## Chemistry of naphthazarin derivatives 13.\* Conformational analysis of 3-(alk-1-enyl)-2-hydroxy-1,4-naphthoquinones by quantum chemistry methods

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The molecular structures of various conformers of 2-hydroxy-1,4-naphthoquinone; 3-(alk-1-enyl)-2-hydroxy-1,4-naphthoquinones; 2,5,8-trihydroxy-1,4-naphthoquinone; and 3-(alk-1-enyl)-2,5,8-trihydroxy-1,4-naphthoquinones were studied by density functional theory (B3LYP/6-31(d), B3LYP/6-31(d,p)) and *ab initio* (MP2/6-31G, MP2/6-31(d)) methods. The strengths of the intramolecular hydrogen bonds formed by the  $\beta$ -hydroxy group with the O atom at C(1) and with the double bond  $\pi$ -electrons of the alkenyl substituents in the quinonoid rings were estimated. The compounds studied mainly exist as rotamers with the former-type hydrogen bonds. The splitting of the quinonoid bands of the stretching vibrations of the  $\beta$ -hydroxy group in the IR spectra of 3-(alk-1-enyl)-2-hydroxy-1,4-naphthoquinones and 3-(alk-1-enyl)-2,5,8-trihydroxy-1,4-naphthoquinones in hexane solutions is due to the existence of rotamers formed upon internal rotation of the alkenyl substituent.

**Key words:** *ab initio* quantum chemical calculations; rotamers; 2-hydroxy-1,4-naphthoquinone; 3-(alk-1-enyl)-2-hydroxy-1,4-naphthoquinones; 3-(alk-1-enyl)-2,5,8-trihydroxy-1,4-naphthoquinones.

Scheme 1

When investigating the prototropic tautomerism of hydroxy derivatives of naphthazarins (5,8-dihydroxy-1,4-naphthoquinones) **1** with alkenyl substituents in the

ortho-position to the  $\beta$ -hydroxy group (Scheme 1) by IR spectroscopy, we faced<sup>1</sup> with difficulty in interpreting the stretching bands of  $\beta$ -hydroxy groups (v(OH)).



**1:** R<sup>1</sup> = H, Alk; R<sup>2</sup> = Alk; R<sup>3</sup> = H, OH, OMe, Cl

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The IR spectra of the compounds in hexane solutions exhibited a doublet splitting of both the quinonoid v(OH) bands at 3420–3370 cm<sup>-1</sup> corresponding to the  $\beta$ -hydroxy groups in the quinonoid rings and the benzenoid v(OH) bands at 3540–3510 cm<sup>-1</sup> corresponding to the  $\beta$ -hydroxy groups in the benzenoid rings, the splitting,  $\Delta v$ (OH), being 26–39 and 14–16 cm<sup>-1</sup>, respectively. We suggested that the observed splitting is due to different types of intramolecular hydrogen bonds (IMHB) formed by the  $\beta$ -hydroxy group, namely, IMHB-1 (OH...O=C(1)) in tautomer **Q**, IMHB-1' (OH...O–H) with the O atom of the  $\alpha$ -hydroxy group at the C(1) atom in tautomer **B**, and IMHB-2 (OH... $\pi$ ) with the polarized  $\pi$ -electrons of the C(1')=C(2') bond of the alkenyl substituent in isomers **Q**' and **B**'.

The OH... $\pi$  hydrogen bond was first detected by IR spectroscopy for 2-phenylphenol (2).<sup>2</sup> This type of bond has been studied for *o*-vinylphenol (3) and its derivatives<sup>3-5</sup> and for allylphenol (4) and its derivatives<sup>6,7</sup> where polarized  $\pi$ -electrons of the double bond act as electron donors.



Unlike other known IMHB types (O–H...O, N–H...O, N–H...O, N–H...O), in this case a dynamic equilibrium between the rotamers with bonded and free OH groups is possible at room temperature. In a later study, based on *ab initio* calculations, the OH... $\pi$  interaction was suggested to be mainly electrostatic in character;<sup>6</sup> however, the term "hydrogen bond" is still used.<sup>7</sup>

The magnitudes of the splitting of the benzenoid and quinonoid v(OH) bands in the IR spectra of compounds 1 are difficult to interpret in terms of the model according to which the components of the doublet refer to isomers with different IMHBs. On the one hand, dissociation of the OH... $\pi$  bond in molecule **3** is characterized by  $\Delta v(OH) = 54 \text{ cm}^{-1}$ , which is ~4 times greater than the splitting of the benzenoid bands and ~2 times greater than the splitting of the quinonoid bands (see above). On the other hand, the IMHB-2 is a very weak hydrogen bond with a strength of about 0.75 - 1.5 kcal mol<sup>-1</sup>,<sup>3</sup> whereas according to estimates made in this study, the strength of the IMHB-1 exceeds 6 kcal mol<sup>-1</sup>. A similar splitting,  $\Delta v(OH) = 30 \text{ cm}^{-1}$ , was also observed for 2-hydroxy-1,4-naphthoquinone 5 with an alkenyl substituent in the *ortho*-position to the  $\beta$ -hydroxy group.<sup>1</sup>

