Superoxide-Mediated Base-Catalyzed Autoxidation of Tetraphenylcyclopentadiene

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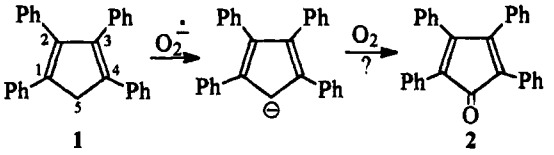
The superoxide (KO_2/18-crown-6)-mediated oxidation of tetraphenylcyclopentadiene (**1**) in aprotic media generated a variety of products following aqueous workup, including 2-hydroxy-2,4,5-triphenylfuranone (**3**), 2,3,4,5-tetraphenylfuran (**4**), *cis*-dibenzoylstilbene (**5**), *cis*- and *trans*-1,2,4,5-tetraphenyl-2-pentene-1,5-dione (**6** and **7**), and the novel benzoylformic anhydride (**8**). Treatment of the acid fraction with diazomethane yielded methyl benzoate (**9**) as the major component. The mechanism of product formation involves a series of well-precedented, base-catalyzed autoxidative processes including deprotonation of **1** by $O_2^{\bullet-}$, oxygenation, dehydration or cyclization of the resulting peroxy anion, and oxidative cleavage. Lactol **3**, furan **4**, and benzoic acid (the putative precursor to **9**) are known oxidative cleavage products of tetracyclone (**2**), which was detected in trace amounts in the reaction mixture. Isomeric 2-ene-1,5-diones **6** and **7** each isomerize to give an equilibrium mixture of the two in a 8:5 ratio. Molecular-modeling studies confirm the greater stability of the *cis*-**6** isomer over that of *trans*-**7**.

Introduction

Over the past two decades the international scientific community has become increasingly aware of the crucial role superoxide anion radical ($O_2^{\bullet-}$) plays in a vast spectrum of metabolic processes.[1,2] In aprotic media, $O_2^{\bullet-}$ reacts with organic substrates via deprotonation, nucleophilic attack, and electron transfer. In our attempt to discover highly sensitive tests for the base properties of superoxide, we explored the superoxide-mediated base-catalyzed autoxidation (BCA)[3] of tetraphenylcyclopentadiene (**1**, eq 1). We naively assumed that, as in the case



(1)

of other polyaryldivinylmethanes,[2d] cyclopentadiene **1**, too, would undergo deprotonation and oxygenation at the diallylic carbon. Such a reaction sequence would be expected to yield the corresponding dark violet and hence easily detectable tetracyclone **2**[4] (eq 1). Instead, as reported below, the superoxide-mediated reaction of **1** proved quite complex, yielding a plethora of fascinating products but only a trace of the desired highly colored dienone **2**.

Results and Discussion

The reaction of superoxide anion radical (generated from KO_2/18-crown-6) with tetraphenylcyclopentadiene (**1**) in toluene proceeded rapidly to completion (<4 h). Following aqueous workup, six products were isolated (see Scheme 1) and identified by their spectral data (*vide infra*) as compounds 2-hydroxy-2,4,5-triphenyl-3(2*H*)-furanone (**3**, 17% yield), 2,3,4,5-tetraphenylfuran (**4**, 9%), *cis*-1,2-dibenzoylstilbene (**5**, 3%), *cis*- and *trans*-1,2,4,5-tetraphenyl-2-pentene-1,5-diones (**6**, 28%, and **7**, 17%), and the novel benzoylformic anhydride (**8**, 0.8%). Diazotization of the acid fraction gave a high yield (40%) of methyl benzoate (**9**). Surprisingly, the expected and desired dark violet tetracyclone (**2**) was detected (TLC) in the product mixture in only trace amounts.

Furanone **3**,[4] furan **4**,[5] butenedione **5**[6] and, of course, methyl benzoate (**9**) are all known and spectroscopically characterized in the literature. *Cis*- and *trans*-2-pentene-1,5-diones **6** and **7**, respectively, were independently synthesized as previously described.[7] Final isomeric

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(1) See the collection of articles in the following: *Superoxide Dismutase*; Oberley, L. W., Ed.; Chemical Rubber Co.: Boca Raton, FL, 1982; Vols. 1 and 2; 1985, Vol. 3.

