JOC The Journal of Organic Chemistry

Article

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Anthrone and Related Hydroxyarenes: Tautomerization and Hydrogen Bonding

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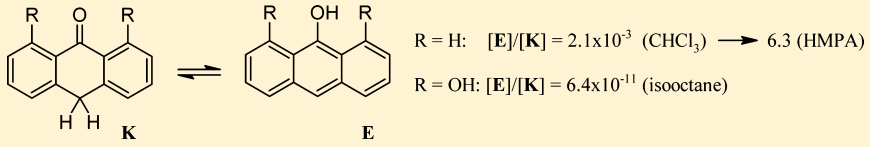
Supporting Information



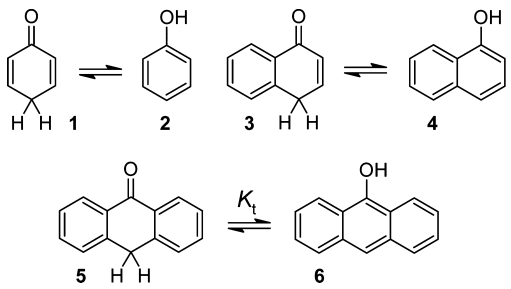
ABSTRACT: The keto−enolization of hydroxyl-substituted naphthols and 9-anthrols has been investigated by means of CBS-QB3 calculations. An excellent agreement between experiment and theory is found for the energetics for the anthrone (**5**) ⇌ anthrol (**6**) equilibrium, with an enthalpy of tautomerization, $\Delta_t H$, of 3.8 kcal mol^{-1}. In contrast, 1-naphthol is the preferred tautomer with a $\Delta_t H$ = −9.0 kcal mol^{-1}. Substitution of the hydrogens at the adjacent carbons by hydroxyl groups leads to the formation of strong intramolecular hydrogen bonds within a six-membered ring in the enones and the enols. Due to the difference in the intramolecular hydrogen bond enthalpy, $\Delta_{HB}H_{intra}$, the equilibrium shifts further to the enone. Thus, for 1,8-dihydroxy-anthrone (anthralin, dithranol) $\Delta_t H$ increases to 12.7 kcal mol^{-1} with an enol/enone ratio of 10^{-10}. The solvent effect on the **5** ⇌ **6** equilibrium has been quantified by considering the formation of intermolecular hydrogen bond(s), leading to an acidity parameter α_2^H for anthrol of 0.42. It is shown that the hydrogen bond donating ability of bulk methanol is greatly attenuated through the formation of cyclic oligomers. The benzylic and phenolic bond dissociation enthalpies for anthrone up to anthralin suggest some antioxidant potency but the precise (radical) mechanism of action remains uncertain.

INTRODUCTION

It has long been recognized that aliphatic aldehydes and ketones can tautomerize into the corresponding enols, an isomerization which encompasses a crucial step in C−C bond formation reactions.[1] The relative amount of the enol in solution depends on a variety of structural features, but in general the carbonyl form predominates for aldehydes and monoketones. That situation is reversed for unsaturated ketones that represent the tautomers of hydroxy-substituted arenes, e.g., **1** or **3** (Scheme 1). Here, the enol, viz. phenol (**2**) or 1-naphthol (**4**), is the exclusive tautomer.[2] However, despite its (relatively) low concentration, the presence of the enone may be crucial for the opening of a certain reaction path, as for example has been demonstrated for the facile desubstitution of 2- and 4-chlorinated phenols at elevated temperatures.[3] About 100 years ago, Meyer published the seminal papers on the tautomerization (desmotroperization) of anthrone (**5**) into 9-anthrol (**6**) (Scheme 1).[4,5] It has been found that the nature of the solvent plays an important role on both the rate of tautomerization and on the thermodynamic equilibrium ratio.[4,6] In benzene, anthrone tautomerizes slowly to a small amount of 9-anthrol at equilibrium conditions while in pyridine the tautomeric equilibrium is established readily at ambient temperature, and the enol is the preferred tautomer.[4,6]

It took more than 50 years before any quantitative thermodynamic data concerning the equilibrium **5** ⇌ **6** became available.[7] In a fully equilibrated mixture the percentage of **6** is 0.2% at 298 K in an inert solvent like isooctane, as determined by UV spectrometry.[7,8] Within a reasonable period of time (a few hours), equilibration could only be achieved by adding a catalytic amount of an (organic) base such as triethylamine.[7,9] At higher concentrations of the base the tautomeric equilibrium shifts further to the enol side due to intermolecular hydrogen bonding (HB) of **6** with the organic base.[7,10] Several studies have reported on the equilibrium shift in various solvents. In hexamethylphosphoric triamide (HMPA), a very strong hydrogen bond acceptor (HBA), the equilibrium is completely shifted to the enol side, and a **6**-HMPA complex can even be isolated in crystalline form.[11] The experiments using UV as the detection method seem to be beset with problems: anthrone is

Scheme 1



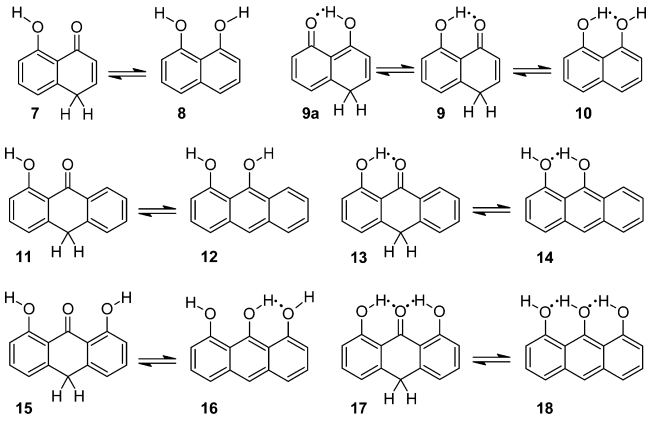
Received: June 9, 2013
Published: July 1, 2013

dx.doi.org/10.1021/jo401243b | J. Org. Chem. 2013, 78, 7674−7682

susceptible to air oxidation and its oxidation product, 9,10-anthraquinone, convolutes the UV recordings. Hitherto, a quantification of the relationship between the tautomeric equilibrium ratio and the nature of the solvent has not been reported.

In polycyclic enones, the keto−enol tautomeric equilibrium might be influenced by adjacent hydroxyl substituents, depending on whether an intramolecular hydrogen bond is formed or not, as exemplified by the hydroxyl substituted naphthol (**7** ⇌ **8**, **9** ⇌ **10**) and mono- and dihydroxy-substituted anthrol systems (**11** ⇌ **12** to **17** ⇌ **18**), respectively (Scheme 2).

Scheme 2



Replacing the hydrogens at C1 and C8 in anthrone by hydroxyl groups, yields 1,8-dihydroxy-9,10-dihydroanthracen-9-one (anthralin, dithranol), an effective drug in the topical treatment of psoriasis.[12] Various conformers can be envisaged, such as **15** and **17**. Although in therapeutic use for many years, its precise mechanism of interaction has not been unraveled, which in part may be related to insufficient knowledge of the physicochemical properties of anthralin. In a variety of solvents, the related enol, 1,9,10-anthracenetriol (**18**), could not be detected by ^{1}H NMR, in equilibrium with **17**, with the exception of HMPA where a 70:30 mixture of [**18**]/[**17**] was found.[11] The energetics of tautomerization of anthralin to 1,9,10-anthracenetriol (**18**) have not been investigated so far in a systematic fashion. Therefore, we embarked on a (computational) study to establish the thermodynamics of the tautomerization for some prototypical hydroxyarenes (phenol, 1-naphthol, and 9-anthrol and its hydroxyl-substituted derivatives) and the effect of intramolecular hydrogen bonding. Furthermore, the influence of intermolecular hydrogen bonding by any solvent on the tautomeric equilibrium has been thoroughly scrutinized. The effect of substitution/intramolecular hydrogen bonding on the benzylic (enone) and phenolic (enol) bond dissociation enthalpies has been established to assess the antioxidant potential of the various tautomers under equilibrium conditions.

RESULTS AND DISCUSSION

Thermochemistry of the Tautomerization of Phenol, 1-Naphthol, and 9-Anthrol. Computations on the energetics of the tautomeric equilibrium between cyclohexa-2,5-dien-1-one (**1**) and phenol (**2**), benzo[*b*]cyclo-hexa-2,5-dien-1-one (**3**) and 1-naphthol (**4**), and anthrone (**5**) and 9-anthrol (**6**) (Scheme 1) have been performed at the CBS-QB3 level of theory. In Table S1 of the Supporting Information, the CBS-QB3-calculated and experimental (literature) heats of formation, $\Delta_fH°$s, for the enols, enones, and reference compounds are compiled. For the compounds listed, it can be inferred that the computation by CBS-QB3 overestimates the experimental $\Delta_fH°$s by about 1−2 kcal mol^{-1}. The enthalpy of tautomerization, Δ_tH, is defined as the difference between $\Delta_fH°$(enol) and $\Delta_fH°$(enone). The variance between the Δ_tH obtained directly from the CBS-QB3-computed $\Delta_fH°$s and the Δ_tH obtained from experimental $\Delta_fH°$s (eventually calculated from isodesmic reactions) is rather marginal (about 0.6 kcal mol^{-1}). In Table S2 (Supporting Information), the computed and literature entropies $S°$ values are summarized.

The thermodynamic parameters, Δ_tH, $T\Delta_tS$, and Δ_tG, for the tautomeric equilibria **1** ⇌ **2**, **3** ⇌ **4**, and **5** ⇌ **6** are presented in Table 1. Table 1 also includes the bond dissociation enthalpies for the benzylic C−H bond, BDE(C−H), and the phenolic O−H bond, BDE(O−H), in the enones and enols, respectively. BDEs are key parameters to assess the reactivity of the enones and enols in (radical) processes such as lipid peroxidation. The BDE(O−H)s are scaled using isodesmic reactions with the BDE(O−H) of 86.7 kcal mol^{-1} for phenol as the anchor.[13] Subsequently, the BDE(C−H) is calculated from the thermodynamic cycle: Δ_tH = BDE(C−H) − BDE(O−H).