Detailed investigation of the reasons for the splitting of the v(OH) bands was beyond the scope of the previous

study<sup>1</sup> and required an additional investigation. In this work, using quantum chemical methods, we carried out the conformational analysis of molecules **1** and **5**, estimated the strengths of the IMHB-1 and IMHB-2, performed the normal-mode analysis and calculated vibration frequencies of the possible rotamers formed upon internal rotation of  $\beta$ -hydroxy and alkenyl groups. Based on the results obtained, the experimental IR spectra of the compounds under study were interpreted. Since compounds **1** exist in solutions mainly as tautomers **Q** (the  $\beta$ -hydroxy group is in the quinonoid ring),<sup>1</sup> only these forms were considered in this study.

### **Results and Discussion**

Previously<sup>1</sup> we excluded the following reasons for splitting of the v(OH) bands in the IR spectra of compounds **1** and **5**: the existence of intermolecular complexes of different compositions, coupling with overtones or compound tones, and the presence of 1,5-tautomers. The possibility of splitting of the v(OH) bands due to the fact that these compounds can exist as several rotamers formed upon internal rotation of the alkenyl substituent, the  $\beta$ -hydroxy group, or both (Scheme 2) was not considered earlier. In rotamers **a** and **b**, the  $\beta$ -hydroxy group forms an IMHB-1 with the oxygen atom of the O=C(1) carbonyl group, while in rotamer **c**, a weak multicenter IMHB-2 (OH... $\pi$ ) is formed. Rotamer **d** corresponds to the configuration of the molecule with formally broken IMHB-2 and completely broken IMHB-1.



R<sup>1</sup>, R<sup>2</sup> = H, Me, Et, Bu<sup>t</sup> (1, 5); R<sup>3</sup> = OH (1), H (5)

Compounds 1 and 5 differ basically from vinylphenol 3 in that the  $\beta$ -hydroxy group is simulta-



Scheme 3

 $i. \Delta E_{7d} = 7.92 \text{ kcal mol}^{-1}; ii. \Delta E_{7c} = 5.65 \text{ kcal mol}^{-1}; iii. \Delta E_{7b} = 0.43 \text{ kcal mol}^{-1} (according to MP2/6-31(d) calculations).$ 

**6:** R<sup>1</sup> = H, R<sup>2</sup> = Bu<sup>t</sup>; **7:** R<sup>1</sup> = H, R<sup>2</sup> = Me; **8:** R<sup>1</sup> = R<sup>2</sup> = Et

neously in *ortho*-position to the carbonyl and vinyl groups, which can form the IMHB-1 or IMHB-2, respectively. The presence of carbonyl groups in positions 1 and 4 changes substantially the conditions of internal rotation of the hydroxy and alkenyl groups. Due to these differences, the ratio of the contents of the rotamers with and without the IMHB-2 is expected to differ markedly from their ratio for compound **3**.

Density functional (B3LYP/6-31(d,p)) and the second-order Møller—Plesset perturbation theory (MP2/6-31(d)) calculations of the total energies  $E = E_0 + ZPE$  ( $E_0$  is the ground-state electronic energy, ZPE is the zero-point vibrational energy) for molecule 7 (Scheme 3) showed that rotamer **a** (Table 1), in which the  $\beta$ -hydroxy group forms IMHB-1 and the alkenyl double bond is as close to it as possible, is the most stable of the four possible rotamers. According to B3LYP/6-31(d,p) calculations, rotamer **7a** has a planar structure, while the MP2/6-31(d) calculations predict a nonplanar structure of this rotamer.

The MP2-calculated dihedral angles,  $\theta_{OH}$ (H(8) - O(7) - C(2) - C(3))and  $\theta_{C=C}$ (C(2')=C(1')-C(3)-C(2)), which characterize the deviation of the hydroxy and alkenyl groups from the quinonoid-ring plane, are 176.36 and -4.07°, respectively, and the dihedral angle  $\theta_{cycl}$  (C(5)–C(4)–C(3)–C(2)), which characterizes the distortion of the quinonoid ring, is equal to 8.36°. B3LYP and MP2 techniques describe very differently the spatial structures of the type 7 compounds, especially the substantial deviation of atoms of the =C(2')HMe group and the hydrogen atom of the  $\beta$ -hydroxy group from the naphthoquinonoid plane and the out-of-plane distortion of the quinonoid nucleus.