(2) (a) Sawyer, D. T.; Gibian, M. J. *Tetrahedron* **1979**, *35*, 1471–1481. (b) Wilshire, J.; Sawyer, D. T. *Acc. Chem. Res.* **1979**, *12*, 105–110. (c) Frimer, A. A. In ref 1, Vol. 2, pp 83–125. (d) Frimer, A. A. In *The Chemistry of Peroxides*; Patai, S., Ed.; Wiley-Interscience: Chichester, England, 1983; pp 429–461. (e) Roberts, J. L., Jr.; Sawyer, D. T. *Isr. J. Chem.* **1983**, *23*, 430–438. (f) Frimer, A. A. In *Oxygen Radicals in Biology and Medicine*; Simic, M. G., Taylor, V. A., Ward, J. F., von Sonntag, C., Eds.; Plenum: New York, 1989; pp 29–38. (g) Frimer, A. A. In *The Chemistry of Enones*; Patai, S., Rappoport, Z., Eds.; Wiley-Interscience: New York, 1989; Part 2, Chapter 17, pp 781–921. (h) Afanas'ev, I. B. *Superoxide Ion: Chemistry and Biological Implications*; Chemical Rubber Co.: Boca Raton, FL; 1989, Vol. 1; 1991, Vol. 2.

(3) (a) Sosnovsky, G.; Zaret, E. H. In *Organic Peroxides*; Swern, D., Ed.; Wiley: New York, 1970; Vol. 1, p 517–557. (b) Russell, G. A.; Janzen, E. G.; Bemis, A. G.; Geels, E. J.; Moye, A. J.; Mak, S.; Strom, E. T. *Adv. Chem. Ser.* **1965**, *51*, 112–171. (c) Russell, G. A. *Pure Appl. Chem.* **1967**, *15*, 185–206. (d) Russell, G. A.; Bemis, A. G.; Geels, E. J.; Janzen, E. G.; Moye, A. J. *Adv. Chem. Ser.* **1968**, *75*, 174–215. (e) Karnojitzky, V. *Russ. Chem. Rev. (Engl. Transl.)* **1981**, *50*, 888–899. (f) For a discussion of the BCA of enones and keto enols, see ref 2g.

(4) The reaction of tetracyclone **2** with $O_2^{\bullet-}$ has been explored: (a) Rosenthal, I.; Frimer, A. *Tetrahedron Lett.* **1975**, 3731–3732. (b) Frimer A.; Rosenthal, I. *Tetrahedron Lett.* **1976**, 2805–2808. (c) Neckers, D. C.; Hauck, G. *J. Org. Chem.* **1983**, *48*, 4691–4695. (d) Pandey, B.; Mahajan, M. P.; Tikare, R. K.; Muneer, M.; Rath, N. P.; Kamat, P. V.; George, M. V. *Res. Chem. Intermed.* **1991**, *15*, 271–291. (e) Frimer and Rosenthal[4a,b] isolated lactol **3** as the major product in high yields (>80%), but no **4**[4d] or **15**[4c,d] was observed. The discrepancy may have to do with the substantially shorter reaction times and lower $O_2^{\bullet-}$:substrate ratios used by the Israeli group.

(5) (a) Haynes, R. K.; Peters, J. M.; Wilmot, I. D. *Aust. J. Chem.* **1980**, *33*, 3653–3661. (b) Bartmann, E.; Gompper, R. *Synth. Commun.* **1987**, *17*, 263–269. (c) Haddadin, M. J.; Agha, B. J.; Tabri, R. F. *J. Org. Chem.* **1979**, *44*, 494–497.

(6) (a) Trogler, W. C.; Ibes, J. A. *Organometallics* **1989**, *1*, 536–542. (b) Cariou M. *Tetrahedron* **1991**, *47*, 799–808.

(7) Basselier, J. J. *Ann. Chim.* **1961**, *6*, 1131–1160. See also: Huabat, R.; Landais, J. *Bull. Soc. Chim. Fr.* **1975**, 2147–2152. Surprisingly, in neither paper are detailed spectral data supplied.