Table 1. Enthalpy (Δ_tH) and Free Energy (Δ_tG) for Tautomerization and the Bond Dissociation Enthalpy, BDE, in the Enones (C−H) and in the Enols (O−H)[a]

	Δ_tH	$T\Delta_tS$	Δ_tG	BDE(C−H)[b]	BDE(O−H)
1 ⇌ **2**	−17.7	−0.4	−17.3	69.0	86.7
3 ⇌ **4**	−9.0	−0.4	−8.6	72.7	81.7
5 ⇌ **6**	3.8	1.1	2.7	76.0	72.2

[a]In kcal mol^{-1} at T = 298 K; the thermodynamic values computed by CBS-QB3 are taken from Table S1 (Supporting Information); Δ_tH = $\Delta_fH°$(enol) − $\Delta_fH°$(enone) = BDE(C−H) − BDE(O−H). The BDE(O−H)s are calculated from isodesmic reactions and using the experimental BDE(O−H) in phenol of 86.7 kcal mol^{-1} as the anchor;[13] see Table S1 (Supporting Information). [b]For comparison, the experimental BDE(C−H)s in corresponding hydroarenes, i.e., 1,4-cyclohexadiene, 1,4-dihydronaphthalene, and 9,10-dihydroanthracene, are 76.8, 78.3, and 79.9 kcal mol^{-1}, respectively.[14]

The data reveal that only anthrone (**5**) is the low enthalpy tautomer, while for the other equilibria the hydroxyarene (enol) prevails.[15] The shift of the tautomeric equilibrium in the series phenol−1-naphthol−9-anthrol can be associated with the relative loss of aromatic stabilization on ketonization. It is well documented that the relative gain of aromatic stabilization decreases with increasing benzoannulation, as reflected by a variety of descriptors of aromaticity.[16] For instance, taking the aromatic stabilization energies of benzene (32 kcal mol^{-1}), naphthalene (53 kcal mol^{-1}), and anthracene (70 kcal mol^{-1}) as a rough measure (see Table 4 in ref 16a), the relative loss of aromatic stabilization on ketonization reduces from 32 to 21 (53−32) to 6 (70− 2 × 32) kcal mol^{-1}. A similar picture can be derived from the HOMA indices[15b] or the heats of hydrogenation of the parent hydrocarbons. The heat of hydrogenation of benzene to 1,4-cyclohexadiene requires 5.2 kcal mol^{-1}, while the hydrogenation of naphthalene to 1,4-dihydronaphthalene and anthracene to 9,10-dihydroanthracene affords −3.1 and −16.6 kcal mol^{-1}, respectively (see Table S1, Supporting Information). Interestingly, the relative decrease in the CBS-QB3 computed Δ_tHs from (0) (**1** ⇌ **2**) to −8.7 (**3** ⇌

dx.doi.org/10.1021/jo401243b | J. Org. Chem. 2013, 78, 7674−7682

4) and −21.6 (**5** ⇌ **6**) kcal mol^{-1} matches perfectly the differences of the heats of hydrogenation of the aromatics of (0), −8.3, and −21.8 kcal mol^{-1} (see above) .

A summary of experimental and computational thermodynamic data for the **5** ⇌ **6** equilibrium from the literature is presented in Table 2. A substantial scatter in the thermodynamic data obtained by theoretical calculations is evident. This is most likely caused by the erroneous handling at some levels of theory of the (unlike) structural elements in **5** and **6**. In such cases the application of isodesmic reactions is required to yield more refined Δ_tH's.[17] The CBS-QB3-computed enthalpy Δ_tH = 3.8 kcal mol^{-1} for the **5** ⇌ **6** equilibrium is in excellent agreement with the sole experimental study, reporting Δ_tH = 3.5 ± 0.4 kcal mol^{-1} in a non-hydrogen bonding solvent (see Table 2).[7] The derived free energy change, Δ_tG = 2.7 kcal mol^{-1} (K_t = 1.0 × 10^{-2}), seems to be slightly at variance with that particular work, Δ_tG = 3.6 ± 0.4 kcal mol^{-1} (K_t = 2.3 × 10^{-3}), but is again in good agreement with the Δ_tG = 2.9 ± 0.2 kcal mol^{-1} (K_t = 7.5 × 10^{-3}) obtained from two independent experimental studies (Table 2).[18,19] In these investigations, 9-anthrol has been generated by flash photolysis of an appropriate precursor in water[18] and by injecting a solution of anthrone in DMF into an aqueous buffer,[19] respectively. In both studies, the equilibrium constants have been derived by means of a thermochemical cycle method. The precursor method also has been applied to quantify the thermodynamics for tautomerization of phenol[20a] and 1-naphthol,[20b] affording Δ_tG(**1** ⇌ **2**) = −15.0 ± 0.2 kcal mol^{-1} and Δ_tG(**3** ⇌ **4**) = −8.5 ± 0.2 kcal mol^{-1} at 298 K. There is again an excellent agreement between the experimental and the CBS-QB3-computed Δ_tG(**3** ⇌ **4**) for tautomerization: −8.5 vs −8.6 kcal mol^{-1}. At variance, the computed gas phase Δ_tG(**1** ⇌ **2**) involving phenol is 2.3 kcal mol^{-1} higher than the experimental one. This deviation may be related to the way the solvent (water) is interacting with the individual tautomers (e. g., the formation of intermolecular hydrogen bonds, see below), and thereby shifting the equilibrium in aqueous solution relative to that in the gas phase.[20c]

Table 2. Experimental and Theoretical Enthalpy (Δ_tH) and Free Energy (Δ_tG) for the Tautomerization 5 ⇌ 6[a]

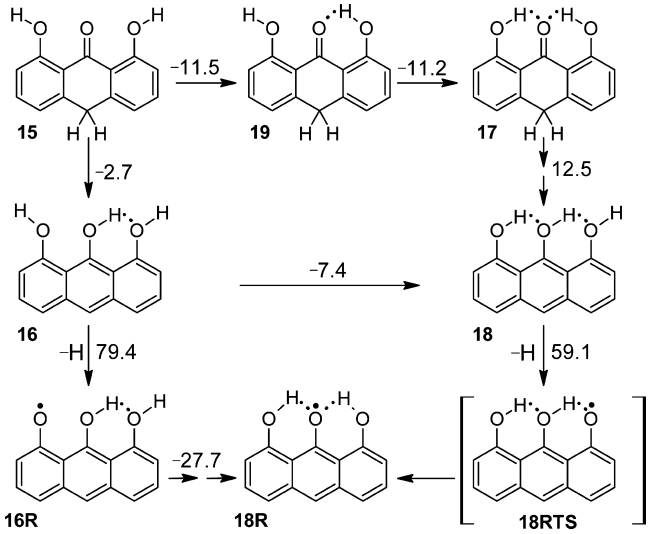
exptl/theor method	Δ_tH	Δ_tG	ref
UV/vis spectrometry	3.5 ± 0.4[b]	3.6 ± 0.4[b]	7
thermochemical cycle		2.9 ± 0.2[c]	18, 19
SCF π-MO	1.4		21
MNDO	3.8		22
B3LYP/6-31G(d)	9.3	8.7	18
B3LYP/6-31G(d,p)	6.6	6.1	3
MP2(FULL)//HF/6-31G(d)	9.9		17b
B3LYP/6-311++G(2df,2p)	3.9	4.2	15b
CBS-QB3	3.8	2.7	this work

[a]In kcal mol^{-1} at T = 298 K. The Δ_tH and Δ_tG by theory are calculated from the computed energies for **5** and **6**. [b]In isooctane, recalculated parameters from the equilibrium constants (three point plot of lnK_t vs 1/T) with an estimated error. [c]Average from two independent studies (in water): Δ_tG = 2.96 kcal mol^{-1},[18] Δ_tG = 2.86 kcal mol^{-1}.[19]

The Effect of Hydroxyl Substitution on the Energies of Tautomerization. The Δ_tH, $T\Delta_tS$, and Δ_tG data for a number of related hydroxyl-substituted naphthalenes and anthracenes, **7**−**19** (Schemes 2, 3), have been determined by CBS-QB3 computations. In Table S4, Supporting Information, the CBS-QB3-computed $\Delta_fH°$ and $S°$ for the tautomers and related radials are presented. The presence of other, nonplanar conformations for the enols **8**, **10**, **12**, **14**, **16** and **18** have been explored. In all cases nonplanar starting geometries optimize back to the planar ones, either to the intramolecularly hydrogen bonded or to the non-intraHB conformers. Furthermore, on optimization, the "inverted" hydroxynaphthone HB structure (**9a**) converts smoothly to **9** (see Scheme 2).

In Table 3, the thermodynamic data for the tautomerization are summarized. In Scheme 3, a thermodynamic cycle is

Scheme 3. Enthalpy of Tautomerization (Δ_tH), Intramolecular Hydrogen Bond Enthalpy ($\Delta_{HB}H_{intra}$), and O−H Bond Dissociation Enthalpy, BDE(O−H) for 1,8-Dihydroxyanthrone (kcal mol^{-1})[a]



[a]The BDE(O−H)s are scaled; see Table 3.

Table 3. Effect of Hydroxyl Substitution on the Enthalpy, Δ_tH, and Free Energy, Δ_tG, for Tautomeriziation and on the BDE(C−H)'s in the Enones and the BDE(O−H)'s in the Enols (Scheme 2)[a]

	Δ_tH	$T\Delta_tS$	Δ_tG	BDE(C−H)	BDE(O−H)
7 ⇌ **8**	−9.5	−0.7	−8.8	72.2	81.7
9 ⇌ **10**[b]	−3.3	0.03	−3.3	70.8	74.1
11 ⇌ **12**	3.7	−0.2	3.9	75.2	71.5
13 ⇌ **14**[c]	8.2	−1.5	10.0	72.3	64.1
15 ⇌ **16**	−2.7	−0.5	−2.2	76.7	79.4
17 ⇌ **18**	12.5	−1.4	13.9	71.9	59.9[d]

[a]In kcal mol^{-1} at T = 298 K; the thermodynamic values computed by CBS-QB3 are taken from Table S4 (Supporting Information); see also Schemes S1−S3 (Supporting Information). Δ_tH = $\Delta_fH°$(enol) − $\Delta_fH°$(enone) = BDE(C−H) − BDE(O−H). The BDE(O−H)s are calculated from isodesmic reactions and using the experimental BDE(O−H) in phenol of 86.7 kcal mol^{-1} as the anchor;[13] see Table S4 (Supporting Information). [b]See also ref 23. [c]A second less stable conformer of **14** has been identified (**14a**, see Scheme S2 in the Supporting Information) with C1−OH as the hydrogen bond donor and C8−OH as the hydrogen bond acceptor; the differences between the two conformers are ΔH = 1.7 kcal mol^{-1} and ΔS = 0.1 cal mol^{-1}K^{-1}. [d]Refers to the BDE(O−H) for C1−OH in **18** versus the doubly intramolecular hydrogen-bonded 1,8-dihydroxyanthracen-9-oxyl radical (**18R**) to which the optimization converges.

