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The Reaction of the 2,6-Di-*tert*-butyl-4-methylphenoxy Radical with Phenols[1]

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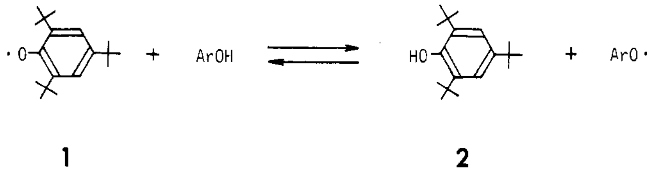
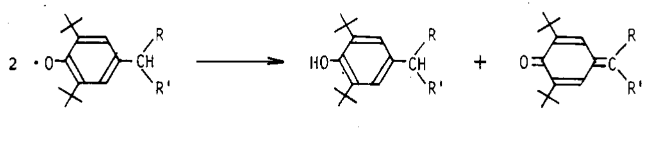
Dimer **3** dissociates in solution to give the phenoxy radical **4**. When solid **3** is dissolved in a solution of phenol **11a**, radical **4** dehydrogenates the phenol to afford phenol **5** and phenoxy radical **12**. Radical **12** couples with more **4** to afford principally bis(cyclohexadienone) **16a** and a minor amount of the dimeric bis(cyclohexadienone) **13**. The preferential formation of **16a** over **13** is explained as the result of a solvent-cage reaction. Compounds **13** and **16a** are isomerized in the presence of silica gel or triethylamine to 4,4′-dihydroxybiphenyl **14** and phenolic dienone **17a**, respectively. Compound **13** is relatively stable in hexane at 30 °C, while **16a** slowly dissociates under these conditions to afford parent radicals **4** and **12**. If **11a** is present, radical **4** either recombines with **12** or dehydrogenates the phenol. Two radicals of **12** generated by the dissociation of **16a** and the subsequent dehydrogenation of **11a** couple to give **13**. Therefore, dissolving **3** in hexane containing excess **11a** and keeping the resulting solution at 30 °C results in the preferential formation of **13**. Dissolving **3** in triethylamine containing phenols **11** or **21** similarly affords dienones **17** or **23**. The yields of these dienones increase with increasing electron-donating capability of the substituent on the phenol ring.

Phenoxy radicals are generated by one-electron oxidation of phenols. 2,4,6-Tri-*tert*-butylphenoxy radical (**1**) thus formed is stable, and addition of a phenol to a solution of **1** results in reversible dehydrogenation of the phenol to yield phenol **2** and a new phenoxy radical.

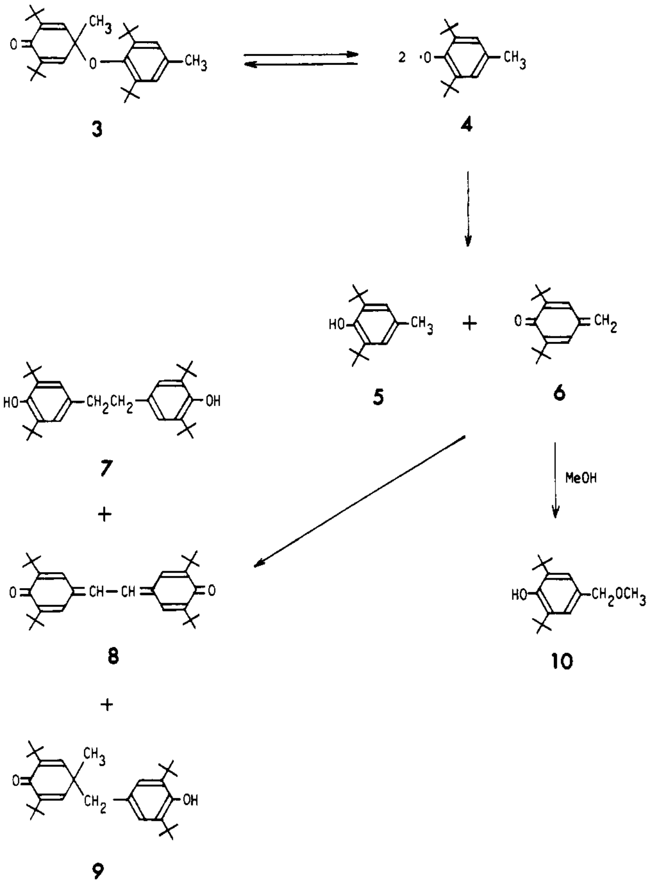


2,6-Di-*tert*-butylphenoxy radicals with an α-CH in the para substituent, on the other hand, decay rapidly to yield the parent phenols and quinone methides.[2] These radicals are ineffective as dehydrogenating agents for phenols because of their rapid decay.[3]



R, R' = H, alkyl or aryl

Scheme I



Although 2,6-di-*tert*-butyl-4-methylphenoxy radical (**4**) disproportionates very rapidly, it can also dimerize to afford quinol ether **3**, which can be isolated as a nearly colorless solid in high yield.[4] The dimerization is reversible, and **3** in solution rapidly regenerates **4**. The author attempted to dehydrogenate phenols with **4** by letting **3** dissolve in solvents containing them,[5] thus allowing immediate access of phenols to **4** as soon as it was generated. Quinone methide **6**, formed by the disproportionation of **4**, is labile and degrades in inert solvents into 1,2-bis(4-hydroxyphenyl)ethane **7** and 4,4′-stilbenequinone **8**.[6] Benzylic dienone **9** is the product of addition of phenol **5** to **6** but has rarely been reported.[7] Methanol adds to **6** to give methyl ether **10** (Scheme I).[4a,b,8]

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(1) This article is dedicated to the memory of the late Professor Daniel Swern.

(2) (a) Forrester, A. R.; Hay, J. M.; Thomson, R. H. In *Organic Chemistry of Stable Free Radicals*; Academic Press: New York, 1968; p 281. (b) Mihailović, M. Lj.; Čeković, Ž. In *The Chemistry of the Hydroxyl Group*; Patai, S., Ed.; Wiley: New York, 1971; Part 1, p 505.

(3) Müller, E.; Mayer, R.; Heilmann, U.; Scheffler, K. *Liebigs Ann. Chem.* **1961**, *645*, 66.

(4) (a) Becker, H.-D. *J. Org. Chem.* **1965**, *30*, 982. (b) Omura, K. *J. Org. Chem.* **1984**, *49*, 3046. (c) Hewitt, D. G. *J. Chem. Soc. C* **1971**, 2967.

(5) The decay of phenoxy radical **4** generated by dissolving **3** in solvents inert to **6** in the absence of phenols has also been studied in detail. The products include **7**, **8**, and **9**. The results will be published elsewhere. A preliminary communication appears in Omura, K. *Bull. Koshien Univ.* **1987**, *15*, 19.

