the hydrogen shift occurs via a highly symmetrical transition state in a concerted process. McCullough[9] has suggested that the thermal hydrogen shift should be a symmetry-forbidden antarafacial process which becomes possible because of the out-of-plane twisting of the exocyclic double bonds.

As with **1**, the reaction of **2** in deoxygenated solvents with "fresh" solutions of nitric oxide gave the ESR spectra of **2*NO*$_2$** and **2*NO***, reaction 6, while "aged" (>40 min) nitric oxide solutions

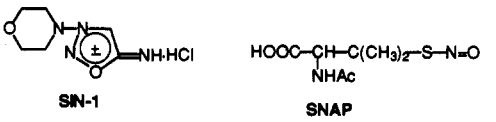


(6)

gave **2*NO*** only (see Figure 3). These two **2**-derived nitroxides exhibited sharper, and hence better resolved, spectra than **1*NO*$_2$** and **1*NO***, indicating that at least part of the line widths in the latter pair of nitroxides is due to unresolved methyl group proton hyperfine splitting. The sharper spectra permitted the more unequivocal identification of splittings by ^{13}C and ^{15}N nuclei at natural abundance than was possible with **1*NO*** and **1*NO*$_2$**, including the observation of an additional ^{13}C splitting with **2*NO*$_2$** (see Table 2).

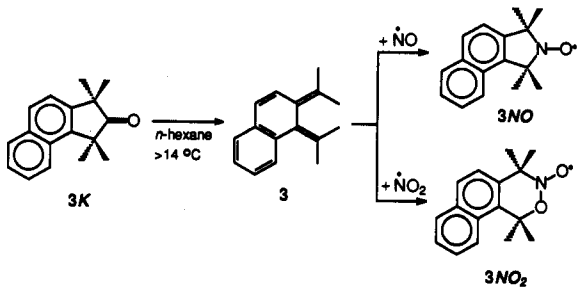
Just as was found with **1**, the reactivity of **2** was significantly higher toward NO_2 than toward NO. Thus, passage of a helium gas stream containing 160 ppm NO and ca. 3 ppm NO_2 through a 1.5×10^{-2} M solution of **2** in acetonitrile at 0 °C (see Experimental Section) gave an ca. ninefold stronger ESR spectrum of **2*NO*$_2$** than of **2*NO***. Neglecting the differences in solubility etc. of NO and NO_2, we can estimate that NO_2 reacts with **2** about 500 times more rapidly than NO, a result which is consistent with the estimated lower limit on the relative reactivity of **1** toward these two oxides of nitrogen.

Chemicals which release nitric oxide *in vivo* have been used to relieve the pains of angina pectoris for over a century. Nitroglycerine, the first of these compounds, has today largely been replaced by other "nitrovasodilators" such as molsidomine (SIN-1), isoamyl nitrite, or isosorbid dinitrate.[22] When solutions



of **2** in CH_3CN were incubated at 37 °C with solutions of *N*-morpholinosydnone imine hydrochloride (SIN-1) and *S*-nitroso-*N*-acetylpenicillamine (SNAP) in HBSS buffer[23] (pH 7.4) for 30 min in the presence of air and were then extracted with hexane, the extracts showed the ESR spectrum of **2*NO*** and **2*NO*$_2$** in a ratio of 2.5:1 from the SIN-1 but ca. 1:100 from the SNAP.[24] By way of contrast, incubation with stimulated Kupffer cells[6] gave an excellent spectrum of **2*NO*** solely.

LFP of 1,1,3,3-tetramethyl-5,6-benzindan-2-one (**3*K***) has been shown to yield a long-lived *o*-quinodimethane, **3**, which survived "...indefinitely in the dark at ambient temperatures (~20 °C) ... but was rapidly destroyed by light from the monitoring beam".[9] We have found that **3*K*** does not decarbonylate upon photolysis nearly as readily as **1*K*** and **2*K***. For instance, 300-nm photolysis of **3*K*** in acetonitrile for 1 h at 0 °C did not lead to any noticeable decomposition of **3*K***. However, decarbonylation could be achieved by photolysis at temperatures ≥14 °C in *n*-hexane. Irradiation (300 nm) for 21.5 h caused an ca. 70% destruction of **3*K*** and produced **3** in a yield of about 1.1% (see Experimental Section).



(7)

When deoxygenated solutions of **3** were mixed with fresh or aged (45 min) solutions of nitric oxide in *n*-hexane,[19] an intense ESR spectrum of **3*NO*$_2$** was obtained but there was only a very weak spectrum of **3*NO*** (ratio ca. 100:1 from the NO solution aged for 45 min). Surprisingly, the latter signal "grows-in" over the course of several hours. Thus, after ca. 4 h the **3*NO*$_2$**/**3*NO*** ratio had changed to about 7:1 with a slight increase of the overall signal intensity. The **3*NO*$_2$** spectrum decayed over a period of 24 h, after which only the ESR signals of **3*NO*** were present.

It would seem that **3** has only one property which would make it attractive as the "base-structure" for biologically useful NOCTs, namely its great thermal stability. This advantage is, however, more than offset by two disadvantages: (i) the apparent slowness of the **3** + NO reaction and (ii) the synthesis of **3*K*** being not at all straightforward (see Experimental Section). On the other hand, it would appear that **3** is a particularly good trap for NO_2, and hence it might be useful for the detection of this nitrogen oxide. An important point is that **3*NO*$_2$** is sufficiently persistent for quantitative determination by ESR .

Replacement of the Geminal Methyl Groups in 1*K* by Cyclopropane Rings, 4*K*. It seemed likely that the 1,5-sigmatropic hydrogen shift seen in **1** (reaction 2) would be strongly retarded

(22) Feelisch, M. *J. Cardiovasc. Pharmacol.* **1991**, *17 (Suppl. 3)*, S25-S33. For a recent review see: Henning, R. *Nachr. Chem., Tech. Lab.* **1993**, *41*, 412–419.

(23) Hank's balanced salt solution contains HEPES buffer.

(24) The reason for these differences in the **2*NO*/2*NO*$_2$** ratios from these two (and other)[25] "nitric oxide" generators is unknown but is currently under active investigation.

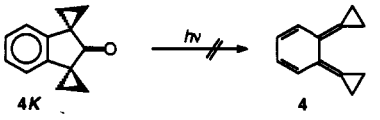
(25) Weber, H.; Grzesiok, A.; Korth, H.-G.; Sustmann, R. *Arch. Pharm.*, submitted.

Table 2. ESR Data for Nitroxide Radicals from NOCTs

radical	T/°C	solvent	hyperfine splittings/G[a]			
			g-value[a]	a^N	a^{13C}	a^{15N}
1*NO*	+14	CD_3CN	2.005 89(2)	14.52(2)	6.6(1) (4 C) 5.5(1) (2 C)	20.3(1)
	+14	*n*-hexane	2.006 06(3)	13.83(5)	6.3(2) (4 C) 5.3(2) (2 C)	20.2(2)
1*NO*$_2$	+20	CD_3CN	2.005 64(2)	27.10(5)	7.70(5) (1C) 2.30(5) (1C)	37.80(5)
2*NO*	+15	CD_3CN	2.005 90(1)	14.55(3)	6.50(5) (4 C) 5.53(5) (2 C)	20.27(5)
	+17	THF	2.005 60(2)	14.17(3)	nd[b]	
	+16	*n*-hexane	2.006 04(2)	13.96(3)	6.33(5) (4 C) 5.3(1) (2 C)	nd
2*NO*$_2$	+14	CD_3CN	2.005 66(1)	27.08(5)	7.50(5) (1 C) 2.53(5) (1 C) 3.3(1) (2 C)[c]	37.87(5)
	+17	THF	2.005 70(1)	27.02(5)	8.05(5) (1C) 2.47(3) (1 C) 3.3(1) (2 C)	37.83(5)
	+16	*n*-hexane	2.005 74(2)	27.25(3)	8.66(5) (1 C) 2.50(5) (1 C)	38.1(1)
3*NO*	+21	*n*-hexane	2.006 10(5)	13.75(5)	nr[d]	
3*NO*$_2$	+21	*n*-hexane	2.005 75(1)	26.85(10)	8.67(5) (1 C) 2.70(5) (1 C)	37.30(5)
5*NO*	+20	CD_3CN	2.006 00(1)	14.02(2)	6.6(1) (3 C) 5.38(5) (2 C)	20.2(2)
	+21	*n*-hexane	2.006 05(2)	13.68(2)	6.6(1) (3 C) 5.4(3) (2 C)	20.2(2)
6*NO*	+20	*n*-hexane	2.006 06(2)	13.72	7.8(5) (1 C)[e] 6.7(1) (2 C)[e] 5.1(5) (2 C)[e]	19.5(5)
	+19	CD_3CN	2.005 97(2)	14.05(3)	nd	
12*NO*	+18	CD_3CN	2.006 1(1)	13.67(5)	nd	
13*NO*	+19	CD_3CN/[D_8]THF	2.006 0(1)	14.20(5)	6.6(1) (4 C) 5.5(1) (2 C)	20.3(2)
14*NO*	+18	D_2O	2.005.48(2)	16.00(5)	6.6(1) (4 C) nd	nd

[a] Errors in the last digit(s) given in parentheses. [b] Not detected. [c] Broad lines, probably two slightly different hfs values. [d] Not resolved. [e] Tentative values based on simulation, not resolved.