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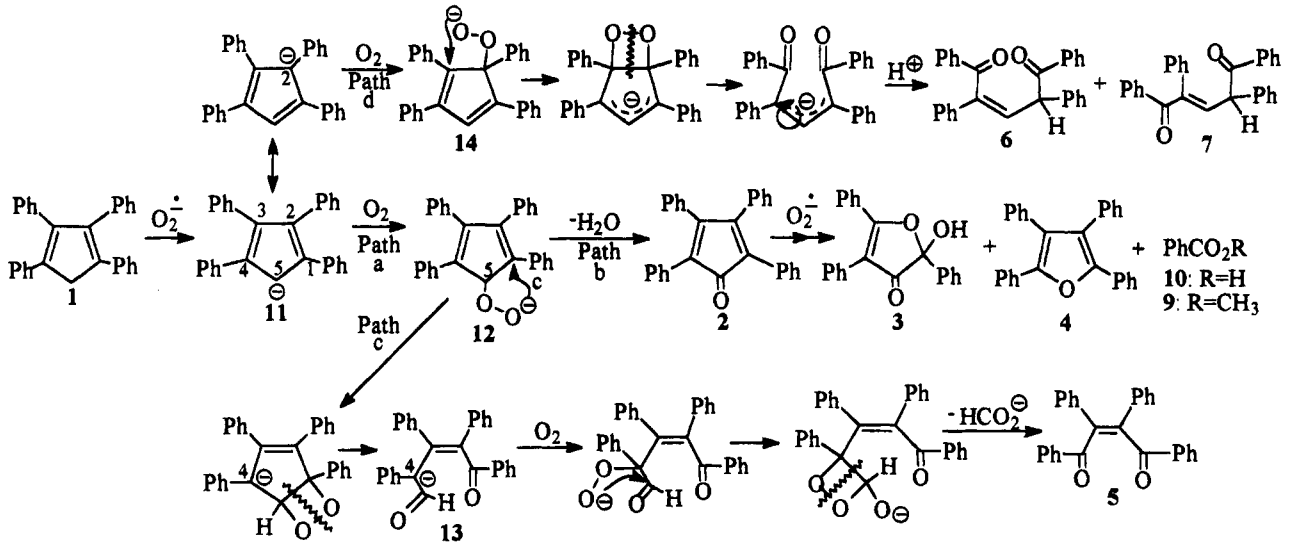
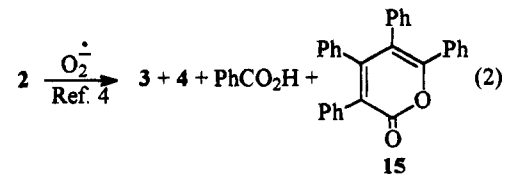
Scheme 1. Mechanism of Product Formation in Superoxide Reaction of Tetraphenylcyclopentadiene 1



assignment was achieved only after COSY, one-bond hetero-COSY, and long-range hetero-COSY were performed. Compounds **6** and **7** isomerize readily to an equilibrium mixture of the two isomers in an 8:5 ratio, a point we will elaborate on further in the mechanistic discussion below. Identification of **8** as the symmetric anhydride of α-oxobenzeneacetic acid (benzoyl formic acid) was primarily based on the mass spectral fragmentation data, which showed the loss of a phenyl moiety and then two consecutive CO groups. All our attempts[8-13] to independently synthesize anhydride **8** failed. Indeed, to the best of our knowledge, no symmetric anhydride of any α-keto acid has been previously reported. Unfortunately, the minuscule quantities of this product formed in this reaction prevented extensive exploration of its properties at this time.

Scheme 1 outlines our proposed mechanism for the superoxide mediated oxidation of tetraphenylcyclopentadiene (**1**). In trying to unravel the mechanistic details, we first had to determine the role played by tetracyclone (**2**) in this process. The $O_2^{\bullet-}$-induced oxidation of the latter has been studied by several groups[4] and has been reported to give varying amounts of lactol **3**, furan **4**, benzoic acid (the probable precursor to **9**), and a product not observed in the present study, pyranone **15** (eq 2).[4e]



(2)

It is natural, then, that we should suggest **2** as the precursor to products **3**, **4**, and **9**. What's more, we know of no simple mechanism to explain the formation of lactol **3** except via dienone **2**. The fact that the highly colored dark violet tetracyclone was detected only as a faint spot in the TLC of the reaction mixture seems to indicate that the cyclone reacts almost as soon as it is formed.