The next in stability is rotamer **7b**. B3LYP/6-31(d,p) calculations predict a planar structure, while the MP2/6-31(d) method predicts a nonplanar structure of this species. The  $\theta_{OH}$ ,  $\theta_{C=C}$ , and  $\theta_{cycl}$  dihedral angles are 176.77, -178.03, and 10.18°, respectively. It is conve-

nient to compare the rotamer stabilities using relative energies

$$\Delta E_{\mathbf{Y}\mathbf{x}} = E(\mathbf{Y}\mathbf{x}) - E(\mathbf{Y}\mathbf{a}),$$

where **Y** is the number of the compound,  $\mathbf{x} = \mathbf{b} - \mathbf{d}$  is the rotamer type. The MP2/6-31(d) and B3LYP/6-31(d,p) calculations give similar  $\Delta E_{7\mathbf{b}}$  values of 0.43 and 0.49 kcal mol<sup>-1</sup>, respectively.

The third in stability is rotamer **7c**. Geometry optimization for this rotamer carried out by both methods results in a nonplanar structure, the MP2-calculated dihedral angles  $\theta_{OH}$ ,  $\theta_{C=C}$ , and  $\theta_{cycl}$  being equal to 5.92, 48.20, and 7.86°, respectively. The relative energy of rotamer **7c** with broken IMHB-1 ( $\Delta E_{7c}$ ) is 8.05 (B3LYP/6-31(d,p)) or 5.65 kcal mol<sup>-1</sup> (MP2/6-31(d)), which is an order of magnitude higher than the relative energy of rotamer **7b**.

The most unstable rotamer is **7d** with the relative energy  $\Delta E_{7d} = 7.92$  (MP2/6-31(d)) and 9.47 kcal mol<sup>-1</sup> (B3LYP/6-31(d,p)). Like rotamer **7c**, compound **7d** is nonplanar: according to MP2 calculations,  $\theta_{OH} = 11.51^{\circ}$ ,  $\theta_{C=C} = 143.31^{\circ}$ , and  $\theta_{cycl} = 8.65^{\circ}$ . Thus, the stability of rotamers of alkenylnaphthoquinone **7** decreases in the order **7a** > **7b** > **7c** > **7d**.

The strengths of the O–H...O and OH... $\pi$  bonds in molecule 7 can be compared by estimating the strength of IMHB-1 as the energy difference between rotamers **7b** and **7d** 

$$\Delta H_{\text{IMHB-1}} = \Delta E_{\mathbf{7b} \to \mathbf{7d}} = E_{\mathbf{7d}} - E_{\mathbf{7b}},$$

and the strength of IMHB-2 as the energy difference between rotamers 7d and 7c

$$\Delta H_{\rm IMHB-2} = \Delta E_{\rm 7c \to 7d} = E_{\rm 7d} - E_{\rm 7c}.$$

In the former case, rotamer **b** was chosen as the reference point due to the most distant position of the double bond of the alkenyl substituent from the  $\beta$ -hydroxy group. In estimating the strength of IMHB-2, rotamer **7d** with broken hydrogen bonds was taken as the reference point.

**Table 1.** Total (*E*) and relative ( $\Delta E$ ) energies with allowance for the zero-point vibrational energy (ZPE), geometric parameters ( $\theta_{OH}$ ,  $\theta_{C=C}$ ,  $\theta_{cycl}$ ,  $R_{O...O}$ ), rotamer contents, and calculated v(OH) frequencies of 3-alkenyl-2-hydroxy-1,4-naphthoquinones and 3-alkenyl-2-hydroxynaphthazarins from DFT (B3LYP) and MP2 data