dx.doi.org/10.1021/jo401243b | J. Org. Chem. 2013, 78, 7674−7682

presented for 1,8-dihydroxyanthrone involving tautomerization, intramolecular hydrogen bond formation, and homolytic cleavage of the phenolic OH. Similar (extended) schemes starting with the enones **7**, **9**, **11**, **13**, **15**, and **17** can be found in the Supporting Information (Schemes S1−S3). Substitution of the hydrogen at C8 in **3** and **4** by a hydroxyl group, such that the hydroxylic hydrogen is in the "away" orientation (compounds **7** and **8**, Scheme 2), does not cause any significant change in the tautomeric equilibrium: Δ_tH(**7** ⇌ **8**) = −9.5 kcal mol^{-1} vs Δ_tH(**3** ⇌ **4**) = −9.0 kcal mol^{-1}. Apparently, there is no substituent effect by OH at C8 on the energetics of tautomerization. Rotation of the hydroxyl group with the hydrogen now pointing toward the neighboring carbonyl (**9**) or hydroxyl (**10**) group results in the formation of an intramolecular hydrogen bond within a six-membered ring. The strength of this bond, i.e., the intramolecular hydrogen bond enthalpy ($\Delta_{HB}H_{intra}$), is defined as the enthalpy difference between the two conformers with the hydroxyl group pointing away and toward the hydrogen bond-accepting,[24] analogously to the definition used in our previous studies on intramolecular hydrogen bonding in phenolic compounds.[25] In Table 4, the CBS-QB3-computed $\Delta_{HB}H_{intra}$ and $\Delta_{HB}S_{intra}$ are listed for the enones and enols under study. For the interaction of the hydroxylic hydrogen with the carbonyl group a $\Delta_{HB}H_{intra}$ of around −12 kcal mol^{-1} is found, and for the interaction of the hydroxylic hydrogen with the hydroxy group a $\Delta_{HB}H_{intra}$ of ca. −6 kcal mol^{-1} is predicted.

Strong intramolecular hydrogen bonds within a six-membered ring (i.e., $\Delta_{HB}H_{intra}$ < −8 kcal mol^{-1}) in 2-X-phenols have been identified previously by computations with carbonyl-containing substituents (X) such as CHO, COOH, COOMe, $CONH_2$.[25] It should be noted that a fraction of the $\Delta_{HB}H_{intra}$ stems from the release of the repulsion enthalpy between the oxygen lone pairs at OH and C═O when the hydroxyl group is rotated from the away to the toward orientation.

When the hydroxyl at C8 is now intramolecularly hydrogen bonded (**9**, **10**), the enthalpy of tautomerization increases from Δ_tH(**3** ⇌ **4**) = −9.5 to Δ_tH(**9** ⇌ **10**) = −3.3 kcal mol^{-1}. This increase is directly related to the difference of 6.2 kcal mol^{-1} between $\Delta_{HB}H_{intra}$ for enone **9** and for enol **10**. Consequently, when 1,8-naphthalenediol (**10**) is dissolved in an inert solvent (isooctane), a detectable amount of ca. 0.4% of the enone **9** is expected to be present after the tautomeric equilibrium is established. However, an experimental confirmation cannot be found in the literature. There is one report suggesting that **9** with its α,β-unsaturated ketone moiety is the reactive intermediate in the biosynthesis of spiro-bisnaphthalenes from derivatives of 1,8-naphthalenediol (**10**).[26] Replacing the hydrogen at C1 in anthrone (**5**) and 9-anthrol (**6**) by a OH group in the away orientation, viz. compounds **11** and **12**, leads to Δ_tH (**11** ⇌ **12**) ≅ Δ_tH (**5** ⇌ **6**); the difference in the equilibrium ratios appears to be determined by entropic factors (see Tables 1,3) and no effect of hydroxyl substitution on Δ_tH is found. Conversely, with the OH groups in the toward orientation (compounds **13** and **14**), the stronger intramolecular hydrogen bond with the carbonyl in **13** relative to that in **14** results in a further shift of the equilibrium toward the enone **13**. There are two conformers for 1,9-anthracenediol (**14**), and they differ by 1.7 kcal mol^{-1}. In the lowest enthalpy conformer the OH at C1 is acting as the hydrogen bond-accepting group canceling the repulsion between C9−OH and C8−H. Substituting C1−H and C8−H by C1−OH and C8−

Table 4. Intramolecular Hydrogen Bond Enthalpies, $\Delta_{HB}H_{intra}$ and Entropies, $\Delta_{HB}S_{intra}$, in Enones and Enols[a]

	$\Delta_{HB}H_{intra}$	$\Delta_{HB}S_{intra}$		$\Delta_{HB}H_{intra}$	$\Delta_{HB}S_{intra}$
7 ⇌ **9**	−12.4	−3.0	**8** ⇌ **10**[b]	−6.2	−0.4
11 ⇌ **13**	−12.4	−1.5	**8R** ⇌ **10R**[c]	−13.4	−2.5
15 ⇌ **19**	−11.5	−0.6	**12** ⇌ **14**	−6.1	−2.3
19 ⇌ **17**	−11.2	2.4			

[a]In (k)cal mol^{-1} (K^{-1}) at T = 298 K; the thermodynamic values computed by CBS-QB3 are taken from Table S4 (Supporting Information); see also Schemes S1−S3 (Supporting Information). The intramolecular hydrogen bond enthalpy, $\Delta_{HB}H_{intra}$, and entropy, $\Delta_{HB}S_{intra}$, are defined as the difference between the two conformers with the hydroxyl group pointing away and toward the hydrogen bond-accepting substituent. [b]See also ref 23. [c]For the corresponding aryloxyl radicals (**8R**, **10R**, see Scheme S1 in the Supporting Information). The decrease in BDE(O−H) between **8** and **10**, see Table 3, is almost entirely caused by the strengthening of the intramolecular hydrogen bond in **10R** vs **8R** relative to **10** vs **8** of 7.2 kcal mol^{-1}.

Table 5. Experimental Equilibrium Ratios for 9-Anthrol/Anthrone, [6]/[5], in Various Solvents[a]

solvent	β_2^H	[6]/[5]	solvent	β_2^H	[6]/[5]
isooctane	0	≥0.001,[b] 0.0021[c]	1-butanol	0.46	0.10 ± 0.01,[b] 0.18[f]
CCl_4	0.05	≤0.001,[b] <0.001[d]	acetone	0.50	0.19,[d] 0.25[f]
benzene	0.14	0.0025,[b] 0.0025,[c] 0.017[e]	THF	0.51	0.2 ± 0.1,[b] 0.59[d]
nitrobenzene	0.34	0.11;[f] 0.11[g]	pyridine	0.62	1.4 ± 0.5,[b] 1.9[d], 1.0[f]
water	0.38	0.0068[h], 0.0079[i]	DMF	0.66	1.3 ± 0.1,[b] 0.09;[f] 0.28,[g] 1.7 ± 0.2,[k] 1.5 ± 0.1[k]
methanol	0.41	0.10 ± 0.03[b], 0.54[d], 0.2[e]	DMSO	0.78	1.6 ± 1[b], 3.3[d], 2.7[f], 3.2[g], 3.3 ± 0.2[k], 3.4 ± 0.1[k]
ethanol	0.44	0.15 ± 0.03[b], 0.12[j]	HMPA	1.00	≈10[l]

[a]Detection method is UV spectrometry at room temperature unless stated otherwise; β_2^H's are the hydrogen-bond-accepting ability parameters of the solvents (see ref 30); error margins are as given in the papers. [b]Reference 31 (cyclohexane and toluene are used instead of isooctane and benzene), [6]/[5] ratios in other solvents (β_2^H in parentheses): 1,4-dioxane 0.07 ± 0.02 (0.41); ethylacetate 0.06 ± 0.01 (0.45); diethylether 0.06 ± 0.02 (0.45); 2-propanol 0.11 ± 0.05 (0.47); triethylamine 1.1 ± 0.05 (0.67); *N*,*N*-dimethylacetamide 1.8 ± 0.5 (0.74). [c]Reference 7a, T = 293 K. [d]Reference 32, exptl method: NMR, T = 300 K; $CDCl_3$ instead of CCl_4; CH_3OD instead of CH_3OH; THF in the presence of a catalytic amount of NaOH. [e]Reference 33; in carefully dried acetonitrile (β_2^H = 0.44) the [6]/[5] is 0.02−0.05 at T = 300 K (ref 33a). [f]Reference 34, exptl method: ^{1}H NMR, T = 313 K. [g]Reference 36, exptl method: ^{1}H NMR (T = 307 K) for solutions containing 0.05 M anthrone and 0.0072 M triethylamine; in acetonitrile **6** is below the detection limit, i.e., [6]/[5] < 0.01. [h]Reference 18, T = 298 K. [i]Reference 19, T = 298 K. [j]Reference 4b, 8, exptl method: Br_2 titration of 9-anthrol; [6]/[5] = 0.013 in acetic acid (β_2^H = 0.42). [k]Reference 35, exptl method: cyclic voltammetry (T = 295 K) or, second entry, ^{13}C NMR (T = 294 K). [l]Reference 11, HMPA = hexamethylphosphoric triamide, O═P(N(CH_3)$_2$)$_3$.

dx.doi.org/10.1021/jo401243b | J. Org. Chem. 2013, 78, 7674−7682

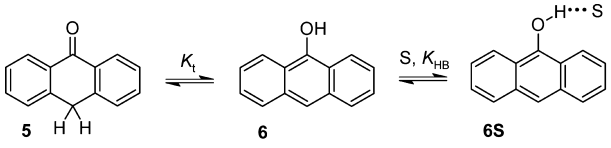
OH leads to three conformers with no (**15**), one (**19**), and two (**17**) intramolecular hydrogen bonds, respectively (Scheme 3). The lowest enthalpy conformer for anthralin is **17** with a total $\Delta_{HB}H_{intra}$ (relative to **15**) of −22.7 kcal mol^{-1}. The Δ_tH(**15** ⇌ **16**) is lower than that for Δ_tH(**11** ⇌ **12**) which is due to the concomitant formation of the intramolecular hydrogen bond in **16**. With a Δ_tG(**17** ⇌ **18**) of 13.9 kcal mol^{-1} for the tautomerization into 1,8,9-anthracenetriol (**18**), a ratio [**18**]/[**17**] of about 10^{-10} is expected in an inert solvent at 298 K.[27]

Effect of Solvent on the Tautomeric Equilibrium Ratios between Anthrone (5) and 9-Anthrol (6) and Their Derivatives. Solvent effects play a crucial role in many areas of chemical transformations. A literature survey on the tautomeric equilibrium ratios, [**6**]/[**5**], determined in various solvents and by a number of techniques is compiled in Table 5, showing a large solvent effect on the tautomeric ratio. However, it is unclear if all the literature data presented in Table 5 actually refer to fully equilibrated mixtures.