(6) (a) Fujisaki, T. *Nippon Kagaku Zasshi* **1956**, *77*, 727. (b) Bauer, R. H.; Coppinger, G. M. *Tetrahedron* **1963**, *19*, 1201. (c) Loy, B. R. *J. Org. Chem.* **1966**, *31*, 2386. (d) Volod'kin, A. A.; Ershov, V. V.; Kudinova, L. I. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1978**, 512. (e) Kudinova, L. I.; Volod'kin, A. A.; Ershov, V. V. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1978**, 1661.

(7) (a) Magnusson, R. *Acta Chem. Scand.* **1966**, *20*, 2211. (b) Benjamin, B. M.; Raaen, V. F.; Hagaman, E. W.; Brown, L. L. *J. Org. Chem.* **1978**, *43*, 2986. See also note 5.

0022-3263/91/1956-0921$02.50/0

Table I. Reaction of Phenoxy Radical 4 with Phenol 11a[a]

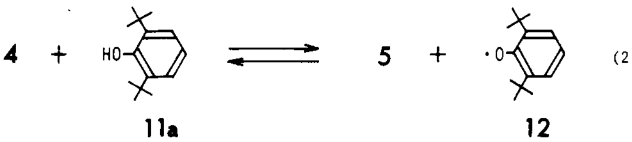
run	solvent	11a, employed (mol/mol 3)	11a, reacted (mol/mol 3)	products (mol/mol 3)			
				5	17a	14	other products
1	hexane	4	1.81	1.89	0.02	0.85	**7** (0.01), **15** (0.01)
2	hexane[b]	4	1.07	1.16	0.80	0.10	**15** (0.01)
3	hexane[b,c]	4	1.05	1.16	0.87	0.04	**15** (trace)
4	ether	4	1.73	1.85	0.03	0.81	**7** (0.02), **15** (0.01)
5	Et_3N	4	1.02	1.02	0.87	0	
6	Et_3N	1	0.85	0.98	0.79	0	**7** (0.06)
7	MeOH	4	1.24	1.36	0.52	0.22	**10** (0.04), **15** (0.06)
8	Et_3N/MeOH[d]	4	1.00	1.03	0.88	0	**10** (0.02)
9	Et_3N/MeOH[d]	1	0.85	1.01	0.82	0	**10** (0.10)

[a] The reaction was conducted at 30 °C using **3** (0.23 mmol/mL solvent). [b] After **3** dissolved, the reaction mixture was, without removing the solvent, soon subjected to column chromatography on SiO_2. [c] The reaction was conducted at 2 °C. Dimer **3** dissolved in 20 min. [d] The reaction was conducted in MeOH containing Et_3N (0.4 mol/mol **3**).

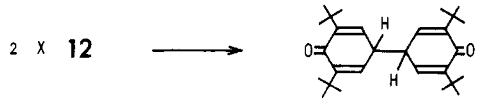
Results and Discussion

A relatively concentrated solution (ca. 0.9 M) of excess 2,6-di-*tert*-butylphenol (**11a**) (4 mol equiv) in hexane was added to freshly prepared solid dimer **3**,[4b] and the light blue-green suspension was stirred at 30 °C for ca. 1 min until it became homogeneous. The resulting yellow solution was let stand at that temperature for 1 h. The mixture obtained after evaporation of the solvent was chromatographed on silica gel (SiO_2). As shown in Table I (run 1), a major product was 4,4′-dihydroxybiphenyl **14**. In addition, about 2 equiv of **5** was produced, while nearly 2 equiv of **11a** was consumed per 1 equiv of **3** employed. The reaction proceeded similarly in petroleum ether, CCl_4, benzene, $CHCl_3$, ether (run 4), acetone, acetonitrile, and acetic acid. Storing the hexane solution in a refrigerator after the reaction instead of chromatographing gave crystalline bis(cyclohexadienone) **13** in 11% yield. By a similar workup, **13** was isolated in 27 and 61% yields from the reactions in acetic acid and acetonitrile, respectively. Compound **13** underwent quantitative rearrangement to give **14** when chromatographed on SiO_2. These results indicate that reversible dehydrogenation of **11a** with **4** by this means is indeed efficient, producing **5** and phenoxy radical **12**, which then dimerizes to **13**.

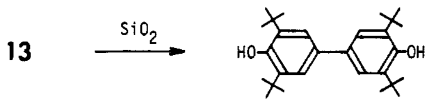
$$3 \rightleftharpoons 2 \times 4 \qquad (1)$$



11a **12** (2)



13 (3)



14 (4)

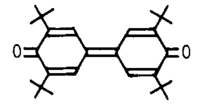
The net process of eqs 1, 2, and 3 is expressed by eq 5.

$$3 + 2\,11a \rightarrow 2\,5 + 13 \qquad (5)$$

The disproportionation of **4** (eq 6) is only a minor process since little **7**, **8**, or **9** was found.

$$2\,4 \rightarrow 5 + 6 \qquad (6)$$

The reaction in triethylamine (Et_3N) took a different course. Compound **14** (or **13**) was not obtained, and phenolic dienone **17a** was produced in high yield. Most of the **17a** formed was isolated before chromatography by treating the product mixture with petroleum ether. In addition, only 1 equiv of **5** was produced, and only 1 equiv of **11a** reacted per 1 equiv of **3** employed (run 5). Formation of **7**, **8**, or **9** was not observed. The reaction in pyridine gave a similar result. The reaction in MeOH containing a catalytic amount of Et_3N also gave **17a** in high yield (run 8). During the course of the reaction, **17a** was deposited from the mixture. A small amount of methyl ether **10** derived from **6** was also obtained. In the absence of Et_3N, however, the reaction in MeOH was relatively complex; both **17a** and **14**, as well as 4,4′-diphenoquinone **15**, were formed (run 7). Even with equimolar amounts of **3** and **11a**, the reactions in Et_3N and in MeOH containing Et_3N gave high yields of **17a** together with only limited amounts of the products derived from **6** (runs 6 and 9). The dehydrogenation of **11a** by **4** is thus also efficient in basic solvents, but it appears that phenoxy radical **12** combines not with itself to form **13** but with more **4** to yield a new bis(cyclohexadienone) **16a**, which is recovered as **17a** after base-catalyzed isomerization.