Rota- mer	Calculation method	<i>—E</i> /a.u.	$\Delta E$ /kcal mol <sup>-1</sup>	Content (%)	v(OH) $/cm^{-1}$	$\theta_{\rm OH}$	$\theta_{C=C}$	$\theta_{cycl}$	$R_{\rm OO}/{\rm \AA}$
						deg			
6a	B3LYP/6-31(d,p)	844.752905	0	71.7	3537.1	180.00	0.00	0.00	2.5718
	B3LYP/6-31(d)	844.724613	0	72.0	3475.9	180.00	0.00	0.00	2.5732
	MP2/6-31	840.961372	0	69.6	3486.9	176.99	-5.24	8.78	2.6607
6b	B3LYP/6-31(d,p)	844.752035	0.55	28.3	3565.8	180.01	-179.81	0.02	2.5816
	B3LYP/6-31(d)	844.723724	0.56	28.0	3502.8	179.98	-179.65	0.03	2.5827
	MP2/6-31	840.960597	0.49	30.4	3514.2	177.88	-168.89	10.38	2.6678
6c	B3LYP/6-31(d,p)	844.740628	7.70	$2 \cdot 10^{-6}$	3698.6	7.71	37.76	5.20	—
	B3LYP/6-31(d)	844.712414	7.65	$2 \cdot 10^{-6}$	3634.2	7.71	38.85	5.59	—
6d	B3LYP/6-31(d,p)	844.737707	9.54	$7 \cdot 10^{-8}$	3793.0	9.54	-155.44	3.62	—
	B3LYP/6-31(d)	844.709247	9.64	$6 \cdot 10^{-8}$	3727.8	9.58	-154.44	3.64	—
7a	B3LYP/6-31(d,p)	726.889048	0	68.9	3540.9	180.00	0.00	0.00	2.5730
	B3LYP/6-31(d)	726.869472	0	69.6	3478.3				
	MP2/6-31	723.711341	0	69.6	3491.7	176.96	-4.41	8.61	2.5749
	MP2/6-31(d)	724.662478	0	67.4	3518.4	176.36	-4.07	8.36	2.5950
7b	B3LYP/6-31(d,p)	726.888335	0.47	31.2	3567.0	180.00	180.00	0.00	2.5824
	B3LYP/6-31(d)	726.868697	0.49	30.4	3504.0	_	—	—	—
	MP2/6-31	723.710567	0.49	30.4	3514.9	177.64	-172.91	9.93	2.5838
	MP2/6-31(d)	724.661786	0.43	32.6	3544.1	176.77	-178.03	10.18	2.6060
7c	B3LYP/6-31(d,p)	726.876234	8.05	$10^{-6}$	3701	8.52	36.54	5.64	—
	MP2/6-31(d)	724.653472	5.65	$5 \cdot 10^{-5}$	3622.3	7.88	46.15	10.24	—
7d	B3LYP/6-31(d,p)	726.873993	9.47	$10^{-7}$	3797	9.49	-158.77	4.03	_
	MP2/6-31(d)	724.649863	7.92	$10^{-6}$	3702	11.51	-143.31	8.65	—
8a	B3LYP/6-31(d)	844.719821	0	79.4	3498	179.29	-47.15	5.52	2.5820
	MP2/6-31	840.957125	0	69.4	3503.4	176.95	-51.10	0.98	2.6830
8b	B3LYP/6-31(d)	844.718521	0.80	20.6	3511	179.97	-140.28	7.07	2.5940
	MP2/6-31	840.956339	0.49	30.3	3515.9	178.26	-136.02	11.09	2.6940
8c	B3LYP/6-31(d)	844.711526	5.20	$10^{-4}$	3638	5.03	55.51	5.64	—
	MP2/6-31	840.951959	3.24	0.3	3545.2	3.65	56.57	0.90	—
8d	B3LYP/6-31(d)	844.709336	6.58	$10^{-5}$	3649.9	5.55	-122.24	-0.53	_
	MP2/6-31	840.949504	4.78	$2 \cdot 10^{-2}$	3572.8	4.70	-120.95	3.03	_
9a	B3LYP/6-31(d,p)	610.221595	0	~100	3585.8	180.00	_	0.00	2.6056
	B3LYP/6-31(d)	610.208160	0	~100	3522.0	_	_	_	_
	MP2/6-31	607.621204	0	~100	3532.3	177.58	_	6.07	2.7067
	MP2/6-31(d)	608.414171	0	~100	3576.2	177.82	_	5.12	2.6278
9b	B3LYP/6-31(d,p)	610.210247	7.13	$6 \cdot 10^{-4}$	3796.6	0.00	_	0.00	2.6486
	B3LYP/6-31(d)	610.196762	7.15	$5 \cdot 10^{-4}$	3728.3	_	_	_	_
	MP2/6-31	607.612235	5.63	$7 \cdot 10^{-3}$	3615.5	2.24	_	5.33	2.7056
	MP2/6-31(d)	608.404055	6.34	$2 \cdot 10^{-3}$	3719.7	1.64	_	4.56	2.6444
10a	B3LYP/6-31(d)	877.318588	0	72.3	3500.7	180.00	0.00	0.00	2.5787
	MP2/6-31	873.608292	0	75.3	3490.4	177.30	-3.87	8.06	2.6502
	MP2/6-31(d)	874.742102	0	74.0	3523.4	177.07	-4.08	8.02	2.5856
10b	B3LYP/6-31(d)	877.318100	0.57	27.6	3525.8	180.00	180.00	0.01	2.5884
	MP2/6-31	873.607242	0.66	24.7	3513.8	178.02	-170.71	8.73	2.6661
	MP2/6-31(d)	874.741112	0.62	26.0	3550.5	177.46	-175.77	8.58	2.5978
10c	B3LYP/6-31(d)	877.306562	7.55	$2 \cdot 10^{-6}$	3634.0	8.08	38.59	4.04	_
10d	B3LYP/6-31(d)	877.303850	9.25	$1 \cdot 10^{-7}$	3731.0	9.71	-156.05	3.10	_
11a	B3LYP/6-31(d)	841.181457	0	99.99	3488.6	178.02	-41.11	1.18	2.5724
	MP2/6-31	837.551867	0	99.8	_	175.39	-46.03	6.85	2.6754
11b	B3LYP/6-31(d)	841.172957	5.33	0.01	3649.3	2.39	52.01	2.91	2.6291
	MP2/6-31	837.546017	3.67	0.20	—	3.02	57.74	5.25	2.6914

The strengths of the IMHB-1 in compound 7 determined by MP2/6-31(d) and B3LYP/6-31(d,p) calculations are equal to 7.48 and 9.00 kcal mol<sup>-1</sup>. respectively. The strengths of the IMHB-2 calculated by the same methods are 2.27 and 1.42 kcal mol<sup>-1</sup>, respectively. Thus, the IMHB-2 in molecule 7 is 3.3 (MP2) and 6.3 (B3LYP) times weaker than the IMHB-1.