Following our work on the kinetic solvent effect (KSE) on the hydroxylic hydrogen atom abstraction from phenols, it seems very likely that the observed change in the [**6**]/[**5**] ratio is due to the formation of one or two intermolecular hydrogen bond(s).[28] The hydrogen bond donor, 9-anthrol (**6**) can form a 1:1 complex with a hydrogen bond accepting (HBA) solvent. On the other hand, anthrone (**5**) acts as a hydrogen bond acceptor in hydrogen bond donating (HBD) solvents. The magnitude of the hydrogen bond equilibrium constant is largely independent of the bulk physical properties of the surrounding medium such as dielectric constant or dipole moment.

The descriptor for the acidity of a solute/solvent (hydrogen bond donating ability) is α_2^H [29] and ranges from 0 to about 1; the descriptor for the basicity of a solute/solvent (hydrogen bond accepting ability) is β_2^H [30] and ranges from 0 to 1, with β_2^H = 0.00 for isooctane as a non-HBA solvent and β_2^H = 1.0 for hexamethylphosphoric triamide (HMPA). For many solutes and solvents α_2^H and β_2^H values are available in the literature and they are determined under dilute conditions and in inert solvents.

The equilibrium constant, K_{HB}, for the formation of an intermolecular hydrogen bonded



(1)

complex between **6** and the solvent (S), eq 1, is given by an empirical relationship,[29,30] eq 2:

$$\log K_{HB} = 7.354\alpha_2^H\beta_2^H - 1.094 \quad (2)$$

The tautomeric equilibrium ratio, [**6**]$_t$/[**5**], in a HBA solvent, with [**6**]$_t$ = [**6**] + [**6S**] is presented by eq 3:

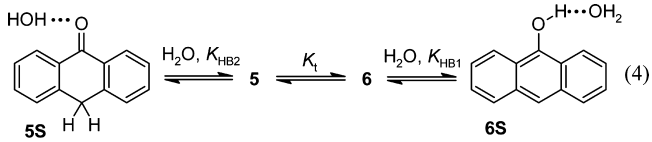
$$[\mathbf{6}]_t/[\mathbf{5}] = K_t + K_tK_{HB}[S] \quad (3)$$

The α_2^H for 9-anthrol has not been determined but can be derived from data presented in Table 5 in conjunction with eqs 2 and 3. There appears to be a good experimental agreement regarding the tautomeric ratio in neat DMSO, and an average [**6**]$_t$/[**5**] of 3.3 (T = 298 K, see Table S4) is selected. Hence, with [DMSO] = 14.1 M in conjunction with the equilibrium constant derived by CBS-QB3 computations (K_t = 1.05 × 10^{-2}, see Table 1), eq 3 furnishes K_{HB} = 22.3 M^{-1} and eq 2 provides α_2^H (9-anthrol) = 0.43. In neat nitrobenzene with [**6**]$_t$/[**5**] = 0.098 (T = 298 K, see Table S5) yields α_2^H (9-anthrol) = 0.41. It should be noted that the β_2^H values used in this analysis refer to the monomeric and unassociated hydrogen bond accepting solvent. The equilibrium constants for hydrogen bonding, K_{HB}s, for phenol and 1-naphthol with triethylamine, TEA, have been determined under dilute conditions (T = 298 K) and in an inert solvent (n-heptane).[37] According to eq 2, the K_{HB}s for phenol (α_2^H = 0.596)[29] and for 1-naphthol (α_2^H = 0.608)[29] with TEA (β_2^H = 0.67)[30] are calculated as 69 and 80 M^{-1}, in good agreement with the experimental values of 84 M^{-1} and 121 M^{-1}, respectively. In a study on the hydrogen bonding between 9-anthrol and TEA in isooctane[7b] a K_{HB} = 12.1 M^{-1} is derived (recalculated from that work with K_t = 1.05 × 10^{-2}), consonant with the K_{HB} = 9.4 M^{-1} obtained by eq 3. Hence, for future use the hydrogen bond donor ability for 9-anthrol (**6**) is best presented by α_2^H= 0.42.

The pK_a for 9-anthrol (7.8−7.9)[20c] is about the same as that for 4-CN-phenol (7.8)[38] with α_2^H = 0.79,[29] therefore it might be expected that 9-anthrol is a strong HBD as well, which is in contrast with the current findings. A good (quadratic) correlation exists between the α_2^Hs for mono (3-, 4-), and di (3,4-) substituted phenols and their pK_as.[38] However, this correlation breaks down for mono (2-), and di (2,2-) substituted phenols. For example, the pK_as for phenol, 2-methylphenol, and 2,6 dimethylphenol are 10.00, 10.3, and 10.7, respectively, while the α_2^Hs decrease significantly in the order 0.60, 0.52, 0.39, probably for steric reasons caused by the adjacent methyl substituents. It can be easily envisaged that this spacial congestion is also present in 9-anthrol, where the OH group is bracketed by two neighboring CH bonds.

The thermodynamic parameters, $\Delta_{HB}H_{inter}$ and $\Delta_{HB}S_{inter}$, for the intermolecular hydrogen bond formation between 9-anthrol and DMSO have been derived from the data of several studies (temperature range 296 to 413 K, Table S4). With Δ_tH = 3.8 kcal mol^{-1} and Δ_tS = 3.7 cal mol^{-1} K^{-1} (see Table 2), $\Delta_{HB}H_{inter}$ = −5.2 kcal mol^{-1} and $\Delta_{HB}S_{inter}$ = −11.3 cal mol^{-1} K^{-1} are derived. For the weaker HBA solvent nitrobenzene the parameters are $\Delta_{HB}H_{inter}$ = −1.7 kcal mol^{-1} and $\Delta_{HB}S_{inter}$ = −5.8 cal mol^{-1} K^{-1} (see Table S5).[39] Consequently, since ($\Delta_{HB}H_{inter}$ + Δ_tH) < 0, [**6**]$_t$/[**5**] decreases with temperature in a strong HBA solvent, while in weaker HBA solvents the tautomeric ratio increases as the overall process is now endothermic, i.e., ($\Delta_{HB}H_{inter}$ + Δ_tH) >0.

Water, an amphoteric solvent, acts as a hydrogen bond acceptor and as a hydrogen bond donor. This implies that next to hydrogen bonding with 9-anthrol, a second intermolecular hydrogen bond will be formed with anthrone, eq 4:



(4)

The ratio [**6**]$_t$/[**5**]$_t$ with [**5**]$_t$ = [**5**] + [**5S**] and [**6**]$_t$ = [**6**] + [**6S**] is approximated by eq 5:

$$[\mathbf{6}]_t/[\mathbf{5}]_t = K_tK_{HB1}/K_{HB2} \quad (5)$$

According to eq 2, with α_2^H = 0.42 for 9-anthrol and β_2^H = 0.38 for water,[30] K_{HB1} is 1.20 M^{-1}; with α_2^H = 0.353 for water[29] and β_2^H = 0.51 for anthrone,[40] K_{HB2} is 1.70 M^{-1}. In conjunction with K_t = 1.05 × 10^{-2}, eq 5 thus predicts a ratio [**6**]$_t$/[**5**]$_t$ = 7.4 × 10^{-3}, which is in perfect agreement with the ratio of 7.3 ×

dx.doi.org/10.1021/jo401243b | J. Org. Chem. 2013, 78, 7674−7682

10^{-3} found as the average from two studies at T = 298 K.[18,19] Hence, due to the formation of intermolecular hydrogen bonds with both tautomers, the equilibrium ratio in water is close to those found in inert solvents. Theory at the CBS-QB3 level has been used to examine the interactions of **5** and **6** with H_2O in more detail (see Table S6, Supporting Information). There is no noticeable effect on the tautomeric ratio when the intermolecular hydrogen bonded species (**5S** and **6S**) are taken into consideration, consonant with the experimental findings. Hydrogen bond formation between 9-anthrol (**6**) and water may occur in two ways: **6** acting as a hydrogen bond donor, **6**-(OH_2), or as a hydrogen bond acceptor, **6**-(H_2O). The computations suggest the former species predominating, with a ratio **6**-(OH_2)/**6**-(H_2O) of about 1000. The Polarizable Continuum Model, PCM, is used to mimic the effect of solvation on going from the gas phase to the solution phase. Without taking into account any specific hydrogen bonding with either **5** or **6**, the equilibrium ratio in water relative to the gas phase (inert solvent) is predicted to be shifted in favor of anthrone by a factor of 10 (see Table S6, Supporting Information). This, however, is not supported by experiment. This finding demonstrates that when the formation of a (strong) intermolecular hydrogen bond is an important contributor to the overall solvation energy, PCM is not an appropriate tool for the prediction of solvation energies.[15b]

Other nonhydroxylic solvents such as acetonitrile, acetone, or di- and trihalomethanes are acting as HBA and as HBD solvents. For example, chloroform (α_2^H = 0.20,[29] β_2^H = 0.02[30]) is a stronger HBD than a HBA solvent and consequently the equilibrium shifts to the enone. The ratio $[\mathbf{6}]_t/[\mathbf{5}]_t$ is reduced to 2.1 × 10^{-3} (eq 5) , and the (relative) concentration of 9-anthrol is now below the detection limit of many instrumental (e.g., NMR[32]) methods.

A clear deviation between the observed and the predicted tautomeric equilibrium ratios is found for alcoholic solvents. With methanol (α_2^H = 0.367,[29] β_2^H = 0.41[30]), eq 5 estimates $[\mathbf{6}]_t/[\mathbf{5}]_t$ = 8.3 × 10^{-3} which is a far cry from the reported ratio of 0.5 determined by a NMR study.[32] It has been noted that when water or ethanol (HBD solvents) is added to an equilibrated mixture of anthrone and 9-anthrole in DMSO, the equilibrium shifts to the enone.[34] This change demonstrates the additional formation of an intermolecular hydrogen bond with anthrone. Therefore, the unexpected large fraction of 9-anthrol found in bulk methanol points to a difference between the HBD ability of neat methanol relative to that of methanol under dilute conditions.[41] Neat methanol, and other self-associated alcoholic solvents, consists of cyclic oligomers, the monomeric fraction in bulk methanol is about 0.3−1.0%.[42] In e.g., cyclic tetramers the hydroxylic hydrogens are involved in hydrogen bonding and, therefore, are less available for the intermolecular hydrogen bonding with the solute. The degree depends on the balance between the $\Delta_{HB}G$ for solvent−solvent interaction and the $\Delta_{HB}G$ for solvent−solute interaction. Pyridines and aliphatic amines are strong HBA solutes ($\beta_2^H \cong$ 0.70[30]) and their equilibrium constants for intermolecular hydrogen bond formation, K_{HB}s, in neat methanol are lower relative to the K_{HB}s in a dilute solution of methanol.[42] Consequently, the α_2^H value (an empirical descriptor) for neat methanol is reduced. A weaker HBA such as anthrone (β_2^H = 0.51[40]) may not be capable forming an intermolecular hydrogen bond with a cyclic oligomer (by first breaking a solvent−solvent hydrogen bond), and the HBD ability for neat methanol in that case approaches zero.[43] Under those conditions eq 3 needs to be applied, yielding $[\mathbf{6}]_t/[\mathbf{5}]$ = 0.37 which tallies nicely with the experiment (see Table 5). With bulk water the formation of cyclic oligomers occurs as well, but these clusters include free hydroxylic hydrogen(s) still allowing the formation of an intermolecular hydrogen bond with the solute without disrupting a solvent−solvent hydrogen bond.