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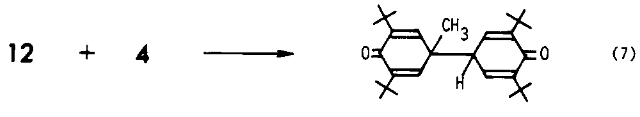
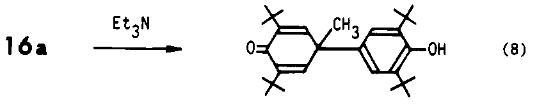


16a (7)



17a (8)

The net process of eqs 1, 2, and 7 is

$$3 + 11a \rightarrow 5 + 16a \qquad (9)$$

To rationalize the different results obtained from the reactions in hexane and in Et_3N, the reaction in hexane was repeated but the mixture was subjected to chromatography on SiO_2 soon after all **3** dissolved. Dienone **17a**

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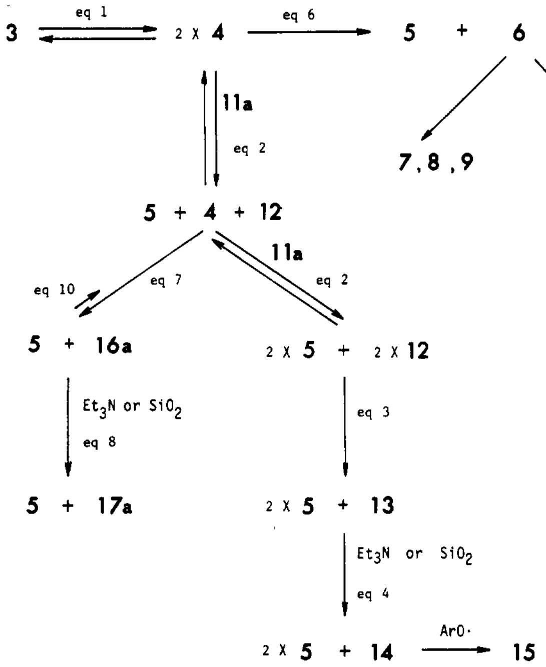
(8) Macomber, R. S. *J. Org. Chem.* **1982**, *47*, 2481.

(9) The relative complexity of the reaction in MeOH may suggest that catalysis of the dienone–phenol rearrangement of **16a** by the solvent is less effective than by Et_3N.

Scheme II



was the major coupling product obtained, while **14** was only a minor product. Moreover, the amounts of **5** formed and **11a** reacted were closer to 1 equiv rather than to 2 equiv per 1 equiv of **3** employed (run 2). Evidently, the result is comparable to that from the reaction in Et_3N (run 5) rather than to that from the prolonged reaction in hexane (run 1). The reaction conducted in hexane at ca. 2 °C instead of 30 °C followed by similar workup gave a still higher product ratio **17a**/**14** (run 3).

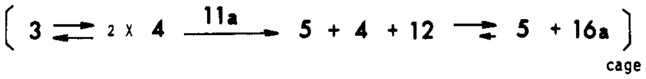
The above observations can be summarized as follows. In all solvents, the principal reaction of **12** generated by eqs 1 and 2 is to couple with **4** to form **16a** (eq 7). Self-coupling of **12** to give **13** (eq 3) is only a minor process. All of these reactions are rapid and are complete soon after all **3** is dissolved. Like **13**, **16a** is easily isomerized by Et_3N or SiO_2 to give stable isomer **17a**. While **13** is relatively stable at 30 °C in inert solvents such as hexane, **16a** is not as stable under the same conditions and undergoes slow dissociation to afford parent radicals **4** and **12** (eq 10, the reverse reaction of eq 7). In the presence of **11a**, **4** thus

$$\mathbf{16a} \rightarrow \mathbf{4} + \mathbf{12} \qquad (10)$$

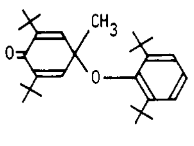
generated either recombines with **12** (eq 7) or dehydrogenates the phenol to provide **5** and **12** (eq 2). The two radicals of **12** left after eq 10 followed by eq 2 combine to give **13**. If the mixture obtained after dissolving **3** in hexane containing excess **11a** is let stand at 30 °C for a sufficiently long time, the primary product **16a** is all consumed, and **13** (and **5**) is obtained in an amount expected from eq 5 (Scheme II).

Isolation of elusive compound **16a** was finally accomplished by conducting the following operations in sequence at ca. 2 °C: dissolving **3** in CH_2Cl_2 containing **11a** (1.2 mol equiv), evaporating the solvent under reduced pressure, and treating the resultant oily mixture with acetonitrile followed by filtration. Compound **16a** was obtained in 51% yield as nearly colorless crystals with mp 82–84 °C dec. The ^1H NMR and IR spectra are consistent with structure **16a** but not with quinol ether structures **18** or **19**. In addition, the UV spectrum is similar to that of **13**. This may be the first instance of isolating a bis(cyclohexadienone) of general structure **20** in which R and R′ are nonequivalent. As anticipated, **16a** was quantitatively

Scheme III



converted into **17a** by Et_3N or SiO_2. Also, the thermal instability of **16a** in solution was shown by following its decomposition by ^1H NMR spectroscopy in CCl_4 at 30 °C. At this temperature its decay was complete in ca. 2 h, and the major products found were **5**, **6**, and **13**, suggesting homolytic scission of the central C–C bond in **16a** (eq 10) followed by eqs 3 and 6.



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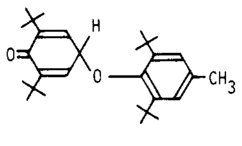

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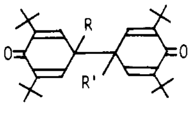

(R ≠ R')

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The selective formation of **16a** in the initial stage of the reaction when **3** is dissolved in the presence of **11a** is striking, since the self-coupling of **12** to give **13** (eq 3) should be as fast as the coupling of **4** to give **16a** (eq 7). This result can be rationalized only by assuming that **11a** enters a solvent cage in which **3** is equilibrated with **4**, and that the dehydrogenation of **11a** (eq 2) and the subsequent coupling reaction to afford **16a** (eq 7) are complete within the cage (Scheme III).

It might be suspected that the formation of **16a** (or **17a**) is rather the result of reaction between **11a** and reactive quinone methide **6** (eq 11).

$$\mathbf{6} + \mathbf{11a} \rightarrow \mathbf{16a} \qquad (11)$$

The net process of eqs 1, 6, and 11 is also expressed by eq 9. If this is indeed the case, however, the rate of eq 11 ought to be quite high. Decay of **6** in the presence of **11a** has been investigated in petroleum ether,[10] and it appears to be relatively slow at room temperature. Dimer **3** was dissolved in $CDCl_3$ to generate **6** (and **5**), and to the solution was added a solution of **11a** (4 molar equiv) in $CDCl_3$ containing pyridine-d_5 (C_5D_5N). After 10 min at 30 °C, the solution was shown by ^1H NMR to contain ca. 75 % of the theoretical amount of **6**. Decay of **6** was slow, and after 20 h about 5% still survived. It is noteworthy that the products included **17a**. For comparison, **3** was dissolved in $CDCl_3$ containing **11a** and C_5D_5N, and the resulting mixture was kept at 30 °C. After 10 min the mixture contained substantial amounts of **5** and **17a** as anticipated, and only about 10% of **6**, which decayed slowly thereafter. The formation of **17a** in low yield in the former experiment was slow compared with its rapid and efficient formation in the latter. A preliminary study showed that the slow formation of **17a** requires not only **6** and **11a** but also **5**.[11] This may suggest that a reaction other than eq 11 gives **17a** slowly. The reaction that yields **17a** rapidly in the latter experiment does not involve **6**.