To estimate the effect of the alkenyl substituent in the *ortho*-position to the  $\beta$ -hydroxy group on the strength of the O—H...O hydrogen bond, we calculated  $\Delta H_{IMHB-1}$  for lawsone (2-hydroxy-1,4-naphthoquinone (9)) (Scheme 4):  $\Delta H_{IMHB-1} = \Delta E = E_{9b} - E_{9a}$ , which gave 7.15 (B3LYP/6-31(d)) and 6.34 kcal mol<sup>-1</sup> (MP2/6-31(d)). Due to these high  $\Delta H_{IMHB-1}$  values, the content of tautomer 9b is at most  $7 \cdot 10^{-3}\%$  (see Table 1). Therefore, lawsone is expected to exist in solutions in aprotic nonpolar solvents mainly as rotamer 9a. Indeed, the IR spectrum of a solution of lawsone in CCl<sub>4</sub> in the high-frequency region exhibits only one absorption band at 3413 cm<sup>-1</sup>, which corresponds to the stretching vibration of the  $\beta$ -hydroxy group, involved in the formation of the intramolecular H-bond (rotamer 9a).

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Comparison of the  $\Delta H_{\rm IMHB-1}$  values for compounds 7 and 9 shows that the IMHB-1 in molecule 7 is 7.48 – 6.34 = 1.14 kcal mol<sup>-1</sup> stronger, probably, due to the enhancement of electron-donating (proton-acceptor) properties of oxygen at the C(1) atom caused by conjugation of the  $\pi$ -system of the alkenyl substituent with the  $\pi$ -system of the quinonoid nucleus.

The unnormalized normal frequencies calculated for compound 7 are listed in Table 1. The frequency differences  $\Delta v_{7b-7a}(OH) = v_{7b}(OH) - v_{7a}(OH)$  calculated by both methods in different basis sets are about 26 cm<sup>-1</sup>, which is in good agreement with the observed splitting of the v(OH) band in the IR spectrum of compound 7 in hexane (28 cm<sup>-1</sup>). According to calculations,  $v_{7a}(OH) \le v_{7b}(OH)$ . In rotamer 7a, the double bond of the alkenyl substituent is most proximate to the OH group and the distance between the O atoms of the carbonyl and  $\beta$ -hydroxy groups  $R_{O...O}$  (parameter determining the strength of the IMHB-1) is 2.5950 Å. In rotamer 7b with the double bond of the alkenyl substituent distant from the  $\beta$ -hydroxy group,  $R_{O...O}$  increases to 2.6060 Å, which indicates weakening of the IMHB-1 resulting in an increase in the v(OH) frequency. Thus, the lowerfrequency component of the v(OH) band at 3362 cm<sup>-1</sup> observed in the IR spectra of alkenylhydroxynaphthoquinone 7 in hexane refers to rotamer 7a and the higherfrequency component at 3390 cm<sup>-1</sup> corresponds to rotamer 7b.

The introduction of a *tert*-butyl or ethyl substituent into position 2' of the substituent vinyl group (compounds **6** and **8**, respectively) does not change the order in which the rotamer stability decreases (a > b > c > d) established for compound **7** with a simpler structure.

The spectrum of compound **8** in hexane shows a much less pronounced splitting of the v(OH) band, probably, due to steric hindrances related to the mutual positions of the methylene protons of the alkenyl substituent and the oxygen atom of the  $\beta$ -hydroxy group. Unlike the sharp v(OH) doublet in the spectra of compounds **6** and **7**, the spectrum of compound **8** exhibits an asymmetric band with a peak at 3385 cm<sup>-1</sup> and a shoulder at ~3398 cm<sup>-1</sup>. Deconvolution of the contour of the v(OH) band into components gives the frequency difference  $\Delta v(OH) =$ 16 cm<sup>-1</sup> (*cf.* 30 and 28 cm<sup>-1</sup> for compounds **6** and **7**, respectively). In addition, compound **8** shows highfrequency shifts of both components (3398.5 and 3382.4 cm<sup>-1</sup>) by 8.5 and 20.8 cm<sup>-1</sup> with respect to compound **7**.