In summary, the effect exerted by a large number of solvents on the tautomeric equilibrium ratio between anthrone and 9-anthrol can now be quantified accurately by eqs 3 or 5. This ratio varies by about 3000 between $CHCl_3$ and HMPA at 298 K. In turn, this equilibrium may be used as a sensitive tool to explore hydrogen-bonding properties of neat solvents or mixtures of solvents.[44] The insights, as outlined above, can now be used to assess the effect of solvent on the equilibria **9** ⇌ **10** and **17** ⇌ **18** (see Table 3). The enone **9** is a hydrogen bond acceptor (carbonyl) as well as a hydrogen bond donor (the intramoleculary bonded hydroxylic hydrogen). The basicity of **9** is probably quite similar to that for 2-hydroxybenzophenone with a β_2^H = 0.34.[40] The hydroxylic hydrogen in **9** is still available for intermolecular hydrogen bonding leading to the formation of a bifurcated species and an α_2^H = 0.35 can be estimated.[45] For the enol, 1,8-naphthalenediol (**10**), an α_2^H = 0.775 is found by means of an infrared spectroscopic study.[46] Hence, **10** is a much stronger hydrogen bond donor than anthrol, despite the fact that their pK_as are reasonably close together.[46] In the literature no reports are found on the solvent effect on the **9** ⇌ **10** equilibrium but it can now be calculated, with the use of eq 5, that in a strong HBA solvent the ratio $[\mathbf{10}]_t/[\mathbf{9}]_t$ increases from 2.6 × 10^2 (isooctane) to 3.5 × 10^5 (HMPA).

The carbonyl stretching frequency for anthralin (**17**) in CCl_4 solution shows no significant shift when a HBD (4-F-phenol) is added.[40] This implies that the carbonyl intramolecularly bonded to two adjacent hydroxylic hydrogens cannot act anymore as a hydrogen bond acceptor and hence $\beta_2^H \cong 0$ for **17**. For anthralin an α_2^H = 0.35 can be used comparable to that for **9** (see above). The "free" hydroxylic group in 1,8,9-anthracenetriol (**18**) is available for hydrogen bond formation with HBA solvents and the α_2^H value is close to that for 1,8-naphthalenediol (**10**), i.e., $\alpha_2^H \cong 0.8$.[46] However, with K_t = 6.4 × 10^{-11} for **17** ⇌ **18** (see Table 3), the effect of solvent on the tautomeric equilibrium will not be detectable. Indeed, in various HBA solvents ranging from chloroform to DMSO only **17** has been observed.[11,27b] In neat HMPA (5.8 M, β_2^H = 1.0[30]) the K_{HB}s are calculated (eq 2) as 3.0 × 10^1 M^{-1} (**17**) and 6.2 × 10^4 M^{-1} (**18**) and eq 5 predicts a ratio $[\mathbf{18}]_t/[\mathbf{17}]_t$ = 1.3 × 10^{-7}. Experimentally, an unexplainable $[\mathbf{18}]_t/[\mathbf{17}]_t$ = 0.43[11] is found, which is probably due to an artifact.

The enones discussed in this work are relatively strong carbon acids[20c] and a pK_a = 9.5 for **17** has been reported.[48] In the presence of an organic base (also acting as a hydrogen bond acceptor) such as pyridine, it is expected that a proton is readily transferred from C10−H in **17** to the base, leading to the formation of a carbanion, a resonance form of the 1,8,9-anthracentriolate ion, without the prerequisite of tautomerization of **17** to the neutral **18**. The aryloxylate ion[49] will be quite susceptible to air-oxidation with a (ionic) mechanism comparable to that for the facile oxidation of anthrone to 9,10-anthraquinone in polar aprotic solvents and in the presence of an organic base.[36] The rate-determining step encompasses an interaction between the aryloxylate ion and oxygen. This in-cage process involves mostly likely an electron transfer, intersystem crossing, and the addition of the

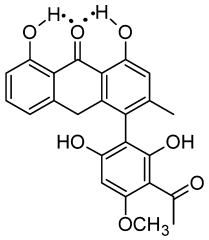
dx.doi.org/10.1021/jo401243b | J. Org. Chem. 2013, 78, 7674−7682

superoxide anion to C10 of the aroxyl radical, yielding a peroxide ion. Ultimately,1,8-dihydroxy-9,10-anthraquinone will be formed as the main product.

Antioxidant Properties of Various Tautomeric Species. In Tables 1 and 3, the scaled bond dissociation enthalpies for the phenolic O−H, BDE(O−H), in the enols are presented. The BDE(O−H) varies from 86.7 kcal mol^{-1} (phenol, **2**) to 59.9 kcal mol^{-1} (1,8,9-anthracenetriol, **18**). The BDE(O−H) can be used to assess the potential antioxidant activity of the enol.[50] An antioxidant is defined as a peroxyl radical-trapping compound retarding the peroxidation of lipids in e.g. human blood. The most effective antioxidants are phenolic compounds such as the synthetic butylated hydroxyl anisol (BHA) or the natural occurring α-tocopherol (Vitamin E). The low BDE(O−H) in these compounds ensures a facile hydroxylic hydrogen transfer between the phenolic compound and the peroxyl radical, the chain carrier in lipid peroxidation. The antioxidant properties of anthrone (**5**) have been investigated by studying the inhibition of the linoleic peroxidation.[51] It has been found that **5** is a more potent antioxidant than α-tocopherol. However, it seems most likely that anthrol (**6**) and not **5** is acting as the radical scavenger. The tautomeric equilibrium, **5** ⇌ **6**, indicates that only small fraction is present as the phenolic compound, anthrol (see Table 1), but the effectiveness (the rate of hydrogen atom transfer) of **6** is enhanced due to its low BDE(O−H) of 72.2 kcal mol^{-1} (see Table 1) relative to the BDE(O−H) in α-tocopherol of 77.3 kcal mol^{-1}.[52] It should be noted that a low BDE(O−H) alone does not make a compound a good antioxidant, the potential toxicity of the reaction product needs to be taken into consideration as well.[50]

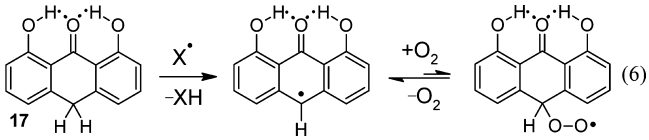
An alternative way to investigate the antioxidant potential of a compound is by measuring the hydrogen atom abstraction reaction by 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals,[51a,53] a kinetically good mimic for peroxyl radicals. Knipholone anthrone (**20**), a compound that can be isolated from an Ethiopian medicinal plant, *Kniphofia foliosa*, has the same base structure as anthralin (**17**), and the energetics for tautomerization and the BDEs are not expected to be any different. Surprisingly, the DPPH assay method suggests that **20** is a potent antioxidant.[53] The consequence of the two strong intramolecular hydrogen bonds in **17** (and **20**) is that the hydroxylic hydrogens at C1 and C8 are protected against hydrogen atom abstraction as has been demonstrated for 2-formylphenol and 7-hydroxyindanone, compounds with similar strong intramolecular hydrogen bonds within a six-membered ring.[25a] Tautomerization of **17** yields **18** but this compound is only present in microscopic amounts in any solvent, and due to its extremely low BDE(O−H) the free hydroxyl group reacts readily with molecular oxygen leading two radical species, hydroperoxyl and aryloxyl, capable of an inducing peroxidation. When present, **18** is likely to act as a pro-oxidant rather than an antioxidant. Therefore, the reported antioxidant activity of **20** cannot be associated with any hydroxylic hydrogen atom transfer reaction inhibiting the lipid peroxidation.[53b]

The benzylic BDE(C−H)s listed in Tables 1 and 3 are crucial parameters to assess the susceptibility of the enone species to (liquid phase) autoxidation. The BDE(C−H) in anthralin (**17**) is 4 kcal mol^{-1} lower than in anthrone (**5**) and even about 8 kcal mol^{-1} lower than in 9,10-dihydroanthracene. A low BDE(C−H) implies that the benzylic hydrogen in RH is easily abstracted by radical species. A key step in the radical chain mechanism for oxidation of RH, after the generation of



Knipholone anthrone, **20**

the benzylic radical, R$^{\bullet}$, is the addition reaction of molecular oxygen forming a peroxyl radical, ROO$^{\bullet}$, eq 6.



(6)

In general, there exists a good linear correlation between the BDE(C−H) in RH and the BDE(C−OO) in ROO$^{\bullet}$.[54] With a BDE(C−H) in **17** of 71.9 kcal mol^{-1} (see Table 3), it can be estimated that BDE(C−OO) in the corresponding peroxyl radical is about 7 kcal mol^{-1}; while for **5** a BDE(C−OO) = 11 kcal mol^{-1} is suggested. These insights lead to the conclusion that the addition of oxygen to the anthralinyl radical is fully revisible[55] despite claims of the contrary.[56,57] Instead, the anthralinyl radical may combine with other radical species and thereby terminate an oxidative radical chain reaction. In that respect anthralin and naturally occurring derivatives may belong to the class of "radically different anti-oxidants" such as lactone-based compounds.[58]

COMPUTATIONAL METHODS

Quantum-chemical computations on the CBS-QB3[59] level of theory were performed with the Gaussian 09 suite of programs.[60] All geometries were optimized to minimum stationary points (no imaginary frequencies). Zero point vibrational energies (ZPVE) were scaled by a factor of 0.99.