The reaction of phenoxy radical **4** derived from **3** was studied with other phenols in Et_3N (Table II). The reactions with 2,6-diisopropylphenol (**11b**) and 2,6-dimethylphenol (**11c**) gave the corresponding phenolic dienones **17b** and **17c**, respectively, together with nearly theoretical amounts of **5**. 2,6-Dimethoxyphenol (**11d**) reacted similarly to yield dienone **17d**. These reactions also proceeded efficiently in MeOH (TLC analysis). The reaction of 2,4-dimethylphenol (**21b**) gave phenolic dienone

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[10] Neureiter, N. P. *J. Org. Chem.* **1963**, *28*, 3486.
[11] Unpublished results.

Table II. Reaction of Phenoxy Radical 4 with Phenols[a]

phenol	solvent	products (%, mol/mol 3 × 100)		
		5	17 or 23	products derived from 6
11a[b]	Et_3N	102	**17a** (87)	
11b	Et_3N	102	**17b** (79)	**7** (tr)
11c	Et_3N	104	**17c** (69)	**7** (0.3)
11d	Et_3N	107	**17d** (60)	**7** (1.5)
21b	Et_3N	99	**23b** (54)	**7** (3.9), **24b** (17)
21c	Et_3N	89	**23c** (8.7)	**7** (11), **8** (1.1), **9** (3.1), **24c** (43)
21c	MeOH	101	**23c** (17)	**7** (1.2), **9** (2.7), **10** (47), **24c** (0.8)
21c	Et_3N/MeOH[c]	103	**23c** (33)	**10** (34), **24c** (11)
21d	Et_3N	87	**23d**[d] (0)	**7** (14), **8** (1.8), **9** (4.6), **24d** (43)
21d	Et_3N/MeOH[c]	102	**23d**[d] (0)	**7** (tr), **9** (2.0), **10** (53), **24d** (21)

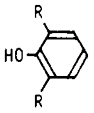
[a] Using 4 molar equiv of phenols to **3**. [b] Data taken from Table I, run 5. [c] MeOH containing a catalytic amount (0.4 mol/mol **3**) of Et_3N. [d] Compound **17** (R = H) was not obtained.

Table III. Time Required for Dissolving Dimer 3[a]

additive	time (min)	
	in Et_3N[b]	in MeOH[c]
none	100+[d,e]	290[f]
11a	14[g]	15
11b	39	9
11c	56	22
11d	33	–[h]
21b	71	45
21c	97	100
21d	100	190
21a	93	93
5	112	118
2	95	–[i]
benzene	–[j]	164

[a] To **3** (240 mg, 0.55 mmol) was added a solvent (2.4 mL) containing an additive. The time required for the stirred suspension to become homogeneous was measured. [b] At 15 °C with 1 molar equiv of an additive. [c] At 30 °C with 4 molar equiv of an additive. [d] Most of **3** dissolved in 100 min. Further observation was obstructed as product **8** began to precipitate. [e] At 30 °C, **3** dissolved in 11 min. [f] At 20 °C, **3** dissolved in 23 h. [g] With 4 molar equiv of **11a**, **3** dissolved in 3 min. [h] Not measurable because of formation of an insoluble colored substance. [i] Measurement was not attempted because of limited solubility of **2** in MeOH. [j] Not examined.

23b as a principal product. In addition, there was obtained in lower yield an isomer of **23b**, 4-hydroxybenzyl phenyl ether **24b**, whose ^1H NMR spectrum ($CDCl_3$) displayed a singlet at δ 4.88 attributable to $ArCH_2OAr'$. Ether **24b** is presumed to be formed by Et_3N-promoted 1,6-addition of **21b** to **6**.[12] Dienone **23c** was obtained from the reaction with 4-methylphenol (**21c**) but in poor yield. Benzyl phenyl ether **24c** was isolated as the main product, and compounds **7**, **8**, and **9** were also found. The yield of **23c** was improved by conducting the reaction of **21c** in MeOH. In this solvent, **6** was recovered mainly as methyl ether **10** rather than as **24c**. For a reason that is not clear, the reaction in MeOH containing a small amount of Et_3N further increased the yield of **23c**. The reaction of phenol (**21d**) in Et_3N or in MeOH containing Et_3N only gave the products derived from **6**, including benzyl phenyl ether **24d**. Phenolic dienones **17** or **23** may be formed via bis(cyclohexadienone)s **16** or **22** by a mechanism similar to that suggested for **17a**. The results indicate that **17** or **23** becomes predominant over the products derived from **6** as the degree of alkylation of a phenol increases at the ortho and/or para positions. This occurs because the dehydrogenation of a phenol with **4** is facilitated by an electron-releasing substituent on the phenol ring (Scheme II). Finally, the reactions of **4** with 2,4-di-*tert*-butylphenol (**21a**) and phenol **2** were investigated, but no products were indicated to by TLC other than those obtained when **3** is dissolved in Et_3N or MeOH without added **21a** or **2**.[5] This is not believed to mean that reversible hydrogen abstraction from these highly alkylated phenols by **4** is sluggish, but to mean that the resultant phenoxy radicals and **4** cannot form stable coupling products (e.g. **22a**) because of steric repulsion. The radical will thus be driven to revert to the parent phenol (**21a** or **2**) by reverse dehydrogenation. When a solution of **2** was added to solid **3**, the supernatant immediately exhibited a deep blue color typical of stable phenoxy radical **1**. The apparent lack of a stable adduct (e.g. **24a**) may indicate that addition of **21a** (or **2**) to **6** is subject to steric hindrance.



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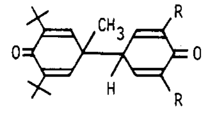

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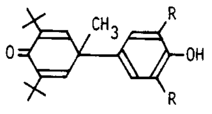

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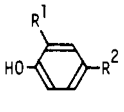
b : R = $CH(CH_3)_2$

c : R = CH_3

d : R = OCH_3



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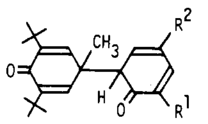

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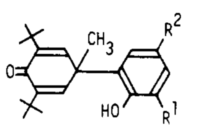


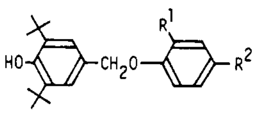
23

a : R^1 = R^2 = $C(CH_3)_3$

b : R^1 = R^2 = CH_3

c : R^1 = H, R^2 = CH_3

d : R^1 = R^2 = H



24

During the study, it was noted that the time required for complete dissolution of dimer **3** is markedly dependent on solvent, temperature, and an added phenol (Table III). In the absence of an added phenol, **3** dissolved much faster in Et_3N than in MeOH. In general, **3** tended to dissolve faster in nonpolar than in polar solvents, probably because it is more soluble in the former.[13] A remarkable acceleration of the dissolution of **3** was observed when Et_3N or MeOH contained phenol **11a**. Other phenols also pro-

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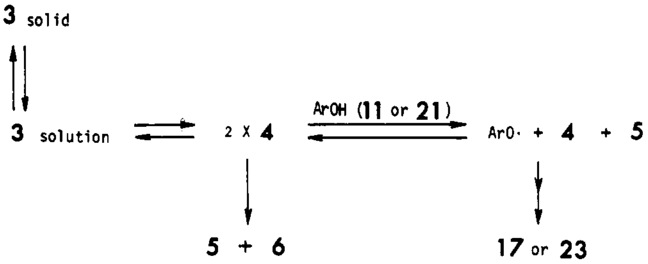
(12) Zanarotti, A. *J. Org. Chem.* **1985**, *50*, 941.