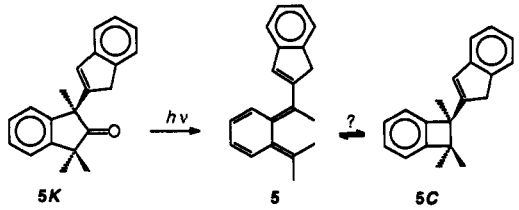
if the geminal methyls were constituted into cyclopropane rings, i.e., **4**. The starting ketone, ***4K***, is readily synthesized from indan-



(8)

2-one (see Experimental Section), but to our disappointment, photolysis of 5×10^{-2} M solutions of ***4K*** with 254- or 300-nm irradiation in *n*-hexane (–40 to 62 °C) and in CD_3CN (–20 to +40 °C) appeared not to cause any significant decarbonylation. There was no noticeable change in the UV/vis spectrum, the vinylic protons of **4** could not be observed by (600 MHz) ^1H NMR, and no more than a trace of a nitroxide ESR spectrum was produced when the photolysates were mixed with nitric oxide solutions.

Serendipitous Discoveries of Long-Lived o-Quinodimethanes. In one preparation of **1** we were astonished to discover that a sample of the ***1K*** photolysate solution left at room temperature overnight gave a three-line ESR spectrum of a nitroxide when mixed with a solution of nitric oxide the next morning. This spectrum could not, of course, be due to ***1NO*** because of the short lifetime of **1**, and indeed, the ESR parameters differed slightly from those of authentic ***1NO*** (see Table 2). The "impurity" in the ***1K*** photolysate was christened "magic dust", the precursor of which was eventually identified as 1-(2-indenyl)-1,3,3-trimethyl-2-indanone (***5K***). In some preparations of ***1K*** (from 2-indanone, CH_3I, and KOH)[26a] the raw product contained as much as 40% ***5K***, which allowed its ready separation from ***1K*** by preparative gas chromatography.[27] Photolysis (254 nm, 1 h, –40 °C) of ~7×10^{-2} M solutions of purified ***5K*** was carried out in CD_3CN and in *n*-hexane. The expected ^1H NMR signals due to 7-(2-indenyl)-7,8,8-*o*-quinodimethane (**5**), reaction 9, could



(9)

not be detected in the CD_3CN photolysate (for other photoproducts see Experimental Section). Nevertheless, this solution (and the *n*-hexane solution) contained a very effective NOCT, *vide infra*. It is possible that the characteristic ^1H NMR signals of an *o*-quinodimethane were masked by the numerous signals

(26) (a) Lissel, M.; Neumann, B.; Schmidt, S. *Liebigs Ann. Chem.* **1987**, 263–264. (b) Langhals, E.; Langhals, H. *Tetrahedron Lett.* **1989**, 859–862.

(27) In other ***1K*** preparations, there was relatively little ***5K*** but there were significant quantities of mixtures of mono- and dimethyl-substituted ***5K***'s. These compounds were separated from ***1K*** but not from each other by sublimation and chromatography and were identified by GC/MS and ^1H NMR (see Experimental Section). Photolysis (254 nm, 1 h, –40 °C) of ca. 3×10^{-2} M solutions of these mixed mono- and dimethyl-substituted ***5K***'s in CD_3CN, *n*-hexane, and *n*-hexadecane gave solutions which, like the ***5K*** photolysates, contained NOCTs which were thermally stable for days at ambient temperatures. These photolysates gave very strong nitroxide signals on mixing with fresh solutions of nitric oxide. As in the case of the ***5K*** photolysates we assume that the active NOCTs are *o*-quinodimethanes. However, since such compounds could not be detected in the ^1H NMR of the photolysates, the corresponding benzocyclobutenes may serve as "reservoirs" for the reversible formation of the NOCTs. Similar observations were made on "impurity" ketones analogous to ***5K*** and its permethylated derivatives which were formed during the synthesis of ***2K*** and also on the photolytic products obtained from these ketones (see Experimental Section).

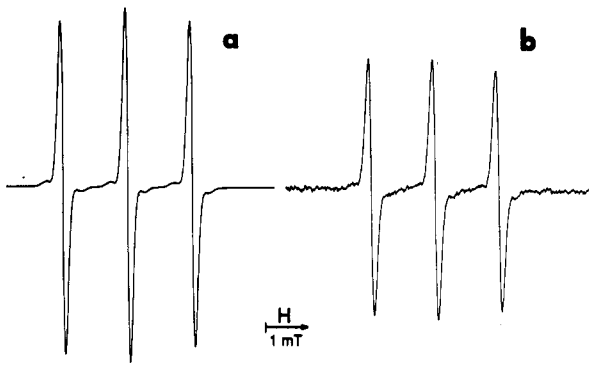
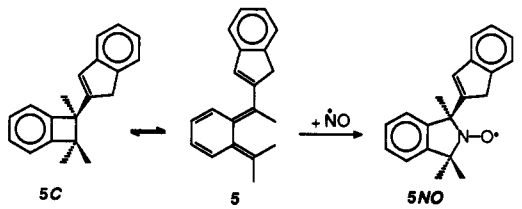


Figure 4. ESR spectrum of **5*NO*** in *n*-hexane at 293 K (a) from reaction of **5** with a saturated NO solution in *n*-hexane and (b) after 1-h incubation of **5** with Kupffer cells at 37 °C.

due to the various aromatic hydrogens. A more intruiging possibility is that **5** is present in these solutions only in a very low concentration but that it is available in much larger quantitites for NO trapping because it exists in a rapid equilibrium with its cyclized isomer, 7-(2-indenyl)-7,7,8-trimethylbenzocyclobutene (**5*C***), with the equilibrium strongly favoring **5*C***.

At all events, there can be no doubt that the **5*K*** photolysates contained a very effective NOCT. Thus, GC/MS (70 eV) showed that **5** and/or **5*C*** (parent ion of m/z = 260, M^+) was present at a concentration of ca. 3.5×10^{-4} M in the CD_3CN photolysates, a concentration, incidentally, which may have been just below the detection limit of the ^1H NMR measurements under the applied conditions. The identity of this GC peak as being due to the NOCT was confirmed by the fact that this peak disappeared if the photolysate was treated with an NO solution prior to the GC/MS analysis. Furthermore, upon mixing the **5*K*** in CD_3CN photolysate with a fresh solution of NO in CD_3CN, the concentration of **5*NO*** (measured by double integration of the **5*NO*** ESR signal, see Experimental Section) corresponded to a concentration of ca. 1.5×10^{-4} M (prior to its dilution with the nitric oxide solution). Thus, the ESR-measured concentration of **5**/**5*C*** is in acceptable agreement with the concentration estimated from the GC analysis. There was no ESR signal attributable to **5*NO*$_2$** in this experiment. The yield of **5**/**5*C*** in the irradiated *n*-hexane solution was even higher, viz., ca. 8×10^{-4} M by GC/MS and 4.1×10^{-4} M by double integration of the derived **5*NO*** ESR spectrum (see Figure 4a). Again there was no ESR signal attributable to **5*NO*$_2$**. After 20 days at 20 °C the ESR signal due to **5*NO*** decreased by only 20%. That is, **5*NO*** is a very persistent radical.

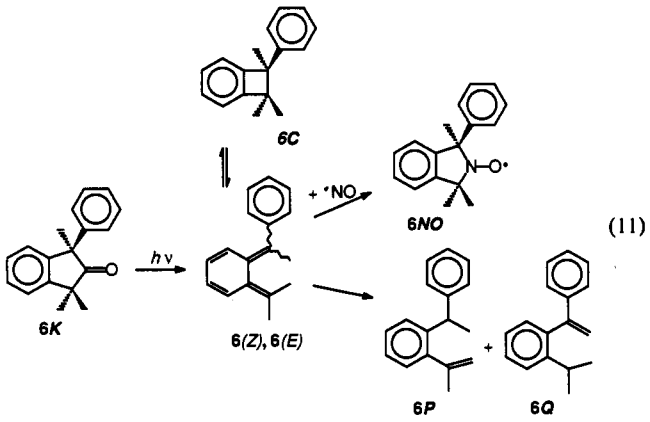


(10)

The long lifetime implied for the NOCT obtained by photolysis of **5*K*** by its method of discovery was confirmed most simply by nitric oxide trapping: storage of a **5*K*** photolysate solution for 3 days at room temperature had no measurable effect on the yield of **5*NO*** produced on mixing with fresh nitric oxide solutions. Thus, **5*K*** provides a NOCT (**5**/**5*C***) which can be considered to be thermally stable at 37 °C for most conceivable biological experiments.