In any case, as outlined in Scheme 1, the formation of tetracyclone **2** from the starting dihydro analog **1** should be understood as a straightforward example of BCA. Initial deprotonation of **1** indeed occurs at C-5, giving the highly stabilized carbanion **11**, for which a total of 17 resonance structures can be written.[14] At this point several pathways are possible: (a) Oxygenation at C-5 of **11** (path a) generates peroxy anion **12** which undergoes dehydration (path b) to tetracyclone (**2**). The latter reacts rapidly in turn, as discussed above, yielding **3**, **4**, and **10** (trapped as its methyl ester **9**). (b) However, peroxy anion **12** could also cyclize into C-1 (path c), undergoing oxidative cleavage to dicarbonyl anion **13**. Oxygenation at C-4 followed by oxidative cleavage yields enedione **5**. (c) Finally, returning to anion **11**, oxygenation at C-2 (path d) followed by cyclization into C-3, oxidative cleavage and rotation about the allylic anion ultimately yields *cis* and *trans* isomers **6** and **7**.

In comparing paths d and a, we would expect the former to be the preferred mode of action. This is because the electron density of anion **11** should be higher at C-2 than at C-5 since the former is not only doubly allylic but also benzylic. The fact that path d products **6** and **7** were obtained in a combined yield of 45%, as compared to 34% for path a products **3**–**5** and **8**, is consistent with this prediction.

Thus, Scheme 1 represents a plausible, though certainly not an exclusive, mechanism for the formation of nearly all the reaction products observed, and each step is well precedented.[3f,4a,b] Nevertheless, we are at a loss to explain the formation of the small amounts (<1%) of benzoylformic anhydride (**8**) observed in this reaction.

There remains one last issue which deserves our attention, namely, the formation of the *cis* and *trans* isomers **6** and **7**. It is mechanistically clear that oxidative cleavage of a cyclopentadiene should initially yield the *cis* isomer (Scheme 1, path d). This does not require that

(8) For references see: March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley-Interscience: New York; 1985; p 355.
(9) Shen, T. Y. U.S. Patent 3,316,260, April 25, 1967; *Chem. Abstr.* **1968**, *68*, 49447a.
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(12) Staab, H. A.; Walther, G.; Rohr, W. *Chem. Ber.* **1962**, 2073–2075.
(13) Zehavi, U. *J. Org. Chem.* **1977**, *42*, 2821–2825.
(14) Taber, D.; Becker, E. I.; Spoerri, P. E. *J. Am. Chem. Soc.* **1954**, *76*, 776–781.

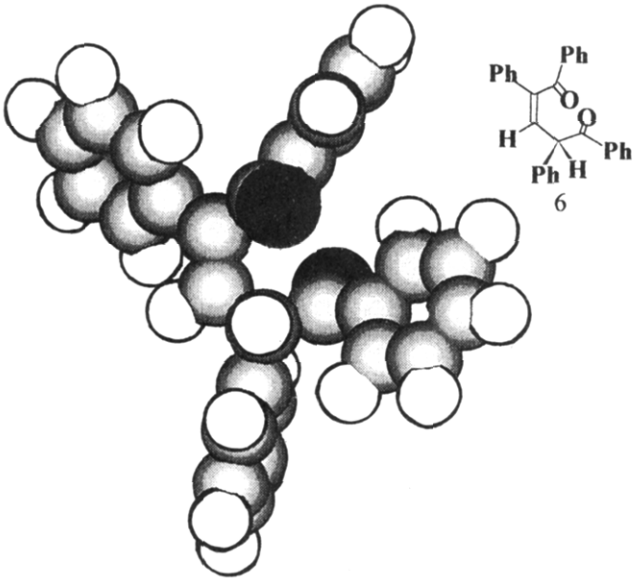

Figure 1. PC model representation of *cis*-pentenedione **6**.