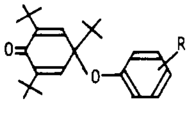
(13) The rate of the disproprtionation of **4** is assumed to be independent on solvent polarity.

Scheme IV

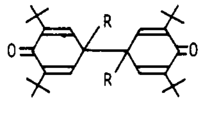


moted the dissolution in varying degree. The effect of an added phenol is greatest when it bears an electron-donating substituent(s). This may reflect that the shift to the right of the equilibrium between 3 in solid state and 3 in solution is promoted by adding an electron-releasing phenol, as its dehydrogenation and the subsequent coupling reaction of the resulting phenoxy radical accelerates the consumption of 4 which is reversibly generated from 3 in solution. Hence a phenol that facilitates the formation of 16 or 22 (or, 17 or 23 after isomerization) necessarily facilitates the dissolution of 3 (Scheme IV). The accelerated dissolution of 3 by electron-releasing phenols suggests that the disproportionation of 4 is overwhelmed by the dehydrogenation of these phenols with 4. Exceptionally slow dissolution of 3 in Et$_3$N or in MeOH in the presence of highly alkylated phenols 2 or 21a is not surprising since these phenols are unreactive toward 4 (see above). Nevertheless, 3 dissolved much faster in MeOH in the presence of 21a than in its absence. Even addition of phenol 5 was effective in stimulating the dissolution of 3, while dehydrogenation of 5 by 4 caused no net consumption of 4. Another factor that affects the rate of dissolution by adding a phenol appears to be the change in solvent polarity, which affects the solubility of 3. The time required for dissolving 3 in MeOH alone was nearly halved when the MeOH contained a small amount of benzene, which is inert to 4.

As shown above, the reaction of phenoxy radical 4 with phenoxy radicals gives in all cases bis(cyclohexadienone)s of type 16 or 22 by C–C coupling. In contrast, the reaction of phenoxy radical 1 with phenoxy radicals appears always to afford quinol ethers of type 25 (or the ortho isomers) by C–O coupling. In this regard, structure 3 of the dimer of 4 deserves reexamination. This quinol ether structure has been proposed by Becker[4a] on the basis of a quinolide band and the lack of a phenolic hydroxy band in the IR spectrum (KBr pellet). But this fact alone does not seem sufficient to exclude bis(methylcyclohexadienone) structure **26a**. Matsuura and co-workers[14] have suggested that the structure of the solid dimer of 2,6-di-*tert*-butyl-4-(ethoxycarbonyl)phenoxy radical is bis(cyclohexadienone) **26b** rather than quinol ether **27a**, based on the lack in the IR spectrum of very pronounced absorptions at 980–990 cm^{-1} and at 1235–1250 cm^{-1}, typically displayed in the spectra of a number of related aromatic quinol ethers. Reinspection of the spectrum of 3 reveals that it shows no such absorptions in these regions. These bands were also absent from the IR spectra of 13, 16a, and bis(bromocyclohexadienone) 26c, whose structures were all supported by ^{1}H NMR spectra. It was suggested by a space-filling molecular model that C–C coupling of two radicals of 4 to give 26a is less hindered than C–O coupling to give 3. The author is not aware of substances whose structures have been unambiguously established (by NMR) to be quinol ethers with general formula 27.

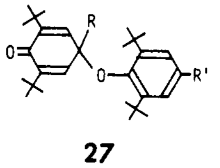


25



26

a : R = CH$_3$
b : R = CO$_2$Et
c : R = Br



27

a : R = R' = CO$_2$Et

Experimental Section

All melting points are uncorrected. ^{1}H NMR spectra were obtained in CDCl$_3$ relative to TMS on a Hitachi R-20B spectrometer (60 MHz). IR spectra were taken in CHCl$_3$ with a Hitachi EPI-G3 spectrophotometer. UV spectra were measured in cyclohexane with a Hitachi U-3200 spectrophotometer. GC analyses were performed with a Shimadzu GC-14A gas chromatograph at 150 °C on a column packed with 10% FAP-S on Chromosorb W. Column chromatography was conducted by using Merck SiO$_2$ 60. TLC was run on SiO$_2$. Authentic samples of 8,[15] 9,[7a] 13,[16] 14,[16] and 26c[4a] were prepared according to the literature. Compounds 7, 10, 15, and 17a were obtained in a previous study[4b] and were used as authetic samples.

General Procedure for Reaction of Phenoxy Radical 4 with Phenol 11a (Table I). To a solid of dimer 3 (or 26a)[4b] (1.200 g, 2.74 mmol) was added at once a solution of phenol 11a (2.258 g, 10.96 mmol) in a solvent (12 mL, see Table I). The mixture was magnetically stirred in a screw-capped bottle at 30 °C until it became homogeneous in 1–15 min. The resultant mixture was let stand at 30 °C for 1 h. The mixture was evaporated under reduced pressure at or below 35 °C to leave a residue, which was chromatographed on a column packed with SiO$_2$ (35–45 g). When products were eluted as a mixture, their contents were estimated by ^{1}H NMR spectroscopy.

Run 1. Elution with petroleum ether gave a colorless solid which was a mixture of phenol 5 (1.14 g, 189%) and phenol 11a (1.24 g, 55% recovery) as analyzed by GC. Further elution afforded a crystalline mixture (210 mg) which contained diphenylethane 7 (15 mg, 1.3%) and dihydroxybiphenyl 14 (180 mg, 16%). Elution with petroleum ether/benzene (10:1) provided 14 (772 mg, 69%): light yellow crystals from CHCl$_3$/ethanol, identical with the authentic sample (mp, ^{1}H NMR, IR, and TLC); mp 184.5–185.5 °C (lit.[16] mp 185 °C). Elution with benzene afforded an orange oil (48 mg) that contained dienone 17a (22 mg, 1.9%) and diphenoquinne 15 (7 mg, 0.6%).