Injection of a **5*K*** in CH_3CN photolysate into the incubation fluid above cultured Kupffer cells (rat liver macrophages) which had been stimulated to produce nitric oxide by addition of lipopolysaccharides (bacterial endotoxin) was followed after 1 h by extraction with *n*-hexane and examination of the hexane layer by ESR.[6] A strong signal due to **5*NO*** (Figure 4b) was obtained, stronger in fact than that obtained when solutions of **1**[6] or **2** were used in such experiments—a result that is not unexpected in view of the "infinite" lifetime of **5** at 37 °C (on the 1–4-h time scale of these experiments) vs the lifetimes of only minutes for **1** and **2** (*vide supra*). Integration of the ESR spectrum obtained in this Kupffer cell culture experiment gave a **5*NO*** concentration of 4.5×10^{-6} M, which corresponded to the trapping of 2.7 nmol of the NO produced by the macrophages in 1 h in a single culture tube. This yield of NO is 3–4 times greater than the 0.8 (nmol/h)/culture tube which would have been expected[28] on the basis of other NO measurement methods.[29,30]

Attempt to Simplify and Improve upon the Serendipitously Discovered Long-Lived o-Quinodimethanes. The improved thermal stability of **5** (and its methylated and trideuteriomethylated relatives),[27] relative to **1**, is presumably due to the extension of the polyene system by the indenyl group, since such an extension should increase the thermodynamic stability of the quinodimethane. We therefore reasoned that a more simple but similarly strongly delocalizing substituent should also produce a long-lived *o*-quinodimethane with useful NOCT properties. With this idea in mind, we synthesized 1-phenyl-1,3,3-trimethyl-2-indanone (**6*K***) from dibenzyl ketone via a fairly simple route but in relatively low yield (see Experimental Section). This ketone proved to be rather resistant to photoinduced decarbonylation, almost no conversion of **6*K*** being achieved with 254-nm light in CH_3CN between −40 and 0 °C. However, eventually the photolysis succeded using 300-nm light and a 5×10^{-2} M solution of **6*K*** in *n*-hexane at 20 °C. The ^1H NMR spectra of the photolysate showed the characteristic resonances of both of the sigmatropic 1,5-hydrogen-transfer products expected from **6**, viz. *o*-(1-phenylethyl)-α-methylstyrene (**6*P***) and 1-(2-isopropylphenyl)-1-phenylethene (**6*Q***) (reaction 11).



(11)

Interestingly, the predominant mode of hydrogen transfer (≥80%) was from the dimethylmethylene group to form **6*P***, rather than from the methylphenylmethylene group to form **6*Q***. We suggest that the most probable explanation for this regioselectivity is connected with the relative stability of *(Z)*- and *(E)*-7-phenyl-7,8,8-trimethyl-*o*-quinodimethane (**6*(Z)*** and **6*(E)***). This as-

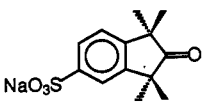
(28) For details see ref 21 in the present ref 6.
(29) The usual other methods were chemiluminescence and spectrophotometry; see ref 7.
(30) Since no direct comparison was made on identical Kupffer cell cultures between the NO yield measured via **5** and that measured by any of the usual methods,[29] this result does not necessarily imply that **5** is the most reliable quantitative probe for NO production. What it does necessarily imply is that **5** is at least as good as any of the more traditional analytical methods. The problems involved in quantitative analyses for NO are further illustrated by the different rates of NO production found for the same experiment when measured by an ESR method and by the release of nitrite: Mülsch, A.; Schray-Utz, B.; Mordvintcev, P. I.; Hauschildt, S.; Busse, R. *FEBS Lett.* **1993**, *321*, 215–218.

sumption is supported by MM2ERW force field[31,32] calculations, which indeed predict **6(Z)** ($\Delta H_f°$ = 69.6 kcal/mol) to be thermodynamically slightly favored over **6(E)** ($\Delta H_f°$ = 71.8 kcal/mol). Since the minor product **6Q** ($\Delta H_f°$ = 42.0 kcal/mol) is calculated to be only 2.1 kcal/mol more stable than **6P** ($\Delta H_f°$ = 44.1 kcal/mol), the activation barriers and, hence, the hydrogen-transfer rates for the **6(Z)** → **6P** and the **6(E)** → **6Q** reactions should be almost identical; i.e., the **6P**/**6Q** ratio should reflect the **6(Z)**/**6(E)** concentration ratio.

To our surprise, addition of a fresh saturated solution of nitric oxide to the **6K** photolysate described above did not produce the ESR signal of **6NO** "instantaneously" (i.e., in ≤1 min), as was the case when **5NO** was formed from **5**. Instead, the **6NO** ESR signal "grew in" slowly only reaching its final intensity after ca. 3 h (Figure 5). The signal was very strong, and we presume that all **6** had been converted to **6NO** because the signal did not change in intensity for the next 4 days. No trace of the NO_2 adduct **6NO₂** could be detected. However, our failure to obtain NMR evidence for **6** combined with the slowness of the reaction with NO does suggest to us that the stable form of **6** may be the corresponding benzocyclobutene **6C** and that this only undergoes a slow ring opening to give the active trap **6**.

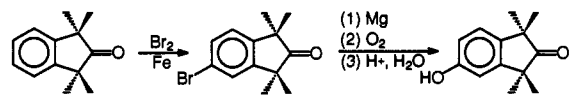
It was readily demonstrated that **6**/**6C** had a very satisfactory thermal stability by showing that a sample of the photolysate stored for 4 days at 20 °C and then mixed with a fresh solution of NO gave (after the 3-h grow-in period) an ESR signal due to **6NO** which was just as intense as that of the product produced with a sample of the same photolysate which had been stored at −78 °C.

Studies on Water-Soluble, Tetra-Alkyl-Substituted 2-Indanones and the Corresponding o-Quinodimethanes. Sulfonation (H_2SO_4/SO_3) of the aromatic ring of **1K** and **2K** followed by neutralization with NaOH yielded the water-soluble indanones **7K** and **8K**. Unfortunately, we were unable to photodecarbonylate these compounds.

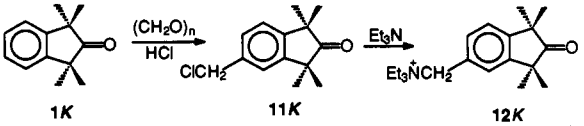


7K
8K (all $CH_3 \Rightarrow CD_3$)

Two other attempts to produce water-soluble NOCTs were tried before success was achieved. Briefly, the first involved the bromination of **1K** to form **9K** followed by Grignard formation and oxygenation to yield the hydroxy-substituted indanone **10K** (reaction 12), and the second the chloromethylation of **1K** to



1K **9K** **10K** (12)



1K **11K** **12K** (13)

form **11K** followed by treatment with triethylamine to give the tetraalkylammonium-substituted indanone **12K** (reaction 13). No products could be detected by ^1H NMR upon photolysis of **9K** (5×10^{-2} M, 254 nm, 1 h, −40 °C in CD_3CN) and **10K** (5×10^{-2} M, 254 nm, 5 h, 15 °C, and 300 nm, 2.5 h, 15 °C, both in CD_3-

(31) Roth, W. R.; Adamczak, O.; Breuckmann, R.; Lennartz, H. W.; Boese, R. *Chem. Ber.* **1991**, *124*, 2499–2521.

(32) The MM2ERW force field has been claimed[31] to predict the heats of formation of conjugated hydrocarbon compounds within ±1 kcal/mol. We thank Professor F.-G. Klärner, Essen, for performing the calculations.

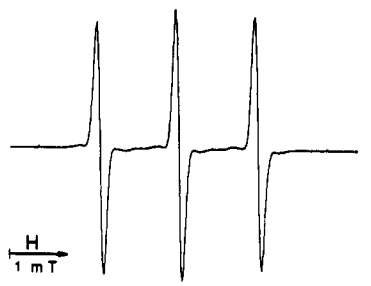
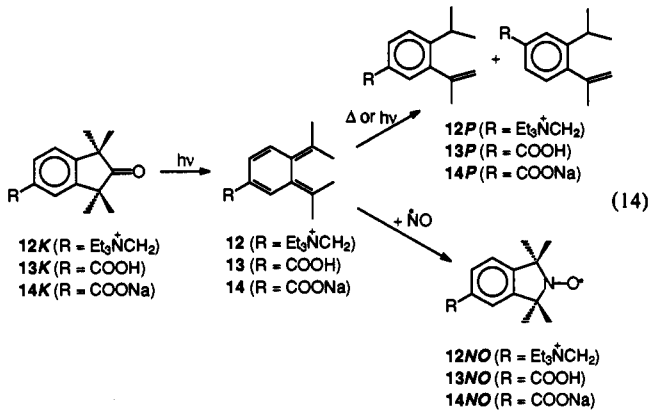


Figure 5. ESR spectrum of **6NO** in *n*-hexane at 293 K 3 h after mixing with a fresh NO solution.

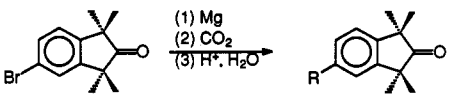
CN). The fact that treatment of these photolysates with nitric oxide did not produce any nitroxide ESR signals was therefore not entirely unexpected. Photolysis of **12K** (4×10^{-2} M, 300 nm,



(14)

2 h, 20 °C) gave a small yield of the two regioisomeric tetraalkylammonium-substituted *o*-isopropyl-α-methylstyrenes (**12P**) in approximately equal amounts. On admixing this photolysate with a fresh solution of NO in D_2O,[19] a weak ESR spectrum of **12NO** was obtained. Surprisingly, the buildup of the **12NO** ESR signal was not as rapid as was the case for **1NO** or **2NO**. Instead, after an initial "instantaneous" growth there was a further slow growth of the signal which eventually (after ca. 3 h) doubled in intensity.