Geometry optimization by the MP2/6-31 and B3LYP/6-31(d) methods showed that unlike compounds **6** and **7**, all rotamers of compound **8** are nonplanar (see Table 1). The steric hindrances induce a considerable deviation of the alkenyl substituent from the molecular plane, which decreases the conjugation of the double-bond  $\pi$ -electrons with the  $\pi$ -system of the naphthoquinone skeleton. As a result, the spectrum of compound **8** shows a less pronounced splitting of the quinonoid v(OH) band. The theoretical  $\Delta v_{b-a}$ (OH) value for compound **8** is equal to 13 cm<sup>-1</sup>, which is in good agreement with the observed splitting (16 cm<sup>-1</sup>).

Conformational analysis of 2-hydroxynaphthazarin derivative **10** (Scheme 5; the relative energies of the rotamers (kcal mol<sup>-1</sup>) were obtained by B3LYP/6-31(d) calculations) showed that the stabilities of rotamers **a**–**d** decrease in the order established for compounds **6**–**8**, namely, **10a** > **10b** > **10c** > **10d**. The theoretical  $\Delta v_{b-a}$ (OH) value for compound **10** is 27–28 cm<sup>-1</sup>, which is in good agreement with the observed splitting of the v(OH) quinonoid band in the experimental IR spectrum (28 cm<sup>-1</sup>).

The effect of the nature of the substituent at the C(3) atom on the characteristics of the v(OH) band in the IR spectra are clearly illustrated by the spectra of 2-hydroxy-3-phenyl-1,4-naphthoquinone (11) (Scheme 6).

The orientation of the hydroxy group relative to the C(1)=O carbonyl group determines the condi-



Scheme 5

*i*.  $\Delta E_{10d} = 9.25 \text{ kcal mol}^{-1}$ ; *ii*.  $\Delta E_{10c} = 7.55 \text{ kcal mol}^{-1}$ ; *iii*.  $\Delta E_{10b} = 0.57 \text{ kcal mol}^{-1}$ .

10: R<sup>1</sup> = H, R<sup>2</sup> = Me





tions under which the phenyl group rotates. Due to symmetry, each internal rotation potential  $V_{\mathbf{a}}(\theta_{C(1')=C(2')})$  and  $V_{\mathbf{b}}(\theta_{C(1')=C(2')})$  has four minima with equal energies, which correspond to equivalent structures. According to calculations, the energies of rotamers **11b** are higher than those of the most stable rotamers **11a** by 3.6 (MP2/6-31) and 5.3 kcal mol<sup>-1</sup> (B3LYP/6-31(d)), respectively. The content of rotamer **11b** is only 0.20 (MP2) and 0.01% (B3LYP). Thus, although compound **11** could exist as a mixture of optical isomers of the types **a** and **b**, it exists predominantly as a single degenerate rotamer **11a**. The content of the other rotamer **(11b)** is below the experimental detection limit. Indeed, the experimental spectrum exhibits a single v(OH) band at 3378 cm<sup>-1</sup>.

The relative energies of the rotamers of the compounds studied (see above) show that only rotamers **b** can occur in the gas phase in noticeable amounts apart from the major rotamers **6a**—**8a** and **10a**. At room temperature, the populations of the vibrational levels with energies exceeding the zero-point vibrational energy by at least 5 kcal mol<sup>-1</sup> are negligible. Hence, at the angles  $0^{\circ} \leq \theta_{OH} \leq 90^{\circ}, 0 \leq \theta_{C=C} \leq 90^{\circ}$  and  $0^{\circ} \leq \theta_{OH} \leq 90^{\circ}, -180^{\circ} \leq \theta_{C=C} \leq -90^{\circ}$  formally corresponding to

rotamers  $\mathbf{c}$  and  $\mathbf{d}$ , the values of the statistically averaged distribution function for rotation of the hydroxy and alkenyl groups is five or more orders of magnitude lower than the values attained near the equilibrium configurations  $\mathbf{a}$  and  $\mathbf{b}$ .

For compounds **6**–**8** and **10**, the statistical weights  $g_a$  and  $g_b$  (percentages of rotamers **a** and **b**) at 298.15 K are 70.8 and 29.2%, 69.0 and 31.0%, 69.4 and 30.3%, and 73.0 and 27.0%, respectively. The ratios of the percentages of rotamers **a** and **b** for compounds **6**–**8** and **10** are close to the ratios of the areas under the components of the v(OH) bands in the IR spectra of their hexane solutions, in particular, 64 : 36, 69 : 31, 66 : 34, and 70 : 30, respectively.