Run 5. The oily residue was crystallized from petroleum ether to provide 17a (685 mg, 59%) as light yellow crystals: colorless crystals from diisopropyl ether, identical with the authentic sample (mp, ^{1}H NMR, IR, and TLC); mp 157–158 °C (lit.[4b] mp 154–156.5 °C); UV 276 nm (log ϵ 3.47), 236 (4.32), 204 (4.65). The petroleum ether filtrate was condensed and chromatographed to furnish an additional crop of 17a (327 mg, 28%).

Run 8. While the reaction mixture stood at 30 °C, a crystalline substance began to separate. Filtration after the reaction provided 17a (625 mg, 54%) as colorless crystals, mp 157–158 °C. The filtrate was evaporated, and the residue was chromatographed. An additional crop of 17a (403 mg, 35%) was obtained by elution with petroleum ether/benzene (10:1). Elution with benzene gave methyl ether 10 (15 mg, 2.2%) as yellow crystals: colorless crystals from diisopropyl ether, identical with the authentic sample (mp, ^{1}H NMR, and TLC); mp 100–101 °C (lit.[4b] mp 100–101 °C). In run 9, crystals of 17a began to precipitate before dissolution of 3 was complete. After addition of methanolic 11a to 3, the mixture was stirred for 2.5 h at 30 °C and worked up in the manner described above.

Isolation and Properties of Bis(cyclohexadienone) 13. The reaction of 4 with 11a in hexane (Table I, run 1) was repeated. The reaction mixture was stored overnight in a refrigerator.

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(14) Matsuura, T.; Nishinaga, A.; Cahnmann, H. J. *J. Org. Chem.* **1962**, *27*, 3620.

(15) Fujisaki, T. *Nippon Kagaku Zasshi* **1956**, *77*, 869.

(16) Kharasch, M. S.; Joshi, B. S. *J. Org. Chem.* **1957**, *22*, 1439.

Filtration afforded **13** (119 mg, 11%) as nearly colorless crystals, identical with the authentic sample (mp, ^{1}H NMR, and IR): mp 140–150 °C dec (lit.[17] mp 140–150 °C); ^{1}H NMR δ 6.48 (d, J = 3 Hz, 4 H), 3.43 (t, J = 3 Hz, 2 H), 1.19 (s, 36 H); UV 243 nm (log ε 4.21). The ^{1}H NMR spectrum of related bis(cyclohexadienone) **26c** exhibited singlets at δ 6.83 (4 H) and 1.19 (36 H). The reactions in acetic acid and acetonitrile gave **13** in 27 and 61% yields, respectively, after a similar workup. Compound **13** was almost quantitatively isomerized into **14** when dissolved in hexane containing a catalytic amount of Et_3N or when chromatographed on SiO_2 with petroleum ether. A solution of **13** (25 mg) in $CDCl_3$ (0.4 mL) or CCl_4 containing TMS was let stand overnight at 30 °C, and ^{1}H NMR analysis indicated that most of the **13** remained intact.

Isolation and Properties of 1-Hydro-1′-methyl-3,5,3′,5′-tetra-*tert*-butyl-2,5,2′,5′-bis(cyclohexadiene)-4,4′-dione (16a). To **3** (3.600 g, 8.22 mmol) was added a cold (ca. 2 °C) solution of **11a** (2.033 g, 9.87 mmol) in CH_2Cl_2 (25 mL), and the mixture was stirred at ca. 2 °C for 70 min until it became homogeneous. The mixture was evaporated at ca. 2 °C under reduced pressure to leave a light orange oil, which was treated with cold (ca. 2 °C) acetonitrile (8 mL) to yield a crystalline deposit. Filtration furnished **16a** (1.772 g, 51%) as pale yellow crystals: mp 82–84 °C dec; ^{1}H NMR (CCl_4) δ 6.51 (d, J = 4 Hz, 2 H), 6.25 (s, 2 H), 3.00 (t, J = 4 Hz, 1 H), 1.43 (s, 3 H), 1.16 (s, 36 H); IR (KBr disk) 1655, 1630 cm^{-1}; UV 244 nm (log ε 4.20). Anal. Calcd for $C_{29}H_{44}O_2$: C, 82.02; H, 10.44. Found: C, 81.79; H, 10.58. Dienone **16a** was quantitatively converted into **17a** when dissolved in hexane containing a catalytic amount of Et_3N or when chromatographed on SiO_2 with petroleum ether/benzene (10:1). A solution of **16a** (35 mg) in CCl_4 (0.5 mL) containing TMS was kept at 30 °C, and the progress of its decay was followed by ^{1}H NMR spectroscopy. The signals due to **16a** disappeared from the spectrum in ca. 2 h, and it appeared that **5**, quinone methide **6**,[6d,10] and **13** were the principal products.

^{1}H NMR Study on the Decay of Quinone Methide 6, Derived from Phenoxy Radical 4, in the Presence of Phenol 11a. To **3** (100 mg) was added $CDCl_3$ (1 mL) containing pentachloroethane (PCE) (50 mg) and TMS, and the mixture was stirred for ca. 4 min until it became homogeneous. After 1 min, a solution of **11a** (188 mg, 4 molar equiv) in $CDCl_3$ (0.3 mL) containing C_5D_5N (two drops) was added to the resulting mixture. A portion of the solution was transferred to an NMR tube, and the progress of the reaction at 30 °C was followed by ^{1}H NMR spectroscopy. After 10 min, the solution contained **5** in substantial quantity and **6** in ca. 75% yield as estimated by comparing the integrated peak area of a singlet at δ 5.66 due to **6**[18] with that of δ 5.97 due to PCE. Amounts of **6** estimated were approximately 60, 30, and 5% after reaction for 1, 5, and 20 h, respectively. As **6** decayed, there appeared singlets at δ 6.49 ascribable to **17a** and at δ 2.80 ascribable to **7**. These singlets were essentially absent initially. The formation of **17a** and **7** was also indicated by TLC.

To **3** (100 mg) was added a solution of **11a** (188 mg) in $CDCl_3$ (1.3 mL) containing PCE (50 mg), C_5D_5N (two drops), and TMS, and the mixture was stirred for ca. 2 min until it became homogeneous. The solution was kept at 30 °C, and the progress of reaction was followed in the manner described above. After 10 min the solution contained substantial amounts of **5** and **17a**, and approximately 5 mg (10%) of **6**. Quinone methide **6** decayed quite slowly and was detectable even after 20 h.

Reaction of Phenoxy Radical 4 with Phenols Other Than 11a (Table II). Unless otherwise stated, the reaction was conducted in Et_3N (24 mL) using **3** (2.400 g, 5.48 mmol) and a phenol (21.9 mmol, 4 molar equiv), and the reaction mixture was worked up by a procedure similar to the general procedure described for the reaction of **4** with **11a**. Dimer **3** dissolved in 1–10 min. The residual mixture of products was chromatographed on SiO_2 (80–100 g).