Success in making a water-soluble NOCT was finally achieved by treating the **9K** Grignard with carbon dioxide to form the carboxylic acid derivative **13K** (reaction 15). Photolysis (254



9K **13K** (R = COOH) **14K** (R = COONa) (15)

nm, 1 h, −40 °C) of ca. 5×10^{-2} M **13K** in CD_3CN/[D_8]THF (3:1, v/v) yielded some of the desired *o*-quinodimethane **13**, as shown by ^1H NMR (300 MHz). This compound was also synthesized by LFP (308 nm) of **13K** in CH_3CN. The decay of **13** at 298 K was monitored by UV/vis spectroscopy (λ_{max} = 378 nm), and in two separate experiments the rate constant for decay, k_2(**13**), was found to be 1.2×10^{-3} s^{-1} (see Figure 6). This decay rate constant is not sensibly different from the k_2(**1**) values recorded in Table 1 at the same temperature. This means that the attachment of a carboxylate group to the aromatic ring of **1** does not influence the rate of the 1,5-sigmatropic rearrangement to any significant extent. We can therefore plan to use the same water-solubilizing group with long-lived NOCTs without any fear of destroying their desirable properties.

On mixing the **13K** in CH_3CN photolysate with a fresh solution of nitric oxide in the same solvent, a fairly strong ESR spectrum of **13NO** was obtained (reaction 14), there being no trace of

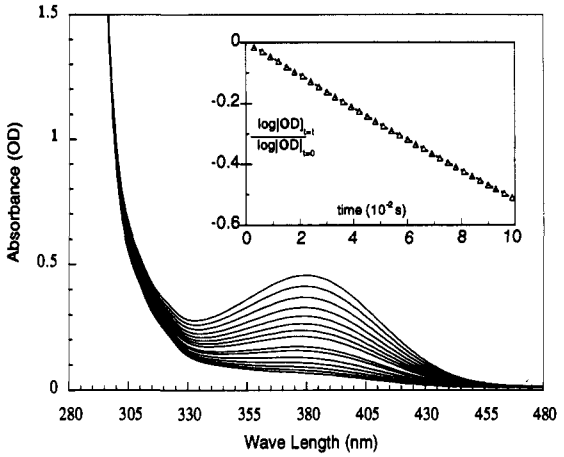
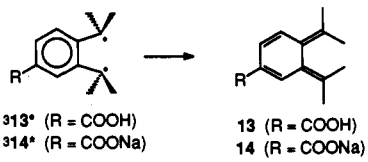


Figure 6. UV/vis absorption spectrum of **13** in CH_3CN at 298 K. Individual traces were recorded at 100-s intervals. Inset: first-order decay trace of the absorption recorded at 378 nm.

13*NO*$_2$ (in agreement with a fairly high water content in the photolysate,[19] as indicated by ^{1}H NMR). The spectrum was rather asymmetric, probably because of the presence of two (or more) isomers of **13*NO***. These isomers might be conformational; i.e., the C=O group of the carboxyl moiety might adopt an *s-cis* and an *s-trans* orientation with respect to the neighboring double bond and/or they might involve unionized **13*NO*** and its ionized carboxylate anion.[33] The origin of the asymmetry in the ESR spectrum of **13*NO*** was not explored.

The sodium salt of **13*K*** was also prepared (**14*K***). Photolysis (254 nm, 1 h, 0 °C) of a 5 × 10^{-2} M solution in D_2O gave no photoproducts detectable by ^{1}H NMR. However, photolysis with 300-nm light (2 h, 7 °C in D_2O/phosphate buffer, pH 7.5) gave measurable yields by ^{1}H NMR of the two substituted *o*-isopropyl-α-methylstyrenes **14*P***. Although the concentration of the carboxylate anion **14** was too low to be detected by ^{1}H NMR (300 MHz) under any of the above conditions, nitric oxide trapping from the foregoing photolysate proved the presence of **14** in that a good ESR spectrum of **14*NO*** was observed (Figure 7) after mixing of the photolysate with a fresh solution of NO in pH 9 buffer. Of course, **13** and **14** would not, themselves, be suitable as NOCTs in biological systems because of their short lifetimes. What **13** and **14** have shown is that the addition of a carboxylate group does not destroy the nitric oxide trapping capability of an *o*-quinodimethane, nor does it affect the thermal stability the *o*-quinodimethane.

In LFP experiments the decays of the triplet biradicals ^{3}**13*** and its sodium salt ^{3}**14*** were monitored, the rate constants for



^{3}**13*** (R = COOH)
^{3}**14*** (R = COONa)

13 (R = COOH)
14 (R = COONa)

(16)

decay being 1.5 × 10^6 and 1.7 × 10^6 s^{-1}, respectively, at 20 °C. These values are equal within experimental error to the rate constants obtained by Scaiano and co-workers[10,13] and by ourselves for the process ^{3}**1*** → **1** (reaction 3), viz., 1.7 × 10^6 and 1.4 × 10^6 s^{-1}, respectively. Thus, the carboxylate group appears to be "inert" with respect to all properties of **1**—other than its water solubility and λ_{max}—which relate to its utility as a NOCT.

Conclusion

The nitric oxide cheletropic trap generated by photolysis of **5*K***—which may be entirely **5** or may be an equilibrium mixture of **5** and **5*C***—has a sufficiently long lifetime that it would serve as a very effective lipophilic NO trap in biological systems. Structural modification to achieve water solubility would simply require the addition of a carboxylate group to one of the aromatic rings.

We are currently exploring the equilibrium between benzocyclobutenes and *o*-quinodimethanes with a view to utilizing the former as long-lived precursors for the latter which would then serve as effective NOCTs.

(33) Asymmetry due to slow tumbling may also contribute to the observed spectral shape.

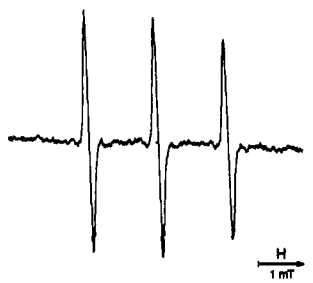


Figure 7. ESR spectrum of **14*NO*** in D_2O/phosphate buffer, pH 7.5, at 292 K.

Experimental Section

Analytical instruments. ^{1}H, ^{2}H, and ^{13}C NMR spectra (internal standard TMS): Bruker AMX-300, -400, and -600, Varian Gemini 200. MS (EI 70 eV): Finnigan MAT 312/188, ion source temperature 180–200 °C. GC/MS (EI 70 eV): Hewlett-Packard HP 5971 A (ion source temperature 180 °C) and HP 5890 Series II chromatograph (50 m HP1 octamethyltetrasilicon capillary column). GC: Varian 3700, 25-m OV-101 capillary column. Preparative GC: Varian 940 Aerograph, 1-m OV-101. HPLC: Varian Vista and HP 1040A UV/vis detector, 30-cm Varian MCH-10 column. IR (neat or KBr pellet): Perkin Elmer 1600 series FTIR. UV/vis: Cary 219 and Hewlett-Packard HP8452A ,1-cm cell. ESR: Bruker ER-420 X-band spectrometer. Elemental analyses: Heraeus EA 301. Melting points (uncorrected): Reichert Thermovar 300 429.

Photogeneration of NOCTs from 2-Indanones (General Procedure). Typically 2–7 x 10^{-2} M solutions of the 2-indanones in a deoxygenated solvent (acetonitrile, water, cyclopentane, THF, or *n*-hexane) were transferred into a long-necked, septum-capped 1-cm UV quartz cell and the cell was placed in an externally cooled methanol bath in a double-walled quartz jacket. Irradiation was performed in a Rayonet photoreactor (#RPR-100; The Southern New England Ultraviolet Company) at 254 (RPR 2537 lamps) or 300 nm (RPR 3000 lamps) with continuous stirring of the solution by a slow stream of argon which was passed through the solution via a hypodermic needle. In the following, the photolysis conditions which are given in parentheses refer to concentration of ketone, solvent, wavelength of irradiation, duration of the irradiation period, and temperature. Photolysates were analyzed by GC/MS and ^{1}H and ^{13}C NMR spectroscopy and were stored on dry ice.

In-Vitro Reaction of NOCTs with NO Solution for ESR Experiments (General Procedure). Saturated NO solutions (typically 1.5 × 10^{-2} M[14]) were prepared by bubbling NO from a cylinder (Messer-Griesheim 2.8; 99.8% NO) for 15 min through a deoxygenated solvent in a septum-capped vial by means of hypodermic needles. The solvents were deoxygenated by bubbling with argon for 1 h prior to the bubbling with NO. Typically a 0.2–0.5-mL solution from the photolysis of the indanones was transferred using a hypodermic syringe into a septum-capped, argon-flushed, and dry quartz ESR tube (external diameter 3 mm for acetonitrile, 4 mm for nonpolar solvents) or a 0.4-mm quartz flat cell (for water). After additional flushing of the solution with argon for 5 min, 0.02–0.1 mL of the NO solution was added using a hypodermic syringe, the solutions were briefly mixed by the Ar stream, and the ESR tube was then placed in the cavity of the ESR spectrometer.

ESR Measurements. ESR experiments were performed at ambient temperature in a double cavity at microwave power levels of 1 mW and 0.4–1-G modulation amplitude. The second cavity contained a calibrated spin concentration standard. ESR parameters were refined by computer simulation. Spin concentrations were determined by double integration of the best fit simulated spectra of the nitroxide radicals and comparison with the double integration of the signal from the spin standard. The spin standard was recorded with the same instrument settings (except,

when necessary, for the signal gain) as those for the nitroxide signal. Microwave power saturation curves were measured for **2*NO***, **2*NO*$_2$** and **5*NO***. For **2*NO*** and **2*NO*$_2$**, saturation (maximum ESR signal intensity) was observed at power levels of about 10 mW, whereas the signals of **5*NO*** did not saturate up to 160 mW.