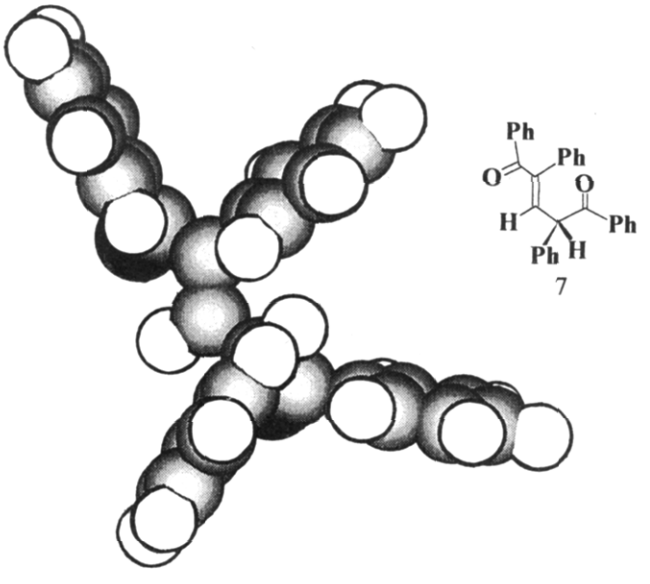

Figure 2. PC model representation of *trans*-pentenedione **7**.

cis-**6** therefore be the more abundant of the two isomers in the product mixture; however, this does seem to be the case. We have noted above that both a relatively pure sample of *cis*-**6** and an isomer-enriched sample of *trans*-**7** isomerize to give an equilibrium mixture of the two isomers in a *cis*:*trans* ratio of 8:5 as determined by ^{1}H NMR. Not surprisingly, this is the same ratio of isomers observed in the product mixture. A K_{eq} of 1.6 suggests that the *cis* isomer is ca. 400 cal more stable than the *trans* isomer. Indeed, molecular-modeling studies[15] confirm that the *cis* isomer is more stable, though the energy difference calculated is somewhat higher, by approximately 1.7 kcal (53.04 and 54.72 kcal for the *cis* and *trans* isomers, respectively). The modeling (Figures 1 and 2) further reveals that the *trans* isomer has a large dipole, with the two carbonyl moieties pointed in essentially the same direction. By contrast, these carbonyls are pointed in opposite directions in the *cis* isomer, giving a small net dipole moment, which is particularly favorable in aprotic media.

Steric considerations may also be at play here. In the *cis* isomer, the C-5 benzoyl has to sterically contend with the C-1 benzoyl carbonyl; for the *trans* isomer the former is crowded by the C-2 phenyl group. Since a phenyl group is reported to be bulkier than a carbonyl,[16] the *trans* isomer is likely to be less stable.

We should note that the modeling studies were also of assistance in the elucidation of the ^{13}C-NMR assignments, supplying additional evidence that the major and minor isomers were *cis*-**6** and *trans*-**7**, respectively. Conjugation of a double bond with a carbonyl shifts the β-olefinic carbon of the enone system (C_β) to lower field; the stronger the conjugation, the greater the downfield shift.[17] Thus, when the double-bond–carbonyl dihedral angle is small, corresponding to a higher degree of conjugation, a chemical shift for the C_β is expected at lower field. The modeling calculations yielded a smaller dihedral angle (51°) for the *trans* isomer than for the *cis* isomer (63°). It is therefore reasonable to assume that the lower amplitude peak at 141.11 ppm in the ^{13}C-NMR of the product mixture belongs to the *trans* isomer **7**, whereas the higher amplitude peak at 130.72 ppm belongs to the major product, the *cis* isomer **6**.

In conclusion, then, the initial step in the reaction of cyclopentadiene **1** with superoxide is deprotonation. Because of the variety of resonance structures available to the corresponding carbanion **11**, C-5 oxygenation (to yield tetracyclone **2**) is not the sole mode of action and a plethora of products are formed. The mechanism of product formation subsequent to carbanion formation involves a series of well-precedented autoxidative processes including oxygenation, dehydration or cyclization of the resulting peroxy anion, and oxidative cleavage. We have also shown that the predominance of the *cis* isomer in the equilibrium mixture of 2-ene-1,5-diones **6** and **7** results from both electronic and steric factors.