ASSOCIATED CONTENT

Supporting Information

Tables S1−S3 with CBS-QB3 computed and experimental enthalpies and entropies. Experimental data for hydrogen bonding in DMSO and nitrobenzene (Tables S4 and S5). CBS-QB3 computed effect of water on tautomerization (Table S6). Schemes S1−S3 with tautomerization, hydrogen bonding, and O−H dissociation enthalpies for hydroxyl-substituted naphthols and anthrols. Atomic charges in 1-naphthol and 1,8-naphthalenediol (Scheme S4). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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with DMSO are $\Delta_{HB}H_{inter} = -7.2$ kcal mol^{-1} and $\Delta_{HB}S_{inter} = -13.6$ cal mol^{-1} K^{-1}. The parameters for the intermolecular hydrogen bond formation of **6** with DMSO or nitrobenzene show that when ΔH_{HB} increases, ΔS_{HB} increase as well. This phenomenon (which can be related to an enthalpy−entropy compensation effect) has been found before for hydrogen bond formation between, e.g., phenol (or 4-F-phenol) and a large number of bases: Arnett, E. M.; Joris, L.; Mitchell, E.; Murty, T. S. S. R.; Gorrie, T. M.; Schleyer, P.v.R. *J. Am. Chem. Soc.* **1970**, *92*, 2365−2377.

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(44) There is no reason to conclude that the observed variation between the UV/vis spectra for 9-anthrol in methanol and for those in triethylamine or H_2O is due to a change from a neutral hydrogen-bonded complex to an ion-pair complex (see ref 10).

(45) In a computational study, a $\Delta_{HB}H_{inter} = -3.9$ kcal mol^{-1} for the intermolecular hydrogen bond between intramolecularly hydrogen-bonded 7-hydroxyindanone and DMSO has been found.[25a] Combined with an estimated $\Delta_{HB}S_{inter} = -9$ cal mol^{-1} K^{-1} [39] this value gives a $\Delta_{HB}G_{inter} = -1.2$ kcal mol^{-1} and an equilibrium constant of $K_{HB} = 7.8$ M^{-1} at $T = 298$ K. From eq 2 an $\alpha_2^H = 0.35$ for 7-hydroxyindanone is calculated. It seems reasonable to assume that $\alpha_2^H = 0.35$ holds as well for **9**.

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NOTE ADDED AFTER ASAP PUBLICATION

Scheme 2 was replaced on July 17, 2013.

Supporting information

Anthrone and Related Hydroxyarenes: Tautomerization and Hydrogen Bonding

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Table S1. CBS-QB3-Calculated and Experimental Heats of Formation, $\Delta_f H^o$, for Hydroxyarenes, the Tautomers and Their Radicals, and Reference Compounds[a]

compound	$\Delta_f H^o_{calc}$	$\Delta_f H^o_{exp}$ [b]	Δ [c]
hydrogen (H)	52.1	52.1	0.0
benzene (C_6H_6)	21.2	19.8 ± 0.2	1.4
1,4-cyclohexadiene (1,4-C_6H_8)	27.6	25.0 ± 0.2	2.6
cyclohexadienyl ($C_6H_7^\bullet$)	49.9	49.7 ± 0.9[d]	–0.2
toluene ($C_6H_5CH_3$)	12.9	12.0 ± 0.3	0.9
benzyl ($C_6H_5CH_2^\bullet$)	51.5	49.5 ± 0.6	2.0
cyclo-hexa-2,5-dien-1-one (C_6H_6O) (**1**)	–4.6	–6.0 ± 2.4[e]	1.4
phenol (C_6H_5OH) (**2**)	–22.3	–23.0 ± 0.2	0.7
phenoxyl ($C_6H_5O^\bullet$)	12.8	11.6 ± 0.7[f]	1.2
naphthalene ($C_{10}H_8$)	36.4	36.0 ± 0.4	0.4
1,4-dihydronaphhtalene (1,4-$C_{10}H_{10}$)	34.4	32.9 ± 1.0[g]	1.5
1,4-dihydronaphthalenyl (1,4-$C_{10}H_9^\bullet$)	59.0	59.1 ± 0.5[h]	–0.1
benzo[*b*]cyclo-hexa-2,5-dien-1-one (1-$C_{10}H_{10}O$) (**3**)	2.1	1.7 ± 2.4[i]	0.4
1-naphthol (1-$C_{10}H_7OH$) (**4**)	–7.0	–7.4 ± 0.4	0.4
1-naphthoxyl (1-$C_{10}H_9O^\bullet$)	23.1	22.2 ± 0.8[j]	0.9
anthracene ($C_{14}H_{10}$)	55.3	54.8 ± 0.7	0.5
9,10-dihydroanthracene (9,10-$C_{14}H_{12}$)	39.3	38.2 ± 1.0[g]	1.3
9,10-dihydroanthracenyl (9,10-$C_{14}H_{11}^\bullet$)	68.1	66.0 ± 1.3[k]	2.1
anthrone ($C_{14}H_{10}O$) (**5**)	9.2	9.3 ± 2.4[l]	1.7
9-anthrol (9-$C_{14}H_9OH$) (**6**)	13.0	12.6 ± 1.0[m]	0.4
9-anthroxyl (9-$C_{14}H_9O^\bullet$)	33.6	32.7 ± 0.8[n]	0.9
diphenylmethane ($C_6H_5CH_2C_6H_5$)	40.4	39.4 ± 0.5	1.0
benzophenone ($C_6H_5C(O)C_6H_5$)	12.9	11.9 ± 0.7	1.0
9,10-anthraquinone (9,10-$C_{14}H_8O_2$)	–20.0	–18.1 ± 0.7	–1.9

[a]In kcal mol^{-1} at T = 298 K. [b]The experimental $\Delta_f H^o$s are taken from the NIST Chemistry WebBook[1] unless stated otherwise. Some experimental $\Delta_f Hs$ are derived from isodesmic reactions in conjunction with auxiliary thermodynamic data. [c]$\Delta = \Delta_f H^o_{calc} - \Delta_f H^o_{exp}$. [d]Ref 2. [e]Ref 3, derived from a computational study at the CBS-QB3 level, and with the use of various isodemic reactions,

error margin of 2.4 kcal mol^{-1} as given in that paper. [f]Ref 4. [g]Ref 5, estimated error. [h]The experimental heat of addition for a hydrogen atom to C1 in naphthalene of –29.0 ± 0.5 kcal mol^{-1} [6] furnishes $\Delta_f H^o_{exp}$(1,4-$C_{10}H_9^\bullet$) = 59.1 ± 0.5 kcal mol^{-1}; for comparison the isodesmic reaction 1,4-C_6H_8 + 1,4-$C_{10}H_9^\bullet$ → $C_6H_7^\bullet$ + 1,4-$C_{10}H_{10}$, $\Delta_r H_{calc}$ = –2.3 kcal mol^{-1}, yields $\Delta_f H^o_{exp}$(1,4-$C_{10}H_9^\bullet$) = 59.8 ± 1.4 kcal mol^{-1}. [i]Isodesmic reaction C_6H_6O (**1**) + 1,4-$C_{10}H_{10}$ → 1,4-C_6H_8 + 1-$C_{10}H_8O$ (**3**), $\Delta_r H_{calc}$ = –0.2 kcal mol^{-1}, affords $\Delta_f H^o_{exp}$(1-$C_{10}H_8O$) = 1.7 ± 1.5 kcal mol^{-1} (estimated error). [j]Isodesmic reaction $C_6H_5O^\bullet$ + 1-$C_{10}H_7OH$ (**4**) → C_6H_5OH (**2**) + 1-$C_{10}H_7O^\bullet$, $\Delta_r H_{calc}$ = –5.0 kcal mol^{-1}, yields $\Delta_f H^o_{exp}$(1-$C_{10}H_7O^\bullet$) = 22.2 ± 0.8 kcal mol^{-1}. According to an electrochemical study $\Delta_r H_{exp}$= –5.9 ± 1.0 kcal mol^{-1} without compensating for the difference in hydrogen bond enthalpy between phenol and 1-naphthol with the solvent, DMSO.[4,7] Another electrochemical study using water as the solvent[8] and not accounting for hydrogen bonding effects has yielded $\Delta_r H_{exp}$ = –7.5 ± 1.0 kcal mol^{-1}. [k]Reported values for $\Delta_f H^o$(9,10-$C_{14}H_{11}^\bullet$) are 62.4,[9a] 63.8,[9b] 64.1,[9c] 64.5,[9d] and 69.1 kcal mol^{-1},[9e] the range in $\Delta_f H^o$(9,10-$C_{14}H_{11}^\bullet$) is ca. 7 kcal mol^{-1}. It is demanding to assess the way the $\Delta_f H^o$(9,10-$C_{14}H_{11}^\bullet$)s have been determined in most of these studies. The isodesmic reaction $C_6H_5CH_2^\bullet$ + 9,10-$C_{14}H_{12}$ → $C_6H_5CH_3$ + 9,10-$C_{14}H_{11}^\bullet$, $\Delta_r H_{calc}$ = –9.8 kcal mol^{-1}, yields $\Delta_f H^o_{exp}$(9,10-$C_{14}H_{11}^\bullet$) = 66.0 ± 1.3 kcal mol^{-1}. [l]Isodesmic reaction C_6H_6O (**1**) + 9,10-$C_{14}H_{12}$ → 1,4-C_6H_8 + $C_{14}H_{10}O$ (**5**), $\Delta_r H_{calc}$ = –2.1 kcal mol^{-1}, affords $\Delta_f H^o_{exp}$($C_{14}H_{10}O$) = 9.3 ± 1.5 kcal mol^{-1} (estimated error); Isodesmic reaction 9,10-$C_{14}H_8O_2$ + 9,10-$C_{14}H_{12}$ → 2 $C_{14}H_{10}O$ (**5**), $\Delta_r H_{calc}$ = –1.0 kcal mol^{-1}, affords $\Delta_f H^o_{exp}$($C_{14}H_{10}O$) = 9.6 ± 1.5 kcal mol^{-1} (estimated error). Isodesmic reaction $C_6H_5CH_2C_6H_5$ + $C_6H_5C(O)C_6H_5$ → C_6H_6 + C_6H_6 + $C_{14}H_{10}O$ (**5**), $\Delta_r H_{calc}$ = –2.8 kcal mol^{-1}, affords $\Delta_f H^o_{exp}$($C_{14}H_{10}O$) = 8.9 ± 1.5 kcal mol^{-1} (estimated error). Three studies have reported on the $\Delta_f H^o_{exp}$($C_{14}H_{10}O$) obtained by combustion calorimetry: 5.0 ± 0.4,[10] 5.6 ± 0.5,[11] and 7.5 ± 0.8 kcal mol^{-1}.[12] [m]Isodesmic reactions: (1) C_6H_5OH (**2**) + $C_{14}H_{10}$ → C_6H_6 + 9-$C_{14}H_9OH$ (**6**), $\Delta_r H_{calc}$ = 0.6 kcal mol^{-1}; (2) 1-$C_{10}H_7OH$ (**4**) + $C_{14}H_{10}$ → $C_{10}H_8$ + 9-$C_{14}H_9OH$ (**6**), $\Delta_r H_{calc}$ = 1.1 kcal mol^{-1}, leading to an average $\Delta_f H^o_{exp}$(9-$C_{14}H_9OH$) of 12.6 ± 1.1 kcal mol^{-1}. [n]Isodesmic reaction: $C_6H_5O^\bullet$ + 9-$C_{14}H_9OH$ (**6**) → C_6H_5OH (**2**) + 9-$C_{14}H_9O^\bullet$, $\Delta_r H_{calc}$ = –14.5 kcal mol^{-1}, yields $\Delta_f H^o_{exp}$(9-$C_{14}H_9O^\bullet$) = 32.7 ± 0.8 kcal mol^{-1}.