Trapping of NO and NO_2 from the Gas Phase. This experiment was performed using a stainless steel apparatus normally employed for investigations of heterogeneous gas-phase catalysis.[34] Briefly, a helium/NO/NO_2 mixture (1030 ppm NO, 20 ppm NO_2) from a cylinder (UCAR) was further diluted with helium to give a NO concentration of about 160 ppm and a NO_2 concentration of about 3 ppm. The gas stream was injected at a flow rate of 10 mL/min via a fine glass frit into a glass absorption vessel containing a cool (0 °C), deoxygenated 5×10^{-2} M solution of **2*K*** in acetonitrile (liquid column height 3 cm), previously photolyzed at 254 nm for 1 h at −40 °C. The NO and NO_2 concentrations in the gas stream were registered automatically by combined IR (for NO) and UV (for NO_2) absorption measurement (NO/NO_2 BINOS: Leybold-Heraeus) before entering and after having left the absorption vessel. The initial NO concentration (160 ppm) decreased by about 85% within 3 min of switching on the gas flow, mainly because of the physical dissolution of NO in the solvent. Within 15 min the NO concentration returned to its initial level, a result which reflects both the achievement of the dissolution equilibrium and the consumption of **2** (NOCT-2). During this period no NO_2 could be detected (<0.1 ppm) in the gas stream which had passed through the NOCT-2 solution. Samples of the solution were taken with a hypodermic syringe and subjected to ESR measurement as described above, showing signals of **2*NO*** and **2*NO*$_2$** in a 1:9.2 ratio. After 25 min the ESR concentration of **2*NO*$_2$** (7×10^{-6} M) corresponded rather well with the maximum possible concentration of NO_2 in the solution (1×10^{-5} M), as calculated from the integrated quantity of NO_2 which had been passed into the solution. In contrast to the nearly quantitative formation of **2*NO*$_2$**, the concentration of **2*NO*** indicated that only 0.1% of the NO passed through the solution had reacted. This means that the reaction of **2** with NO_2 is about 500 times faster than its reaction with NO (provided, any physical, e.g., solubility, phase transfer, etc., differences between the two gases can be neglected).

Cell Culture Experiments. These experiments were carried out as described previously.[6]

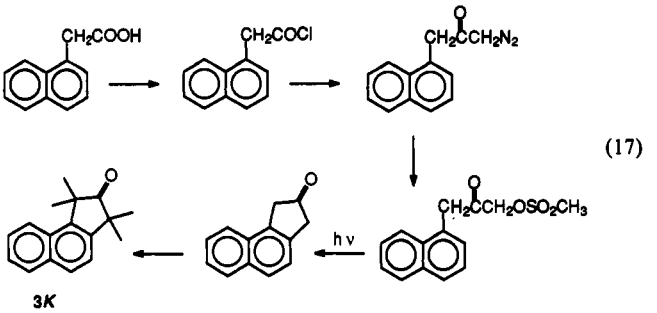
1,1,3,3-Tetramethyl-2-indanone (1*K*). This compound was prepared by literature procedures[26] and was purified by double sublimation at 40 °C/10^{-3} mbar, mp 74 °C (lit.[26b] 76 °C). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.34 (s, 12H), 7.28 (m, J = 1.8 Hz, 2H), 7.29 (m, J = 1.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.3, 49.2, 123.8, 128.4, 146.3, 226.9.

Photolysis of 1*K* in [D_3]Acetonitrile. Photolysis (5.3×10^{-2} M, CD_3CN, 254 nm, 1 h, −40 °C) led to a 24.8% conversion of **1*K*** (by GC) to give mainly *o*-isopropyl-α-methylstyrene (**1*P***) (21%). ^{1}H NMR (300 MHz, CD_3CN): δ 1.14 (d, J = 6.9 Hz, 6H), 1.97 (dd, J = 1.0, 1.5 Hz, 3H), 3.05 (sept, J = 6.9 Hz, 1H), 4.73 (qd, J = 1.0, 2.3 Hz, 1H), 5.12 (qd, J = 1.5, 2.3 Hz, 1H), 7.0–7.25 (m, 4H). 7,7,8,8-Tetramethyl-*o*-quinodimethane (**1**, NOCT-1) was formed in about 1.4% yield, corresponding to a 7.4×10^{-4} M concentration. ^{1}H NMR (300 MHz, CD_3CN): δ 1.53 (s, 6H), 1.88 (s, 6H), 6.01 (dd, J = 7.85, 3.1 Hz, AA′XX′, 2H), 6.86 (dd, J = 7.85, 3.1 Hz, AA′XX′, 2 H). The remaining 2.4% of products were distributed among a number (>10) of byproducts. Similar results were obtained in other solvents such as cyclopentane, *n*-hexane, and THF.

1,1,3,3-Tetra[D_3]methyl-2-indanone (2*K*). This compound was prepared as described for **1*K*** by reaction of 2-indanone (Aldrich) with [D_3]-methyl iodide and purified by sublimation at 10^{-3} mbar; yield 52%, mp 77 °C. ^{1}H NMR (300 MHz, CD_3CN): δ 7.28–7.35 (m). ^{2}H NMR (46 MHz, CH_3CN): δ 1.23 (s). ^{13}C NMR (75 MHz, CD_3CN): δ 25.9, 49.3, 142.1, 128.8, 146.9, 227.0. MS *m/z* (%) 200 (M^+, 95), 182 (33), 172 (52), 154 (100).

Photolysis of 2*K* in [D_3]Acetonitrile. (5.3×10^{-2} M, CD_3CN, 254 nm, 70 min, −40 °C). About 16% of the **2*K*** (^{1}H NMR analysis) was photolyzed to give mainly [D_{12}]-*o*-isopropyl-α-methylstyrene (**2*P***) (13%). ^{1}H NMR (300 MHz, CD_3CN): δ 7.0–7.25 (m). ^{2}H NMR (46 MHz, CH_3CN): δ 1.54 (6D), 2.05 (3D), 3.15 (1D), 4.86 (1D), 5.28 (1D). The yield of 7,7,8,8-tetra[D_3]methyl-*o*-quinodimethane (**2**, NOCT-2) was about 2.6%, corresponding to a 1.4×10^{-3} M concentration. ^{1}H NMR (300 MHz, CD_3CN): δ 6.01 (dd, J = 7.8, 3.2 Hz, 2H, AA′XX′), 6.84 (dd, J = 7.8, 3.2 Hz, 2H, AA′XX′). ^{2}H NMR (46 MHz, CH_3CN): δ 1.54 (s, 6D), 2.0 (s, 6D). Reversed-phase HPLC (1 mL min^{-1} methanol/water, gradient 50:50–90:10) of the photolysate showed three major peaks (UV detection at 250 nm) assigned to **2*K*** (t_r = 19 min), **2** (t_r = 28 min), and **2*P*** (t_r = 29 min). At 350-nm detection wavelength only the t_r = 28 min peak was visible. The assignment of **2** was further based on (i) the complete UV spectrum recorded for the 28-min peak, which showed the expected absorption band with a maximum at 352 nm, (ii) the decrease in the 28-min peak intensity when the samples were stored for 30 min, 1 h, and 2 h at 20 °C prior to analysis, and (iii) the absence of the 28-min peak when the sample was pretreated with excess NO solution. No other peak in the HPLC trace decreased with time or by addition of NO; thus, a significant amount of benzocyclobutene **2*C*** formed in a slow equilibrium with **2** can be ruled out. A rapid equilibrium between **2** and **2*C*** (which would result in just one HPLC peak) also is unlikely. In this case the corresponding peak should have a broader width than the other peaks. This was not observed.

1,1,3,3-Tetramethyl-5,6-benz-2-indanone (3K). This compound was synthesized following the general procedure of Tuinman[35] using the sequence



(17)

1-Naphthylacetyl chloride: by reaction of 66 mL (891 mmol) of thionyl chloride with 30 g (161 mmol) of 1-naphthylacetic acid (Aldrich); yield 33 g, 100%. IR (neat): 1800 cm^{-1}.

(1-Naphthylacetyl)diazomethane. 1-Naphthylacetyl chloride (1 g, 4.9 mmol) was dissolved in 20 mL of a 1:1 homogeneous mixture of dry acetonitrile and tetrahydrofuran. This solution was added under a nitrogen atmosphere to 5 mL (10 mmol) of a previously cooled (2 °C) solution of (trimethylsilyl)diazomethane (Aldrich). The resulting solution was stirred at 2 °C for 18 h, after which time the solvent was removed under vacuum. The residue was then chromatographed (silica gel; 2% ethyl acetate/hexane) to afford 640 mg (64%) of pure (1-naphthylacetyl)-diazomethane; yellow crystals, mp 66–67 °C (lit.[35] 67 °C). ^{1}H NMR (60 MHz, $CDCl_3$): δ 4.1 (s, 2H), 4.8 (s, 1H), 7.3–8.0 (m, 7H). IR (KBr): 1740 cm^{-1}.

1-Naphthylacetyl mesylate. (1-Naphthylacetyl)diazomethane (0.6 g, 2.8 mmol) in 11 mL of diethyl ether was added with stirring under a nitrogen atmosphere at 20 °C during 30 min to a solution of 0.185 mL (2.8 mmol) of methanesulfonic acid in 3 mL of diethyl ether. The mixture was stirred a further 30 min, and the white crystals were filtered off and used without purification for the subsequent photolytic step; yield 0.56 g (80%), mp 88–89 °C (lit.[35] 85 °C). MS *m/z* (%): 268 (M^+, 24), 154 (16), 141 (100), 115 (20).