Experimental Section

^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were obtained on Bruker AM 300 Fourier transform spectrometer. Assignments (see supporting information) were facilitated by correlating proton and carbon chemical shifts through analysis of residual couplings in off-resonance decoupled spectra. In all cases, TMS served as the internal standard. EI and CI mass spectra were run on a Finnigan-4021 GC/MS machine, except where exact mass data are given. In the latter instance, the EI data reported are based on the high-resolution mass spectra (HRMS), performed by the Mass Spectroscopy Center at the Technion, Haifa, Israel. FTIR spectra were obtained on a Nicolet 60 SXB FTIR spectrometer while UV–visible spectra were taken with a Varian DMS-100S spectrometer. Analytical thin layer chromatography (TLC) was performed using Merck silica gel microcards. Preparative TLC runs were carried out on Merck silica gel F_{254} precoated plates, and the products were extracted from the silica by stirring overnight in a solution of 30% CH_3OH in $CHCl_3$. Preparative column chromatography was done using silica gel (230–400 mesh, Merck). 1,2,3,4-Tetraphenyl-1,3-cyclopentadiene (**1**), tetracyclone (**2**), 2,3-diphenylmaleic anhydride, and benzoylformic

(15) (a) PC Model, Serena Software, Bloomington, Indiana. (b) We note that, in calculating the correct model conformations, it is imperative to take into account the observed ^{1}H NMR coupling constants ($^3J_{H\text{-}H}$ = 10.2 and 10.3 Hz for **6** and **7**, respectively).

(16) See ref 8, p 126.

(17) Steric inhibition to resonance and its effect on the chemical shift of C_β has been well studied. See, for example: (a) Strothers, J. B. *NMR Spectroscopy*, Academic Press: New York, 1972; see especially pages 192 and 429. (b) Gottlieb, H. E. In *The Chemistry of Enones*; Patai, S., Rappoport, Z., Eds.; Wiley-Interscience: New York, 1989; Part 1, Chapter 5, pp 129–150; see especially page 131 and references cited therein.

acid were purchased from Aldrich. Potassium superoxide (Callery, supplied as a fine powder in 1 kg cans) was transferred to 25 cc bottles in a glovebag under dry argon prior to use. 18-Crown-6 polyether (Aldrich) was recrystallized from acetonitrile[18] and stored along with the above potassium superoxide salt in a desiccator. Analytical grade methyl iodide was stored at 5 °C under argon.

Reaction of 1,2,3,4-Tetraphenyl-1,3-cyclopentadiene (1) with $O_2^{\bullet-}$. Cyclodiene **1** (3.2 g, 8.5 mmol) was reacted with superoxide anion radical, generated in sodium dried toluene from KO_2 (2.4 g, 34 mmol) with 18-crown-6 polyether (4.5 g, 17 mmol). The reactions were followed by TLC (20% acetone in hexane) and, upon disappearance of the substrate (4 h), were quenched with aqueous acid and worked up as usual.[19] Products were then separated by column chromatography (silica) using 20% acetone in hexane as the eluent. The order of product elution from the column was **4**, **1**, **2**, **5**, **6**, **7**, **8**, and **3**. Each fraction was then further purified by preparative TLC or via a microcolumn until an analytically pure sample was obtained. It should be noted that, throughout the course of the reaction, only a very faint purple TLC spot could be seen corresponding to tetracyclone **2**, but the amounts were much too small to collect. As noted above, compounds **3**,[4] **4**,[5] **5**,[6] **6** and **7**,[7] and **9** (Aldrich) are known; nevertheless, some spectral data are lacking in the literature and are cited below where appropriate.