We also carried out model B3LYP/6-31(d) calculations of the solvent effect on the geometric and energy parameters of the rotamers of compound 7 using the polarizable continuum model (PCM) and cyclohexane as an example. Corrections to the Gibbs energies ( $\Delta G_s =$  $G_s - G$ , where the subscript "s" designates the value calculated with allowance for the solvation effects) of rotamers **7a-d** were -2.62, -2.51, -3.86, and -3.87 kcal mol<sup>-1</sup>, respectively. Thus, the rotamer percentages ( $g_{7a,s} = 72.0\%$ ,  $g_{7b,s} = 28.50\%$ ,  $g_{7c,s} = 4 \cdot 10^{-6}\%$ , and  $g_{7d,s} = 2 \cdot 10^{-7}\%$ ) for a cyclohexane solution differ from those for the gas phase by 1–3%. Apparently, transition from the gas to cyclohexane solution would affect the percentages of rotamers of other compounds studied to the same extent as those of compound 7.

Thus, we carried out the conformational analysis of compounds **6–11** and estimated the statistical weights of the rotamers formed upon internal rotation of the  $\beta$ -hydroxy group and the alkenyl substituent at C(3) by quantum chemistry methods. Based on the results, an interpretation of the splitting of the experimentally observed v(OH) bands was proposed.

It was shown that the content of rotamers **c** and **d** is negligible  $(\sim 10^{-3} - 10^{-7}\%)$  and the splitting of the v(OH) bands in the spectra of these compounds in the gas phase is only due to the internal rotation of the

alkenyl substituent. The theoretical ratios of the statistical weights of the rotamers **a** and **b** for all compounds are similar ((2.4–2.7):1), which is in good agreement with the experimental ratios of the areas under the components of the v(OH) bands measured in *n*-hexane and cyclohexane solutions ((1.8–2.3):1). For compound 7, the effect of the nonpolar solvent (cyclohexane) on the ratio of rotamer percentages was calculated. The solvation effects were shown to change the relative energies of the rotamers of molecule 7 by  $\Delta G_{\rm s} \approx 0.1 \cdot \Delta G_{\rm gas}$ . This suggests that compounds 6, 7, and 10 exist in (cyclo)hexane solutions as mixtures of rotamers **a** (65–70%) and **b** (35–30%).

### Experimental

Ab initio calculations were carried out by the PC GAMESS program<sup>8</sup> with full geometry optimization and with account of electron correlation at the second-order level of Møller-Plesset perturbation theory (MP2) and the density functional theory with nonlocal exchange-correlation functional B3LYP using the split-valence basis sets 6-31G, 6-31(d), and 6-31(d,p). The optimization procedure was carried out to an energy gradient of  $5 \cdot 10^{-6}$  a.u. Å<sup>-1</sup>. For each stationary point located on the potential energy surface (PES), normal-mode vibrational frequencies were calculated. The absence of imaginary frequencies indicated that these stationary points on the PES were minima corresponding to rotamer forms. At similar energies of rotamers c and **d** and low barriers to the reaction  $\mathbf{d} \rightarrow \mathbf{c}$  (<2 kcal mol<sup>-1</sup>, compound 8), the minima were located by scanning the PES over the  $\theta_{C=C}$  angle. The effect of the nonpolar solvent (cyclohexane) on the ratio of the rotamer percentages was estimated using the PCM model.<sup>9</sup>

Melting points were measured on a Boetius apparatus and not corrected. <sup>1</sup>H NMR spectra were recorded on a Bruker AC-250 spectrometer (250.13 MHz) in CDCl<sub>3</sub> (Me<sub>4</sub>Si as the internal standard). EI mass spectra were obtained on an LKB-9000S instrument with direct inlet and an ionizing energy of 70 eV. IR spectra were measured on a Bruker Vector 22 FT-IR spectrophotometer with a resolution of 2.0 cm<sup>-1</sup> in *n*-hexane or cyclohexane using matched cells with CaF<sub>2</sub> windows, layer thickness 1.00-2.50 mm. The frequencies and areas were measured and the contours of the  $\beta$ -hydroxy stretching bands were deconvolved into components using OPUS/IR 02 software, version 3.0.2. The reproducibility of frequency values was at least  $0.5 \text{ cm}^{-1}$ . The solution concentrations were  $5-20 \text{ mmol } L^{-1}$ . The reactions were monitored and the purity of the compounds was checked by TLC on Merck 60F-254 plates in a 3:1 hexane-acetone mixture. Commercial 2-hydroxy-3-phenyl-1,4-naphthoquinone (11) ("pure" grade) was used. The synthesis and the spectroscopic characteristics of 2-hydroxy-3-(3,3-dimethylbut-1-enyl)-1,4-naphthoquinone (6) were described previously.<sup>1</sup> Lawsone (9) was prepared by a known procedure.10

**Condensation of 2-hydroxy- and 2,5,8-trihydroxy-1,4naphthoquinones with propanal and 2-ethylbutanal.** A solution of aldehyde (5 mmol) in benzene was added dropwise in small portions to a boiling solution of a substrate (1 mmol), *p*-TsOH (0.6 mmol) and MeNH<sub>2</sub>·HCl (0.6 mmol) in benzene (10 mL), the course of the reaction being monitored by TLC. The reaction mixture was cooled, washed with water ( $3 \times 2$  mL), dried with anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated. Compounds (7, 8, and 10) were isolated by preparative TLC on plates ( $20 \times 20$  cm) with a 5–40 µm loose silica gel layer (H<sup>+</sup>-form) in a 3 : 1 hexane—acetone system.