5,6-Benz-2-indanone. (1-Naphthylacetyl mesylate (10 g, 4.0 mmol) dissolved in 23 mL of acetonitrile was photolyzed with a 2577-Å lamp for 3 days using a Rayonet photochemical reactor. The resulting dark brown solution was poured into water/ether, and the organic layer was washed with saturated sodium bicarbonate and with water. The solvent was removed under vacuum and the residue purified by column chromatography (silica gel; 10% ethyl acetate/hexane) to give 0.163 g (22.3%) of pure product, mp 112 °C (lit.[35] 112–113 °C). ^{1}H NMR (60 MHz, $CDCl_3$): δ 3.8 (s, 2H), 3.9 (s, 2H), 7.3–8.0 (m, 6H). MS *m/z* (%) 182 (37, M^+), 154 (100), 77 (11).

1,1,3,3-Tetramethyl-5,6-benz-2-indanone (3*K*). Potassium metal (1.23 g, 31.5 mmol) was added in portions to a solution of 20 mL of *tert*-butyl alcohol and 41 mL of THF at room temperature. The resulting mixture was refluxed until the potassium had dissolved, the solution was then cooled in an ice bath, and 0.7 g (3.8 mmol) of 5,6-benz-2-indanone in 20 mL of THF was quickly added, followed immediately by 4.1 mL (6.6 mmol) of iodomethane. A yellow precipitate was formed. The mixture was then refluxed for 2.5 h. Usual workup and column chromatography

(34) Oster, M. Dissertation, Institut für Technische Chemie, Universität-GH Essen, 1993.

(35) Tuinman, A.; Iwasaki, S.; Schaffner, K.; Jeger, O. *Helv. Chim. Acta* **1968**, *51*, 1778–1781. Tuinman, A. Thesis, ETH Zürich, 1970, Diss. Nr. 4448.

(silica gel; 12% ethyl acetate/hexane) afforded 0.148 g of a yellow product. Sublimation (70 °C, 5 × 10^{-2} mbar) afforded 0.122 g (14%) of pure **3K**; white crystals, mp 124 °C (lit.[9] 124–124.5 °C). ^{1}H NMR (300 MHz, CD_3CN): δ 1.35 (s, 6H), 1.59 (s, 6H), 7.40–7.60 (m, 3H), 7.87 (d, J = 8.4 Hz, 1H), 7.93 (dd, J = 8.4, 1.1 Hz, 1H), 8.18 (dd, J = 8.4, 1.1 Hz, 1H). MS m/z (%) 238 (70, M^+), 223 (100), 195 (72), 179 (20), 178 (20), 165 (39), 153 (11), 152 (13).

Photolysis of 3K in *n*-Hexane (2.6 × 10^{-3} M, *n*-hexane, 300 nm, 26.5 h, 14 °C) GC/MS analysis indicated a smooth 69% conversion to 1-(2-propenyl)-2-isopropyl naphthalene (**3P**)[9] (66.7%). ^{1}H NMR (300 MHz, CD_3CN): δ 1.22 (d, J = 6.9 Hz, 3H), 1.28 (d, J = 6.9 Hz, 3H), 2.09 (dd, J = 1.0, 1.5 Hz, 3H), 3.30 (sept, J = 6.9 Hz, 1H), 4.89 (dq, J = 2.4, 1.0 Hz, 1H), 5.52 (dq, J = 2.4, 1.5 Hz, 1H), 7.1–7.9 (m, 6H); MS m/z (%) 210 (30, M^+), 195 (18), 180 (10), 179 (14), 178 (14), 167 (100), 165 (34), 153 (16), 152 (14). Only two other products were formed in >1% yield, one of which (1.1%) had a slightly shorter retention time and a mass spectrum virtually identical to that of **3P**. We tentatively assign this product to **3P**, formed from **3** (NOCT-3) during the GC analysis.

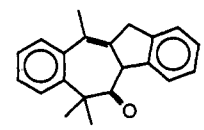
Dispiro[cyclopropane-1,1′-indane-3′,1″-cylopropane]-2′-one (4K). This compound was prepared in 28% yield according to the method of Klages and Voss,[36] mp 82 °C (lit.[36] 88 °C). ^{1}H NMR (200 MHz, CD_3CN): δ 1.40–1.48 (m, 4H), 1.70–1.77 (m, 4H), 6.80–6.90 (m, 2H), 7.17–7.28 (m, 2H). ^{13}C NMR (75 MHz, CD_3CN): δ 22.3, 33.9, 118.2, 126.6, 142.3, 216.8. MS m/z (%) 184 (M^+, 100), 169 (21), 155 (15), 141 (72), 128 (16), 115 (24). IR (KBr, cm^{-1}) 1730 (s, $\nu_{C=O}$).

Photolysis of 4K in [D$_3$]Acetonitrile (5.0 × 10^{-2} M, CD_3CN, 254 nm, 300 nm, –40 to +62 °C, 1–5 h). No photoproducts could be detected by ^{1}H NMR (300 MHz). Prolonged irradiation (300 nm, 96 h, 20 °C) gave two new products (2.5 and 3.4%), the MS spectra of which (M^+ peaks with m/z = 184) revealed that no loss of CO had occurred.

1-(2-Indenyl)-1,3,3-trimethyl-2-indanone (5K). GC analysis of the crude reaction product (1.8 g) from the preparations of **1K** which followed a literature procedure[26a] revealed the presence of a major byproduct and several minor byproducts all having retention times more than twice than that of **1K**. The overall yield of these products could be as high as 55%; the yield and the relative ratio of the byproducts varied dramatically with the reaction conditions. After removal of **1K** by sublimation (40 °C, 10^{-3} mbar), the residue typically contained (GC/MS) about 60% **5K** and several (≥20) minor products in the 13–1% range. **5K** was isolated in 97% pure form by preparative GC of 0.2 g of the residue at 220 °C, yellow oil (79 mg). ^{1}H NMR (300 MHz, CD_3CN): δ 1.29 (s, 3H), 1.35 (s, 3H), 1.63 (s, 3H), 3.30 (q, J = 0.7 Hz, 2H), 6.43 (sext, J = 0.7 Hz, 1H), 7.05–7.45 (m, 8H). ^{13}C NMR (75 MHz, CD_3CN, DEPT-135, COLOC): δ 24.9, 26.6, 27.7, 39.4, 50.0, 56.9, 121.7, 124.1, 124.6, 125.4, 125.5, 127.3, 128.9, 129.3, 144.5, 144.7, 145.2, 147.4, 152.3, 222.7. MS m/z (%) 288 (M^+, 65), 273 (11), 245 (100), 230 (37), 215 (44), 202 (9), 173 (46), 145 (22), 128 (10), 115 (24). Anal. Calc for $C_{21}H_{20}O$ (288.4): C, 87.46; H, 6.99. Found: C, 87.52; H, 6.83.

The minor byproducts were collected as a mixture. They were identified, with some certainty, by GC/MS (molecular masses of m/z = 302 and 316) and ^{1}H NMR spectra to be mainly the various possible regio- and diastereomers of 1-(monomethyl-2-indenyl)-1,3,3-trimethyl-2-indanone and 1-(dimethyl-2-indenyl)-1,3,3-trimethyl-2-indanone (**6K**). The major component (31%) of this mixture was assigned to the two diastereomers (ratio ca. 2.2:1) of 1-(3-methyl-2-indenyl)-1,3,3-trimethyl-2-indanone (which has two chiral carbon atoms). ^{1}H NMR (300 MHz, CD_3CN): δ 0.90/0.81 (d, J = 7.5 Hz, 3H), 1.36/1.37 (s, 3H), 1.38/1.39 (s, 3H), 1.66/1.69 (s, 3H), 3.32/3.33 (qd, J = 7.5, 1.1 Hz, 1H), 6.80/6.66 (d, J = 1.1 Hz, 1H), 7.1–7.4 (m, 8H). MS m/z (%) 302 (M^+, 26), 287 (2), 259 (42), 244 (17), 229 (43), 215 (18), 174 (100), 173 (46), 145 (46), 129 (90), 115 (15). A second component (27%) was identified as 1-(1-methyl-2-indenyl)-1,3,3-trimethyl-2-indanone. ^{1}H NMR (300 MHz, CD_3CN): δ 1.40 (s, 3H), 1.41 (s, 3H) [probably 1.95 (t, 3H); covered by solvent peak], 3.52 (q, J = 1.1 Hz, 1H), 3.54 (q, J = 1.1 Hz), 7.1–7.4 (m, 8H). MS m/z (%) 302 (M^+, 42), 287 (5), 259 (74), 244 (37), 229 (51), 174 (100), 173 (51), 145 (44), 129 (94), 115 (21).

Photolysis of 5K in [D$_3$]Acetonitrile (5 × 10^{-2} M, CD_3CN, 254 nm, 1 h, –40 °C). According to the GC/MS analysis about 9% of **5K** was converted and formed a number of new products most of which had retention times greater than that of **5K** and molecular ion peaks at m/z = 288, indicating that no loss of CO had occurred. The major photoproduct (ca. 5% yield) was identified (in agreement with a related product found in the photolysis of 1-indenyl-1-methyl-2-indanone[37]) as 1,2,6,7-dibenzo-2,5,5-trimethylbicyclo[5.3.0]deca-1,3,6-trien-6-one (**15**).