3: ^{1}H NMR ($CDCl_3$) δ 7.78 (m, 2 H), 7.70 (m, 2 H), 7.52 (tt, J = 7.5 Hz, J = ~1 Hz, 1 H), 7.48–7.30 (m, 8 H), 7.27 (m, 2 H), 4.68 (s, 1 H, exchangeable with D_2O); ^{13}C NMR ($CDCl_3$) δ 198.92, 179.01, 136.02, 132.53, 129.63, 129.60, 129.30, 129.26, 128.75, 128.68, 128.57, 127.94, 127.66, 125.77, 113.16, 101.89; FTIR (KBr) 3245.44 (s, OH) 1690.15 (s, CO) cm^{-1}; UV (EtOH) λ_{max} = 250 nm; FTIR (KBr) 1689.70 (s, CO) cm^{-1}; HRMS calcd ($C_{22}H_{16}O_3$, M$^+$) 328.1099, obsd 328.1127; MS (EI, 70 ev) m/z 328 (M$^+$, 1.57), 223 (M – PhCO, 47.49), 178 (M – PhCO – HCO_2 or PhCCPh, 14.68), 105 (PhCO, 100); MS (CI, CH_4) m/z 329 (MH$^+$, 100), 311 (MH$^+$ – H_2O), 251 (M$^+$ – Ph), 223 (M$^+$ – PhCO).

4: ^{13}C NMR ($CDCl_3$) δ 147.75, 133.25, 130.96, 130.43, 128.34, 127.27, 127.13, 125.88, 125.15; MS (CI, CH_4) m/z 389 (MCH_4^+, 3.82), 373 (MH$^+$, 100), 372 (M$^+$, 8.43).

6: ^{1}H NMR ($CDCl_3$) δ 7.85 (m, 2 H), 7.76 (m, 2 H), 7.15–7.45 (m, 16 H), 6.91 (d, J = 10.3 Hz, 1H), 5.45 (d, J = 10.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 197.88 (2C), 141.35, 137.82, 136.77, 136.56, 135.92, 133.51, 132.99, 130.72, 129.65 (2C), 129.00 (2C), 128.64 (2C), 128.60 (2C), 128.53 (2C), 128.38, 128.05 (4C), 127.26 (1C), 126.35 (2C), 53.24 (1C); FTIR (KBr) 1677.48 (s, CO), 1667.21 (s, CO) cm^{-1}; HRMS calcd ($C_{29}H_{22}O_2$, M$^+$) 402.1620, obsd 402.1611; MS (EI) m/z 402 (M$^+$, 7.45), 297 (M – PhCO, 5.78), 207 (M – PhCO – PhCH, 1.38), 105 (PhCO, 100).

7: ^{1}H NMR ($CDCl_3$) δ 7.85 (m, 2 H), 7.76 (m, 2 H), 7.50 (m, 1 H), 7.15–7.45 (m, 15 H), 7.00 (d, J = 10.2 Hz, 1 H), 5.52 (d, J = 10.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 197.67, 196.21, 141.28, 141.11, 137.61, 137.54, 135.63, 135.41, 133.22, 132.37, 129.89 (2C), 129.31 (2C), 129.20 (2C), 128.44 (2C), 128.21 (2C), 127.50, 127.26, 53.82; FTIR (KBr) 1677.48 (s, CO), 1667.21 (s, CO) cm^{-1}.

8: ^{1}H NMR ($CDCl_3$) δ 7.98 (m, 4 H), 7.66 (tt, J = 7.5 Hz, J = 1.5 Hz, 2 H), 7.52 (tt, J = 7.5 Hz, J = 1.5 Hz, 4 H); HRMS calcd ($C_{16}H_{10}O_5$, M$^+$) 282.0528, obsd 282.0541; MS (EI, 70 ev) m/z 282 (M$^+$, 28.06), 205 (M – Ph, 16.91), 177 (M – Ph – CO, 16.91), 149 (M – Ph – 2CO, 43.77), 105 (PhCO$^+$, 100).

Acknowledgment. We would like to acknowledge the kind and generous support of The Israel Science Foundation administered by the Israel Academy of Sciences and Humanities.

Supporting Information Available: 300 MHz ^{1}H NMR spectra of **8** and the complete ^{1}H and ^{13}C NMR peak assignments for the compounds described in the Experimental Section (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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