With Phenol 11b. Elution with petroleum ether afforded **5** (1.229 g, 102%). Further elution recovered **11b** (2.67 g). Elution with petroleum ether/benzene (10:1) gave a crystalline mixture (2.10 g), which was recrystallized from diisopropyl ether to afford 2,6-di-*tert*-butyl-4-(3,5-diisopropyl-4-hydroxyphenyl)-4-methylcyclohexa-2,5-dien-1-one (**17b**) (1.167 g, 54%) as colorless crystals: mp 122.5–123 °C (hexane); ^{1}H NMR δ 6.86 (s, 2 H), 6.49 (s, 2 H), 4.74 (s, 1 H), 3.11 (hept, J = 7 Hz, 2 H), 1.58 (s, 3 H), 1.21 (d, J = 7 Hz, 12 H), 1.20 (s, 18 H); IR 3580, 1650, 1625 cm^{-1}; UV 276 nm (log ε 3.49), 234 (4.31), 207 (4.59). Anal. Calcd for $C_{27}H_{40}O_2$: C, 81.76; H, 10.17. Found: C, 81.47; H, 10.30. The filtrate was evaporated and the residue was chromatographed to furnish additional **17b** (557 mg, 26%).

With Phenol 11c. Elution with petroleum ether gave **5** (1.251 g, 104%) and **7** (8 mg, 0.3%), successively. Elution with petroleum ether/benzene (10:1) recovered unreacted **11c** (1.74 g). Elution with benzene gave 2,6-di-*tert*-butyl-4-(3,5-dimethyl-4-hydroxyphenyl)-4-methylcyclohexa-2,5-dien-1-one (**17c**) (1.284 g, 69%) as light orange crystals. Colorless crystals from MeOH: mp 145.5–148 °C; ^{1}H NMR δ 6.78 (s, 2 H), 6.50 (s, 2 H), 4.61 (s, 1 H, exchangeable with D_2O), 2.22 (s, 6 H), 1.55 (s, 3 H), 1.24 (s, 18 H); IR 3580, 1651, 1626 cm^{-1}; UV 274 nm (log ε 3.44), 233 (4.29), 207 (4.50). Anal. Calcd for $C_{23}H_{32}O_2$: C, 81.13; H, 9.47. Found: C, 80.96; H, 9.44.

With Phenol 11d. The reaction mixture was poured into water (150 mL) and extracted with petroleum ether (2 × 200 mL). The aqueous layer was acidified with 6 N HCl and extracted with ether (2 × 200 mL). The ethereal extracts were combined, washed with water (2 × 30 mL), dried over anhydrous Na_2SO_4, and evaporated to leave unreacted **11c** (2.28 g). The petroleum ether extracts were combined, dried, and evaporated to leave an oily residue, which was chromatographed with petroleum ether to afford **5** (1.290 g, 107%). Further elution gave **7** (35 mg, 1.5%) as yellow crystals, identical with the authentic sample (^{1}H NMR and TLC). Elution with benzene provided 2,6-di-*tert*-butyl-4-(3,5-dimethoxy-4-hydroxyphenyl)-4-methylcyclohexa-2,5-dien-1-one (**17d**) (1.054 g, 52%) as yellow crystals. Colorless crystals from petroleum ether: mp 104.5–105.5 °C; ^{1}H NMR δ 6.48 (s, 2 H), 6.41 (s, 2 H), 5.41 (s, 1 H, exchangeable with D_2O), 3.82 (s, 6 H), 1.58 (s, 3 H), 1.23 (s, 18 H); IR 3525, 1653, 1626, 1615 cm^{-1}; UV 240 nm (log ε 4.29), 211 (4.60); MS m/e 372 (M$^+$). Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 73.95; H, 8.67. Further elution gave an orange oil (285 mg), which was crystallized from petroleum ether to provide additional **17d** (174 mg, 8.5%). The filtrate contained **11d**.

With Phenol 21b. Elution with petroleum ether gave **5** (1.194 g, 99%) and **7** (94 mg, 3.9%) successively. Further elution afforded 3,5-di-*tert*-butyl-4-hydroxybenzyl 2,4-dimethylphenyl ether (**24b**) (297 mg, 16%) as a yellow oil, which was crystallized from hexane to furnish the pure sample as colorless crystals: mp 88–89 °C; ^{1}H NMR δ 7.18 (s, 2 H), 7.0–6.8 (m, 2 H), 6.79 (s, 1 H), 5.13 (s, 1 H, exchangeable with D_2O), 4.88 (s, 2 H), 2.23 (s, 6 H), 1.43 (s, 18 H); IR 3620 cm^{-1}; UV 279 nm (log ε 3.54), 227 (4.22); MS m/e 340 (M$^+$). Anal. Calcd for $C_{23}H_{32}O_2$: C, 81.13; H, 9.47. Found: C, 80.72; H, 9.52. Further elution gave a semicrystalline mixture (121 mg) containing **24b** (25 mg, 1.3%) and **23b** (see below) (60 mg, 3.2%). Continued elution provided 2,6-di-*tert*-butyl-4-(3,5-dimethyl-2-hydroxyphenyl)-4-methylcyclohexa-2,5-dien-1-one (**23b**) (835 mg, 45%) as yellow crystals. Colorless crystals from hexane: mp 121–123 °C; ^{1}H NMR δ 7.0–6.8 (m, 2 H), 6.53 (s, 2 H), 4.87 (s, 1 H, exchangeable with D_2O), 2.28 (s, 3 H), 2.14 (s, 3 H), 1.59 (s, 3 H), 1.24 (s, 18 H); IR 3520, 1650, 1628 cm^{-1}; UV 280 nm (log ε 3.51), ca. 241 shoulder (4.09), 224 (4.22), 205 (4.61). Anal. Calcd for $C_{23}H_{32}O_2$: C, 81.13; H, 9.47. Found: C, 80.85; H, 9.52. Further elution gave a crystalline mixture of **23b** (115 mg, 6.2%) and unreacted **21b** (50 mg). Elution with benzene gave **21b** (1.96 g).

With Phenol 21c. Elution with petroleum ether gave **5** (1.074 g, 89%) and **7** (204 mg, 8.5%) successively. Elution with petroleum ether/benzene (10:1) gave **7** (60 mg, 2.5%), dienone **9** (75 mg, 3.1%), and **24c** (see below) (250 mg, 14%) as an oily mixture. Further elution furnished 3,5-di-*tert*-butyl-4-hydroxybenzyl 4-methylphenyl ether (**24c**) (522 mg, 29%) as an oil which soldified upon standing in a refrigerator. Colorless crystals from hexane: mp 96–96.5 °C; ^{1}H NMR δ 7.22 (s, 2 H), 7.2–6.7 (m, 4 H), 5.19 (s, 1 H, exchangeable with D_2O), 4.86 (s, 2 H), 2.27 (s, 3 H), 1.42 (s, 18 H); IR 3620 cm^{-1}; UV 278 nm (log ε 3.55), 226 (4.27), 204

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[17] Ley, K.; Müller, E.; Mayer, R.; Scheffler, K. *Chem. Ber.* **1958**, *91*, 2670.