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^{1}H NMR (300 MHz, CD_3CN): δ 1.24 (s, 3H), 1.25 (s, 3H), 2.22 (s, 3H), 3.71 (m, $J \leq 1$ Hz, 1H), 3.76 (m, $J \leq 1$ Hz, 1H), 4.42 (m, $J \leq 1$ Hz, 1H), 7.1–7.4 (m, 6H), 7.5–7.6 (m, 2H). MS m/z (%) 288 (M^+, 49), 273 (11), 245 (100), 230 (42), 215 (51), 202 (10), 173 (45), 145 (20), 128 (11), 115 (22). One of the few GC peaks of shorter retention times (0.5% yield) was tentatively assigned to 7-(2-indenyl)-7,8,8-trimethyl-*o*-quinodimethane (**5**) or to 7-(2-indenyl)-7,8,8-trimethylbenzocyclobutene (**5C**) on the basis of its mass spectrum and NO-trapping capabilities. MS m/z (%) 260 (76, M^+), 245 (100), 230 (56), 215 (76), 183 (12), 156 (59), 144 (43), 141 (23), 129 (66), 115 (44), 104 (47), 91 (14). The ^{1}H NMR (300 MHz) spectrum of the photolysate showed several new, weak resonances in the 3–7 ppm region. Signals which could be assigned to **5** and/or **5C** were not detected with any certainty. Likewise, an intramolecular Diels–Alder adduct of **5** (similar to that reported in ref 37) could not be identified.

1-(2-Indenyl)-1,3,3-tri[D$_3$]methyl-2-indanone and [D$_3$]methylated 1-(2-Indenyl)-1,3,3-tri[D$_3$]methyl-2-indanones. These compounds were formed during the synthesis of **2K**. They were separated from **2K** as a brown oil by repeated sublimation (70 °C, 1.1 × 10^{-2} mbar). GC/MS analysis showed the presence of ≥12 compounds having none (m/z (M^+) = 297), one (m/z (M^+) = 314), two (m/z (M^+) = 331), or three (m/z (M^+) = 348) methyl groups attached to the indenyl group. By ^{1}H NMR spectroscopy the three major components (ca. 63%) of the mixture were identified to be 1-(2-indenyl)-1,3,3-tri[D$_3$]methyl-2-indanone [^{1}H NMR (300 MHz, CD_3CN): δ 3.31 (q, J = 0.8 Hz, 2H), 6.44 (sext, J = 0.8 Hz, 1H). MS m/z (%) 297 (49, M^+), 279 (8), 251 (100), 233 (32), 215 (27), 182 (52), 154 (23).], 1-(1-[D$_3$]methyl-2-indenyl)-1,3,3-tri[D$_3$]methyl-2-indanone [^{1}H NMR (300 MHz, CD_3CN): δ 3.54 (s, 1H), 3.52 (s, 1H). MS m/z (%) 314 (42, M^+), 296 (4), 268 (74), 250 (34), 232 (50), 218 (10), 184 (78), 182 (72), 166 (8), 154 (44), 132 (100).], and 1-(3-[D$_3$]-methyl-2-indenyl)-1,3,3-tri[D$_3$]methyl-2-indanone [^{1}H NMR (300 MHz, CD_3CN) (2 diastereomers): δ 3.31/3.32 (d, J = 1.5 Hz, 1H), 6.66/6.80 (dd, J = 1.5, 0.6 Hz, 1H). MS m/z (%) 314 (28, M^+), 296 (5), 268 (43), 250 (15), 232 (42), 218 (8), 184 (73), 182 (59), 154 (50), 132 (100).] in a relative ratio of ca. 1:1.7:3. No attempt was made to separate these compounds.

On photolysis in [D$_3$]acetonitrile solution (3.3 × 10^{-2} M, CD_3CN, 254 nm, 1 h, –40 °C) about 13% of the above mixture of compounds was converted to products (by 300-MHz ^{1}H NMR analysis). Several (>10) new resonances in the 3.5–4.6 ppm region indicated the formation of rearrangement products similar to compound **15**. Signals which might be attributed to (an) *o*-quinodimethane(s) were below the detection limit (ca. 2 × 10^{-4} M). By GC/MS one peak of shorter retention time than any of the peaks from the unphotolyzed mixture was detected (0.4%), the mass spectrum of which was consistent with the formation of 7-([D$_3$]-methyl-2-indenyl)-7,8,8-tri[D$_3$]methyl-o-quinodimethane or 7-([D$_3$]-methyl-2-indenyl)-7,8,8-tri[D$_3$]methylbenzocyclobutene. MS m/z (%) 286 (14, M^+), 268 (100), 250 (11), 232 (39), 231 (9).

1-Phenyl-1,3,3-trimethyl-2-indanone (6K). Following a literature procedure[38] 1-phenyl-2-indanone was obtained from dibenzyl ketone in 34% yield after purification by column chromatography (silica gel, *n*-pentane). Methylation of the product (1.0 g, 4.8 mmol) was carried out as described for 2-indanone.[26a] Column chromatography (neutral alumina, chloroform/*n*-pentane, 1:5) afforded 0.23 g (19%) of **6K**, colorless oil. ^{1}H NMR (200 MHz, CD_3CN): δ 1.20 (s, 3H), 1.37 (s, 3H), 1.72 (s, 3 H), 7.17–7.46 (m, 9H). ^{13}C NMR (50 MHz, CD_3CN): δ 25.7, 26.3, 49.8, 57.9, 124.0, 125.8, 127.7, 127.7, 128.8, 128.8, 129.2, 144.2, 145.0, 145.5, 223.1. MS m/z (%) 250 (M^+, 43), 222 (2), 207 (100), 192 (54), 77 (9).

Photolysis of 6K in *n*-Hexane (5.1 × 10^{-2} M, *n*-hexane, 300 nm, 6 h, 20 °C). The solvent was removed under vacuum, and the residue was dissolved in CD_3CN. The ^{1}H NMR spectrum indicated a conversion of

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about 16%. The major product (12%) was (1-phenylethyl)-α-methylstyrene (**6P**). ^{1}H NMR (200 MHz, CD_3CN): δ 1.58 (d, J = 7.2 Hz, 3H), 1.97 (dd, J = 1.1, 1.4 Hz, 3H), 4.48 (q, J = 7.2 Hz, 1H), 4.80 (qd, J = 1.1, 2.2 Hz, 1H), 5.26 (qd, J = 1.4, 2.2 Hz, 1H). 1-(2-isopropylphenyl)-1-phenylethene (**6Q**) was formed to about 1.5%. ^{1}H NMR (200 MHz, CD_3CN): δ 1.04 (d, J = 6.9 Hz, 6H), 5.17 (d, J = 1.4 Hz, 1H), 5.86 (d, J = 1.4 Hz, 1H), 7.15–7.50 (m, 8H). ^{1}H NMR signals from **6** could not be identified, implying that its concentration was ≤2 × 10^{-4} M. Also, a product which might have been formed by an intramolecular Diels–Alder reaction of the quinodimethane moiety of **6** with the phenyl substituent (cf. ref 37) was not detected with certainty.

Sodium 1,1,3,3-Tetramethyl-2-indanone-5-sulfonate (7K). **1K** (5.0 g, 26.6 mmol) was chlorosulfonated by a standard procedure[39] to give 5-(chlorosulfonyl)-1,1,3,3-tetramethyl-2-indanone (4.21g), which was hydrolyzed by reflux (2 h) in 50% formic acid and neutralized with sodium hydrogencarbonate. Recrystallization from 90% ethanol and drying (20 h, 250 °C, 10^{-3} mbar) afforded **7K** (3.20 g, 41%), colorless crystals, mp 460 °C dec. ^{1}H NMR (300 MHz, D_2O): δ 1.34 (s, 6H), 1.36 (s, 6H), 7.52 (dd, J = 7.4, 1.4 Hz, 1H), 7.77 (dd, J = 7.4, 1.4 Hz, 1H), 7.79 (d, J = 1.4 Hz, 1H). MS m/z (%) 296 (M^+, 62), 268 (84), 243 (100), 144 (86). Anal. Calc for $C_{13}H_{15}NaO_4S$ (290.3): C, 53.78; H, 5.21. Found: C, 53.40; H, 5.14.

Sodium 1,1,3,3-Tetra[D_3]methyl-2-indanone-5-sulfonate (8K). This compound was prepared from **2K** by following the same procedure as that for the **1K** → **7K** reaction. Sulfonic acid. ^{1}H NMR (60 MHz, [D_6]DMSO): δ 7.4–7.9 (m, aromatic H's). MS-FAB, MF-FAB mode (neg) 279 (M − 1). Sodium sulfonate (**8K**), mp > 300 °C. MS-FAB, MF-FAB mode (neg) 325 (M − 1 + Na). Anal. Calc for $C_{13}H_3D_{12}NaO_4S$ (302.3): S, 10.55. Found: S, 10.50.