The reaction of lawsone (9) (174 mg) with propanal gave 79 mg (48% based on reacted 9) of **2-hydroxy-3-(prop-1-enyl)-1,4-naphthoquinone (7)**, m.p. 127–131 °C. IR (*n*-hexane/cyclohexane), v/cm<sup>-1</sup>: 3390 m, 3361 m ( $\beta$ -OH); 1680 sh w, 1663 vs (C=O); 1636 m, 1619 m (C=C). <sup>1</sup>H NMR (CDCl<sub>3</sub>),  $\delta$ : 1.99 (dd, 3 H, Me,  $J_1 = 1.7$  Hz,  $J_2 = 6.8$  Hz); 6.63 (dq, 1 H, C(1')H,  $J_1 =$ 1.7 Hz,  $J_2 = 16.1$  Hz); 7.08 (dq, 1 H, C(2')H,  $J_1 = 6.8$  Hz,  $J_2 =$ 16.1 Hz); 7.69, 7.75 (both dt, 1 H each, H(6), H(7),  $J_1 = 1.7$  Hz,  $J_2 = 7.5$  Hz); 7.74 (s, 1 H,  $\beta$ -OH); 8.06, 8.13 (both dd, 1 H each, H(5), H(8),  $J_1 = 1.7$  Hz,  $J_2 = 7.5$  Hz). MS, m/z ( $I_{rel}$  (%)): 215 [M + 1]<sup>+</sup> (18), 214 [M]<sup>+</sup> (100), 213 (17), 199 (37), 186 (18), 171 (33), 168 (24), 158 (22).

The reaction of lawsone (9) (174 mg) with 2-ethylbutanal gave 113 mg (44%) of **2-hydroxy-3-(2-ethylbut-1-enyl)-1,4-naph-thoquinone (8)**, m.p. 91–95 °C (from a hexane—acetone mixture). IR (*n*-hexane), v/cm<sup>-1</sup>: 3400 sh m, 3385 m ( $\beta$ -OH); 1663 vs (C=O); 1643 m, 1599 m (C=C). <sup>1</sup>H NMR (CDCl<sub>3</sub>),  $\delta$ : 1.01, 1.16 (both t, 3 H each, Me, J = 7.6 Hz); 2.05 (q, 2 H, CH<sub>2</sub>, J = 7.6 Hz); 2.29 (dq, 2 H, CH<sub>2</sub>,  $J_1 = 1.4$  Hz,  $J_2 = 7.6$  Hz); 5.90 (br.s, 1 H, C(1')H); 7.46 (s, 1 H,  $\beta$ -OH); 7.69, 7.76 (both dt, 1 H each, H(6), H(7),  $J_1 = 1.7$  Hz,  $J_2 = 7.3$  Hz); 8.09, 8.12 (both dd, 1 H each, H(5), H(8),  $J_1 = 1.7$  Hz,  $J_2 = 7.3$  Hz). MS, m/z ( $I_{rel}$  (%)): 257 [M + 1]<sup>+</sup> (83), 256 [M]<sup>+</sup> (90), 255 (11), 242 (29), 241 (37), 228 (17), 227 (47), 203 (14), 202 (100).

The reaction of naphthopurpurin (2,5,8-trihydroxy-1,4naphthoquinone) (206 mg) with propanal gave 38 mg (16%) of **2,5,8-trihydroxy-3-(prop-1-enyl)-1,4-naphthoquinone (10)**, m.p. 160—165 °C. IR (*n*-hexane), v/cm<sup>-1</sup>: 3400 m, 3372 m ( $\beta$ -OH); 1645 sh w, 1620 sh m, 1605 vs (C=O); 1575 m (C=C). <sup>1</sup>H NMR (CDCl<sub>3</sub>), & 2.00 (dd, 3 H, Me,  $J_1 = 1.7$  Hz,  $J_2 = 6.8$  Hz); 6.62 (dq, 1 H, C(1')H,  $J_1 = 1.7$  Hz,  $J_2 = 16.1$  Hz); 7.08 (dq, 1 H, C(2')H,  $J_1 = 6.8$  Hz,  $J_2 = 16.1$  Hz); 7.19, 7.27 (both d, 1 H each, H(6), H(7), J = 9.5 Hz); 7.79 (br.s, 1 H,  $\beta$ -OH); 11.54, 12.87 (both s, 1 H each,  $\alpha$ -OH). MS, m/z ( $I_{rel}$ (%)): 247 [M + 1]<sup>+</sup> (16), 246 [M]<sup>+</sup> (100), 234 (13), 231 (15).

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