References for Table S1.

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Table S2. CBS-QB3-Calculated and Literature Entropies of Formation, S°, for Hydroxyarenes, the Tautomers and Their Radicals, and Reference Compounds[a]

compound	S°_{calc}	S°_{lit}[b]	Δ[c]	Ref
benzene (C_6H_6)	64.2	64.3	–0.1	
1,4-cyclohexadiene (1,4-C_6H_8)	70.5	70.9	–0.4	1
cyclohexadienyl ($C_6H_7^{\bullet}$)	72.0	72.0	0.0	2
toluene ($C_6H_5CH_3$)	80.7	76.7	4.0	3
benzyl ($C_6H_5CH_2^{\bullet}$)	75.2	75.3	–0.1	4
cyclo-hexa-2,5-dien-1-one (C_6H_6O) (**1**)	76.1	74.5	1.6	5
phenol (C_6H_5OH) (**2**)	74.8	75.3	–0.5	5
phenoxyl ($C_6H_5O^{\bullet}$)	74.0	72.7	1.3	6
naphthalene ($C_{10}H_8$)	82.3	80.4	1.9	1
1,4-dihydronaphhtalene (1,4-$C_{10}H_{10}$)	88.1	86.9	1.2	1
1,4-dihydronaphthalenyl (1,4-$C_{10}H_9^{\bullet}$)	87.1			
benzo[*b*]cyclo-hexa-2,5-dien-1-one (1-	89.1	**85.9**	3.2	
1-naphthol (1-$C_{10}H_7OH$) (**4**)	87.8	**86.3**	1.5	
1-naphthoxyl (1-$C_{10}H_9O^{\bullet}$)	88.4			
anthracene ($C_{14}H_{10}$)	95.5	92.5	3.0	1
9,10-dihydroanthracene (9,10-$C_{14}H_{12}$)	97.3	99.2	–1.9	1
9,10-dihydroanthracenyl (9,10-$C_{14}H_{11}^{\bullet}$)	102.6			
anthrone ($C_{14}H_{10}O$) (**5**)	101.9	**101.8**	0.1	
9-anthrol (9-$C_{14}H_9OH$) (**6**)	105.7	**103.2**	2.6	
9-anthroxyl (9-$C_{14}H_9O^{\bullet}$)	101.5			
diphenylmethane ($C_6H_5CH_2C_6H_5$)	102.5	100.4	2.1	7
benzophenone ($C_6H_5C(O)C_6H_5$)	104.2			
9,10-anthraquinone (9,10-$C_{14}H_8O_2$)	104.7			

[a]In cal $mol^{-1}K^{-1}$ at T = 298 K. [b]Most of the S°_{lit}s are derived by group increment rules. In bold: S°_{lit}s derived from isodesmic reactions in conjunction with the literature data using the $S^{\circ}(C_6H_6O)$ = 74.5 or $S^{\circ}(C_6H_5OH)$ = 75.3 cal mol^{-1} K^{-1} as the anchors for enones and enols, respectively, e.g., C_6H_6O (**3**) + 1,4-$C_{10}H_{10}$ → 1,4-C_6H_8 + 1-$C_{10}H_8O$ (**5**), $\Delta_r S_{calc}$ = –4.6 cal $mol^{-1}K^{-1}$, leads to S°_{exp}(1-$C_{10}H_8O$) = 85.9 cal $mol^{-1}K^{-1}$. The entropy of tautomerization, $\Delta_t S_{calc}$, varies from –1.3 (**1** ⇌ **2**), –1.3 (**3** ⇌ **4**), to 3.8 (**5** ⇌ **6**) cal $mol^{-1}K^{-1}$. Small positive values of $\Delta_t S_{calc}$ have been

expected due to the presence of an additional internal rotor in the hydroxyarenes. [c] $\Delta = S^{\circ}_{calc} - S^{\circ}_{lit}$.

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Table S3. CBS-QB3-Calculated Heats of Formation, $\Delta_f H^o$, and Entropies of Formation, S^o, for Hydroxy-Substituted Naphthols, 9-Anthrols, and Their Radicals[a]

compound	$\Delta_f H^o_{calc}$	S^o_{calc}
8-hydroxy-benzo[*b*]cyclo-hexa-2,5-dien-1-one (**7**)	–35.5	95.7
benzo[*b*]cyclo-hexa-2,5-dien-1-one-1-oxy (**7R**)	0.16	97.5
1,8-naphthalenediol (**8**)	–45.1	93.2
8-hydroxy-naphthalene-1-oxyl (**8R**)	–15.4	94.2
8-hydroxy-benzo[*b*]cyclo-hexa-2,5-dien-1-one (**9**)	–47.9	92.7
1,8-naphthalenediol (**10**)	–51.2	92.8
8-hydroxy-naphthalene-1-oxyl (**10R**)	–28.8	91.7
1-hydroxy-anthrone (**11**)	–28.6	108.9
1,9-anthracenediol (**12**)	–25.0	108.3
9-hydroxy-anthracene-1-oxyl (**12Ra**)	3.0	110.1
1-hydroxy-anthracene-9-oxyl (**12Rb**)	–5.1	107.4
1-hydroxy-anthrone (**13**)	–40.9	107.4
1,9-anthracenediol (**14a**)	–31.0	106.0
1-hydroxy-anthracene-9-oxyl (**14aR**)	–18.5	104.8
1,9-anthracenediol (**14**)	–32.7	105.9
9-hydroxy-anthracene-1-oxyl (**14R**)	–13.8	104.5
1,8-dihydroxy-anthrone (**15**)	–67.3	113.2
1,8-dihydroxy-anthrone-1-oxyl (**15R**)	–31.9	114.3
1,8,9-anthracenetriol (**16**)	–70.0	111.5
8,9-dihydroxy-anthracene-1-oxyl (**16R**)	–42.2	112.7
1,8-dihydroxy-anthrone (**17**)	–90.0	115.0
1,8,9-anthracenetriol (**18)**	–77.4	110.4
1,8-dihydroxy-anthrone-9-oxyl (**18R**)	–69.9	108.2
8,9-dihydroxy-anthracene-1-oxyl (**18RTS**)[b]	---	---
1,8-dihydroxy-anthrone (**19**)	–78.8	112.6
1,8-dihydroxy-anthrone-1-oxyl (**19R**)	–42.5	113.7

[a] In (k)cal mol^{-1}(K^{-1}) at T = 298 K, for graphical display of molecules and radicals see Schemes S1–S3. [b] No stationary point found, optimization converges to **18R.**

Thermodynamic Parameters for Intermolecular Hydrogen Bonding of 9-Anthrol with DMSO and Nitrobenzene. The experimental data from various studies on the effect of solvent and temperature on the tautomeric equilibrium anthrone (**5**) $\rightleftharpoons$ 9-anthrol (**6**) have been used to derive the thermodynamic parameters for intermolecular hydrogen bonding with 9-anthrol. Eq 4 has been simplified to $[\mathbf{6}]_t/[\mathbf{5}] = K_t \times K_{HB} \times [S]$

Table S4. Temperature Dependence of the $[\mathbf{6}]_t/[\mathbf{5}]$ Ratio in Neat DMSO [S]

T (K)	$[\mathbf{6}]_t/[\mathbf{5}]$	[S][a]	Ref
296	3.3	14.17	1
307	3.2	14.00	2
313	2.7	13.93	3
353	2.3	13.43	3
373	1.9	13.20	3
413	1.5	12.75	3

[a][DMSO] = 14.12 M at 298 K, with a thermal expansion coefficient, α_v, of $9.28\times10^{-4}\ T^{-1.4}$.[4]

A plot of $\ln([\mathbf{6}]_t/([\mathbf{5}]\times S))$ versus $1/T$ ($r^2 = 0.96$) yields $\Delta H_{exp} = -1.4$ kcal mol^{-1}, $\Delta S_{exp} = -7.6$ cal mol^{-1}K^{-1}, and $[\mathbf{6}]_t/[\mathbf{5}] = 3.3$ in DMSO at 298 K. The thermodynamic parameters for intermolecular hydrogen bond formation between 9-anthrol and DMSO, using $\Delta_t H = 3.8$ kcal mol^{-1} and $\Delta_t S = 3.8$ cal mol^{-1} K^{-1} (see Table 1) are $\Delta_{HB}H_{inter} = \Delta H_{exp} - \Delta_t H = -1.4 - 3.8 = -5.2$ kcal mol^{-1}, $\Delta_{HB}S_{inter} = \Delta S_{exp} - \Delta_t S = -7.6 - 3.8 = -11.4$ cal mol^{-1} K^{-1}, and $\Delta_{HB}G_{inter} = -1.8$ kcal mol^{-1} (298 K).

Table S5. Temperature Dependence of the $[\mathbf{6}]_t/[\mathbf{5}]$ Ratio in Neat Nitrobenzene [S]

T (K)	$[\mathbf{6}]_t/[\mathbf{5}]$	[S][a]	Ref
307	0.11	9.71	2
313	0.11	9.67	3
353	0.11	9.37	3
373	0.18	9.23	3
413	0.25	8.97	3

[a][Nitrobenzene] = 9.78 M at 298 K, with a thermal expansion coefficient, α_v, of $7.9\times10^{-4}\ T^{-1.5}$.[5]

A plot of $\ln([\mathbf{6}]_t/([\mathbf{5}]\times S))$ versus $1/T$ ($r^2 = 0.99$; omitting $T = 353$ K) yields $\Delta H_{exp} = 2.1$ kcal mol^{-1}, $\Delta S_{exp} = -2.1$ cal mol^{-1}K^{-1}, and $[\mathbf{6}]_t/[\mathbf{5}] = 0.096$ in nitrobenzene at 298 K. The thermodynamic parameters (see Table 1) for hydrogen bond formation between 9-anthrol and nitrobenzene are $\Delta_{HB}H_{inter} = \Delta H_{exp} - \Delta_t H = 2.1 - 3.8 = -1.7$ kcal mol^{-1} and $\Delta_{HB}S_{inter} = \Delta S_{exp} - \Delta_t S = -2.1 - 3.8 = -5.8$ cal mol^{-1} K^{-1}, $\Delta_{HB}G_{inter} = 0.03$ kcal mol^{-1} (298 K).