5-Bromo-1,1,3,3-tetramethyl-2-indanone (9K). Bromination of **1K** (10.0 g, 53.1 mmol) by a standard procedure[40] yielded, after purification by sublimation (80 °C, 10^{-3} mbar) **9K** (5.1 g, 34%), mp 76 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (s, 6 H), 1.34 (s, 6H), 7.15 (dd, J =8.0, 0.7 Hz, 1H), 7.40 (dd, J = 2.0, 0.7 Hz, 1H), 7.42 (dd, J = 8.0, 2.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.4, 26.5, 48.7, 49.1, 121.3, 124.8, 126.4, 130.9, 144.8, 148.1, 224.8. IR (KBr, cm^{-1}) 1742 (s, $\nu_{C=O}$); MS m/z (%) 268/266 (M^+, 56/58), 253/251 (39/41), 240/238 (29/31), 225/223 (52/54), 144 (100), 129 (46), 115 (19), 64 (12), 40 (11). Anal. Calc for $C_{13}H_{15}BrO$ (267.2): C, 58.44; H, 5.66; Br, 29.91. Found: C, 58.74; H, 5.74; Br, 29.80.

5-Hydroxy-1,1,3,3-tetramethyl-2-indanone (10K). According to a standard procedure[41] the Grignard reagent was prepared from **9K** (1.0 g, 5.4 mmol) and Mg turnings (0.10 g, 3.7 mmol) in dry THF (15 mL). A stream of dry air was passed through the reaction mixture for 20 h. Standard workup afforded **10K** (0.15 g, 20%), mp 253 °C (from cyclohexane). ^{1}H NMR (200 MHz, CD_3CN): δ 1.25 (s, 6H), 1.26 (s, 6H), 6.75 (m, 2H), 7.16 (m, 1H). ^{13}C NMR (75 MHz, CD_3OD): δ 26.9, 27.2, 49.5, 50.1, 110.4, 116.3, 125.0, 137.6, 148.2, 158.4, 228.9. IR (KBr, cm^{-1}) 3330 (s, ν_{OH}), 1732 (s, $\nu_{C=O}$). Anal. Calc for $C_{13}H_{16}O_2$ (204.3): C, 76.44; H, 7.89. Found C, 76.00; H, 7.90.

5-(Chloromethyl)-1,1,3,3-tetramethyl-2-indanone (11K). **1K** (7.1 g, 38 mmol) and paraformaldehyde (30 g) were suspended in a mixture of concentrated hydrochloric acid (120 mL) and glacial acetic acid (50 mL). The mixture was refluxed for 48 h with vigorous stirring and extracted with diethyl ether, and the organic layer was washed with water to neutrality and dried over magnesium sulfate to give 4.3 g (48%) of a red-brownish oil. Purification by preparative GC (180 °C) yielded colorless crystals, mp 49 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.32 (s, 6H), 1.33 (s, 6H), 4.61 (s, 2H), 7.13–7.45 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.5, 26.6, 46.3, 48.8, 48.9, 123.2, 123.4, 128.2, 136.3, 146.2, 146.5, 225.6. IR (KBr, cm^{-1}) 1744 (s, $\nu_{C=O}$), 703 (s, ν_{Cl}). MS m/z (%) 238/236 (M^+, 80), 223/221 (49), 210/208 (47), 201 (25), 195/193 (100), 173 (11), 157 (52), 141 (24), 128 (37). Anal. Calc for $C_{14}H_{17}ClO$ (236.74): C, 71.03; H, 7.24. Found: C, 70.93; H, 7.33.

5-((Triethylammonio)methyl)-1,1,3,3-tetramethyl-2-indanone Chloride (12K). To a solution of the unpurified **11K** (1.5 g, 4.3 mmol) in 90% ethanol (15 mL) was added triethylamine (0.6 mL, 4.3 mmol) with stirring. The mixture was refluxed for 20 h, the solvent evaporated, and the red-brownish residue recrystallized from ethanol/ethyl acetate (1:1). Drying at 140 °C, 10^{-3} mbar, for 24 h over phosphorus pentoxide gave **12K** (0.1 g, 7%), colorless crystals, mp 207 °C dec. ^{1}H NMR (200 MHz, D_2O): δ 1.36 (2, 13H), 1.40 (t, J = 7.0 Hz, 9H), 3.24 (q, J = 7.0 Hz, 6H), 4.45 (s, 2H), 7.48–7.58 (m, 3H). ^{13}C NMR (75 MHz, D_2O): δ 9.7, 28.2, 28.3, 52.2, 55.0, 62.6, 126.7, 129.6, 129.7, 134.8, 149.2, 150.8, 234.9. IR (KBr, cm^{-1}) 1742 (s, $\nu_{C=O}$). MS m/z (%) 302 (M^+ − Cl, 20), 256 (50), 242 (22), 201 (100), 173 (18), 57 (80). According to the spectral data and the elemental analyses, the compound contains ca. 1.7 mol equiv of water of crystallization which could not be removed without decomposition. Anal. Calc for $C_{20}H_{32}NOCl \cdot 1.7H_2O$ (368.53: C, 65.11; H, 9.60; N, 3.79. Found: C, 65.08; H, 9.51; N, 3.56.

Photolysis of 12K (4.2 × 10^{-2} M, CD_3CN, 300 nm, 2 h, 20 °C). ^{1}H NMR analysis of the photolysate indicated the (approximately equimolar) formation of 2-isopropyl-4-((triethylammonio)methyl)-α-methylstyrene chloride and 2-isopropyl-5-((triethylammonio)methyl) α-methylstyrene chloride (**12P**) in low (ca. 2%) yield. ^{1}H NMR (200 MHz, CD_3CN): δ 1.18/1.19 (d, J = 7.3 Hz, 6H), 3.1 (m, 1H), 4.81 (m, 1 H), 5.25 (m, 1H) . Resonances which might arise from **12** could not be identified.

5-Carboxy-1,1,3,3-tetramethyl-2-indanone (13K). Carboxylation of **9K** (1.0 g, 5.4 mmol) was carried out by reaction of its Grignard compound with gaseous carbon dioxide following a standard procedure[42] to yield 0.51 g of **13K** (59%), mp 215 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36 (s, 6H), 1.37 (s, 6H), 7.37 (dd, J = 7.8, 0.6 Hz, 1H), 8.01 (dd, J = 1.3, 0.6 Hz, 1H), 8.07 (dd, J = 7.8, 1.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.3, 26.6, 49.0, 49.3, 123.3, 125.1, 128.8, 129.9, 146.9, 152.3, 171.7, 224.9. IR (KBr, cm^{-1}) 3000–2500 (s, ν_{OH}), 1750 (s, $\nu_{C=O}$), 1682 (s, $\nu_{C=O}$). MS m/z (%) 232 (M^+, 75), 217 (18), 204 (90), 189 (100), 145 (68), 128 (44), 115 (35), 91 (39). Anal. Calc for $C_{14}H_{16}O_3$ (236.74): C, 72.39; H, 6.94. Found: C, 72.12; H, 7.20.

Photolysis of 13K (5 × 10^{-2} M, CD_3CN/[D_8]THF, 3:1, 254 nm, 1 h, −40 °C). ^{1}H NMR analysis of the photolysate indicated the formation of 3-carboxy-7,7,8,8-tetramethyl-*o*-quinodimethane (**13**) (0.7%, corresponding to a 4 × 10^{-4} M concentration). ^{1}H NMR (300 MHz, CD_3CN/[D_8]THF, 3:1): δ 6.44 (d, J = 9.8 Hz, 1H), 6.92 (d, J = 9.8 Hz, 1H). These resonances decayed with a half-life of 79 min at 5 °C. 3-(2-Propenyl)-4-isopropylbenzoic acid and 4-(2-propenyl)-3-isopropylbenzoic acid (**13P**) were formed in about 13% yield (ratio ca. 4:3, arbitrary assignment). ^{1}H NMR (300 MHz, CD_3CN/[D_8]THF, 3:1): δ 1.14/1.15 (d, J = 6 Hz, 6H), 1.95 (m, 3H), 3.10 (sept, J = 6 Hz), 4.78 (m, 1H), 5.20 (m, 1H), 7.1–7.8 (m, 3H).

Sodium 1,1,3,3-tetramethyl-2-indanone-5-carboxylate (14K): prepared by neutralization of **13K** (0.3 g, 1.3 mmol) with 0.1 M NaOH, yield 0.26 g (86%) of colorless crystals, mp 240 °C dec. ^{1}H NMR (300 MHz, D_2O): δ 1.34 (s, 6H), 1.35 (s, 6H), 7.45 (d, J = 8.6 Hz, 1H), 7.84 (d, J = 8.6 Hz, 1H), 7.86 (s, 1H). ^{13}C NMR (75 MHz, D_2O): δ 28.2, 28.4, 52.1, 52.2, 125.7, 126.4, 131.5, 139.0, 148.1, 151.3, 177.9, 235.7. IR (KBr, cm^{-1}) 1742 (s, $\nu_{C=O}$), 1591, 1554, 1394 (s, $\nu_{C=O}$).

Photolysis of 14K (5 × 10^{-2} M, D_2O/buffer, pH 7.5, 300 nm, 2 h, 20 °C). ^{1}H NMR analysis of the photolysate indicated the formation of sodium 3-(2-propenyl)-4-isopropylbenzoate and sodium 4-(2-propenyl)-3-isopropylbenzoate (**14P**) (12%, ratio ca. 3:2, assignment arbitrary). ^{1}H NMR (200 MHz, D_2O): δ 1.20/1.21 (d, J = 7.0 Hz, 6H), 2.04 (m, J ≤ 1 Hz, 3H), 3.20 (sept, J = 7.0 Hz, 1H), 4.86 (m, J ≤ 1 Hz, 1 H), 5.17 (m, J ≤ 1 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1 H), 7.6–7.9 (m, 2H). Resonances which might arise from **14** were below the detection limit (≤ 2 × 10^{-4} M).

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