[18] A ^{1}H NMR spectrum of a solution obtained by dissolving **3** in $CDCl_3$ alone displays singlets due to **6** at δ 6.87 (2 H), 5.70 (2 H), and 1.27 (18 H), in addition to singlets due to **5**. See also refs 6d and 10 for the ^{1}H NMR spectrum of **6**.

(4.56); MS *m/e* 326 (M^+). Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26. Found: C, 80.77; H, 9.42. Further elution yielded a semicrystalline mixture (106 mg), which was washed with MeOH to provide stilbenequinone **8** (27 mg, 1.1%) as reddish orange crystals, identical with the authentic sample (^1H NMR and TLC). Continued elution afforded a semicrystalline mixture (160 mg), which was washed with petroleum ether, yielding 2,6-di-*tert*-butyl-4-(5-methyl-2-hydroxyphenyl)-4-methylcyclohexa-2,5-dien-1-one (**23c**) (116 mg, 6.5%) as light orange crystals. Colorless crystals from acetonitrile: mp 142–145 °C; ^1H NMR δ 7.1–6.5 (m, 3 H), 6.67 (s, 2 H), 5.00 (s, 1 H, exchangeable with D_2O), 2.30 (s, 3 H), 1.60 (s, 3 H), 1.23 (s, 18 H); IR 3513, 1650, 1628 cm^{-1}; UV 280 nm (log ϵ 3.54), 239 (4.05), 222 shoulder (4.22), 203 (4.60); MS *m/e* 326 (M^+). Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26. Found: C 80.69; H, 9.37. Further elution gave an oil (250 mg) which consisted of **23c** (40 mg, 2.2%) and recovered **21c**. Elution with benzene gave **21c** (1.56 g).

A similar reaction was conducted in MeOH. Dimer **3** dissolved in 100 min. The residual mixture of products was chromatographed as described above to afford **5** (1.214 g, 101%), **7** (28 mg, 1.2%), and a mixture of **9** (65 mg, 2.7%) and **24c** (15 mg, 0.8%), successively. Continued elution with petroleum ether/benzene (10:1) gave a mixture (1.25 g) consisting of **23c**, **10**, and unreacted **21c**. The mixture was chromatographed with petroleum ether on a column packed with neutral alumina (activity III, 50 g) to yield **10** (649 mg, 47%). Elution with petroleum ether/benzene (10:1) provided **23c** (308 mg, 17%). Finally, **21c** was eluted with benzene. The chromatography on SiO_2 was continued with benzene to recover **21c** (1.81 g). The reaction was also carried out in MeOH containing Et_3N (0.21 g, 2.1 mmol), and the reaction mixture was worked up similarly.

With Phenol 21d. Elution with petroleum ether afforded **5** (1.044 g, 87%) and **7** (330 mg, 14%) successively. Elution with petroleum ether/benzene (10:1) yielded 3,5-di-*tert*-butyl-4-hydroxybenzyl phenyl ether (**24d**) (416 mg, 24%) as pale yellow crystals. Colorless crystals from hexane: mp 91–92 °C; ^1H NMR δ 7.5–6.7 (m, 5 H), 7.21 (s, 2 H), 5.20 (s, 1 H), 4.89 (s, 2 H), 1.43 (s, 18 H); IR 3620 cm^{-1}; UV 277 (log ϵ 3.51), 271 (3.53), 221 (4.26), 203 (4.60); MS *m/e* 312 (M^+). Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.74; H, 9.21. Further elution gave a semicrystalline mixture (460 mg) containing **24d** (330 mg, 19%) and **9** (110 mg, 4.6%). Continued elution gave a crystalline mixture (90 mg), which was washed with MeOH to provide **8** (42 mg, 1.8%). Elution with benzene afforded unreacted **21d** (1.80 g).

A similar reaction was conducted in MeOH containing Et_3N (0.21 g). Dimer **3** dissolved in 180 min. Phenol **5** (1.233 g, 102%), **24d** (355 mg, 21%), and **9** (48 mg, 2.0%) were obtained by the chromatographic procedure described above. Further elution with petroleum ether/benzene (10:1) gave **10** (732 mg, 53%). Elution with benzene gave unreacted **21d** (1.38 g).

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Estimating Entropies and Enthalpies of Fusion of Organic Compounds

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A group additivity method recently reported for estimating fusion entropies and fusion enthalpies of hydrocarbons is expanded to include both mono- and multisubstituted derivatives as well. The parameters are derived from experimental fusion enthalpies of 191 hydrocarbons and 225 monosubstituted and 233 multisubstituted hydrocarbon derivatives. Group values are provided for many structural environments. Applications of the technique are described. The average deviation between experimental and calculated fusion entropies and enthalpies obtained for monosubstituted derivatives is ±1.77 eu and ±0.49 kcal/mol, respectively. This increases to ±2.0 eu and ±0.76 kcal/mol, respectively, for multisubstituted derivatives and can be compared with values of ±1.85 eu and ±0.56 kcal/mol previously reported for hydrocarbons.

Fusion, vaporization, and sublimation enthalpies are important physical properties of the condensed phase. A variety of studies including those that reference the gas phase as a standard state require accurate values for these quantities.[1,2] Recently we described a group additivity approach to estimate fusion entropies and enthalpies of hydrocarbons.[3] In this paper, we would like to elaborate further on this method and describe how, with the introduction of some additional parameters, fusion entropies and enthalpies for a large variety of structurally diverse organic compounds can be estimated. The group additivity parameters previously generated from the experimental fusion entropies of 191 hydrocarbons are combined with additional functional group parameters generated from 225 monofunctional and 233 multifunctional hydrocarbon derivatives. Fusion enthalpy estimates are directly obtained from the fusion entropies and the experimental melting point.

As noted previously, our rationale for developing parameters for estimating fusion entropies rather than for fusion enthalpies was influenced mainly by the work of Leclercq, Jacques, and Collet[4] who investigated fusion

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(1) See, for example: Benson, S. W. *Thermochemical Kinetics: Methods for the Estimation of Thermochemical Data and Rate Parameters*, 2nd ed.; Wiley: New York, 1976.

(2) Greenberg, A.; Liebman, J. F. *Strained Organic Molecules*; Academic Press: New York, 1978.

(3) Chickos, J. S.; Hesse, D. G.; Liebman, J. F. *J. Org. Chem.* **1990**, *55*, 3833. For a definition of terms, see also: Chickos, J. S.; Hesse, D. G.; Liebman, J. F. *J. Org. Chem.* **1989**, *54*, 5250.