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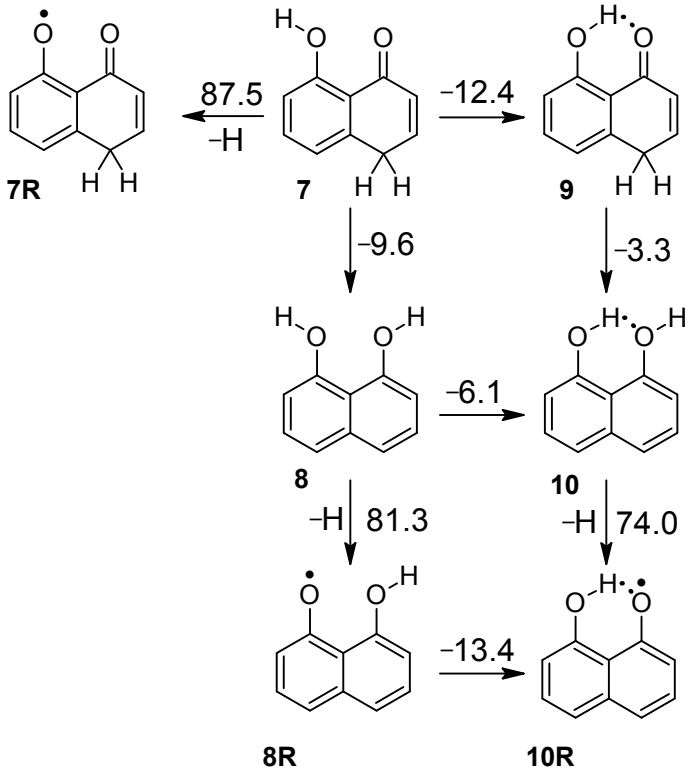
Table S6. CBS-QB3 Computed Energies for Intermolecular Hydrogen Bonding of Anthrone (5) and 9-Anthrol (6) with H_2O, the Effect of Water on the Tautomeric Equilibrium [6]/[5][a]

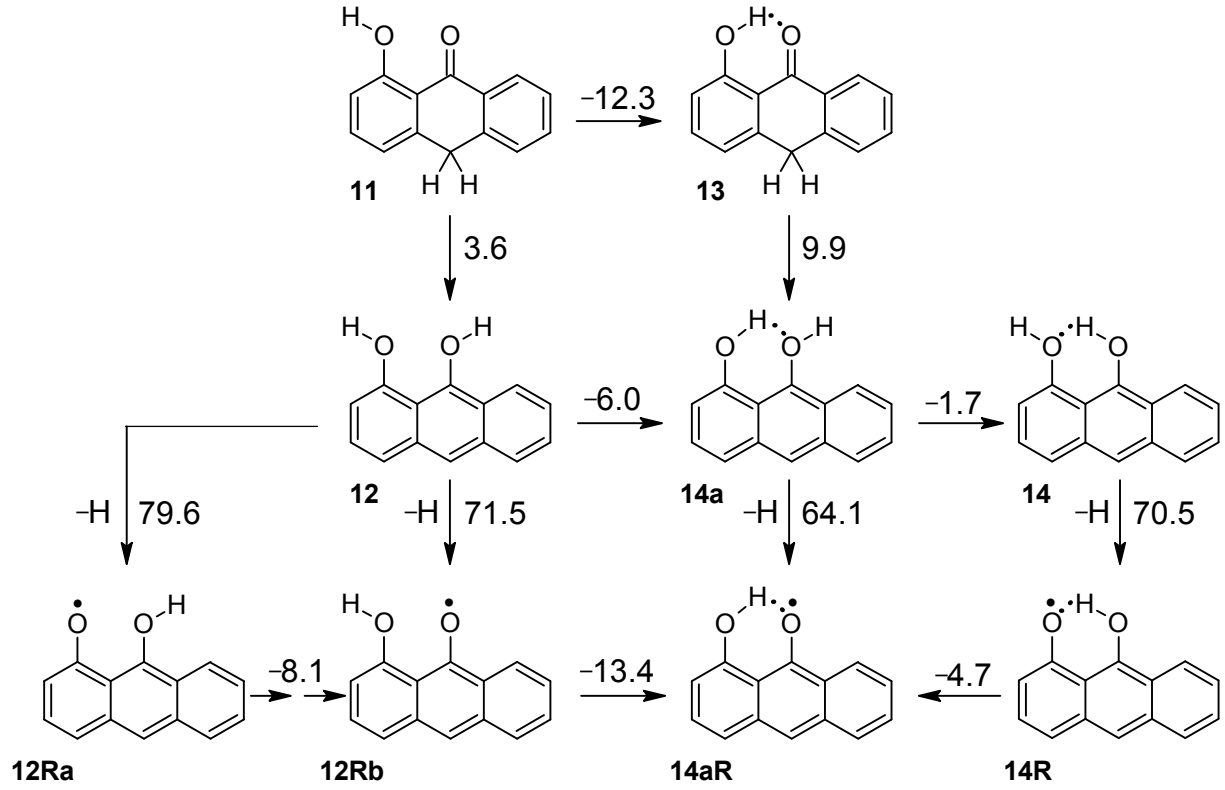
Equilibrium	$\Delta_t H$	$\Delta_t G$	[**6**]/[**5**]	Remarks
5 ⇌ **6**	3.8	2.7	1.0×10^{-2}	
5 ⇌ **6**	4.06	4.04	1.1×10^{-3}	$\Delta E_{solv} = 0.8$[b]
5-(H_2O) ⇌ **6**-(OH_2)	3.17	2.64	1.2×10^{-2}	
5-(H_2O) ⇌ **6**-(OH_2)	2.87	2.35	1.9×10^{-2}	$\Delta E_{solv} = -0.30$[b]
5-(H_2O) ⇌ **6**-(H_2O)[c]	5.76	5.53	1.2×10^{-5}	
5-(H_2O) ⇌ **6**-(H_2O)[c]	5.60	5.53	8.8×10^{-5}	$\Delta E_{solv} = -0.16$[b]

[a] ΔH_t, ΔG_t in kcal mol^{-1} at 298 K. [b] Computed with the Polarizable Continuum Model, PCM, to mimic the effect of solvation by water. [c] 9-Anthrol as the hydrogen bond acceptor, water as the hydrogen bond donor.

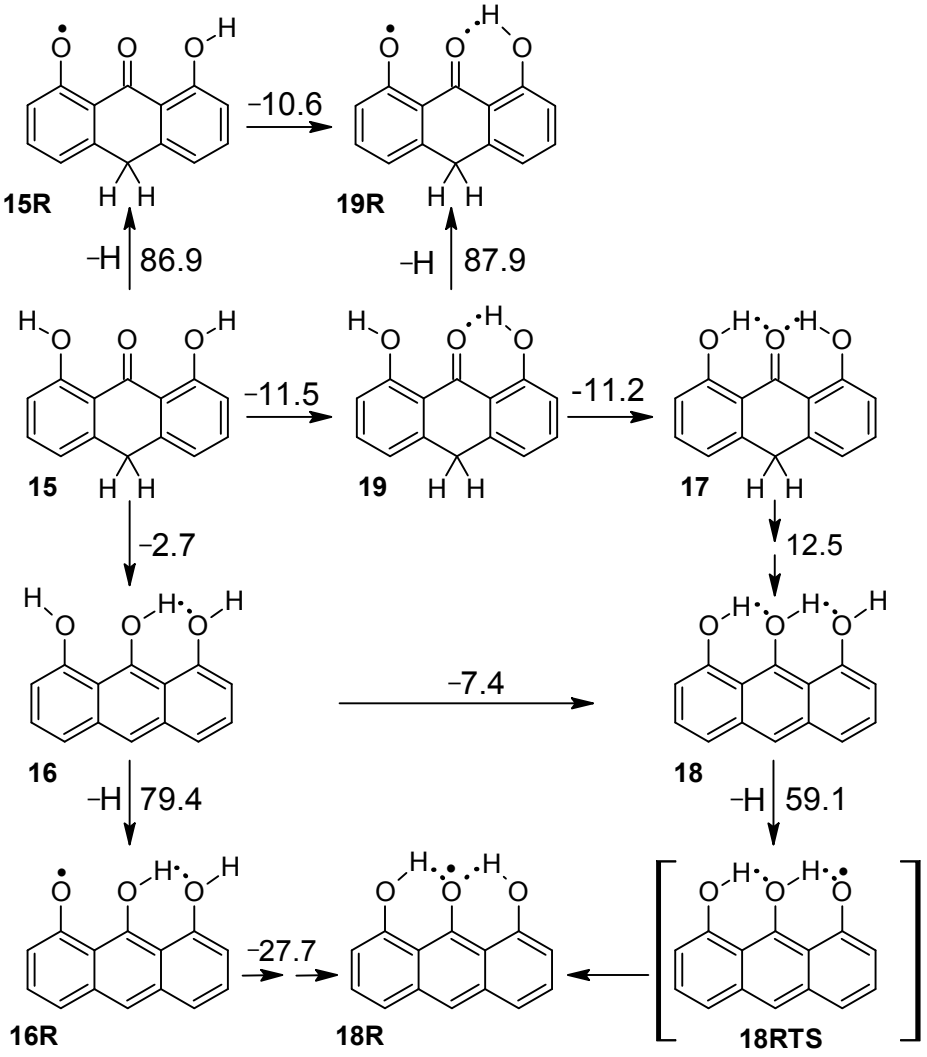
Scheme S1. Enthalpy Changes (kcal mol^{-1}) due to Tautomerization, Intramolecular Hydrogen Bond Formation, and O–H Bond Dissociation for 1-Hydroxy-benzo[*b*]cyclohexa-2,5-dien-1-one (7, 9). The BDE(O–H)s are Scaled, see Table S1.



Scheme S2. Enthalpy Changes (kcal mol^{-1}) due to Tautomerization, Intramolecular Hydrogen Bond Formation, and O–H bond Dissociation for 1-Hydroxy-anthrone (11, 13). The BDE(O–H)s are Scaled, see Table S1.



Scheme S3. Enthalpy Changes (kcal mol^{-1}) due to Tautomerization, Intramolecular Hydrogen Bond Formation, and O–H bond Dissociation for 1,8-Dihydroxy-anthrone (15, 16, and 17). The BDE(O–H)s are Scaled, see Table S1.



Scheme S4. Some Mulliken (Italics) and NPA (Natural Population Analysis; Bold) Atomic Charges in 1-Naphthol (4), 1,8-Napthalenediols (8), and (10) with Their Tautomers (7) and (9). Computational method: B3LYP/CBSB7 on CBS-QB3 Geometry.