NBO-Analysis of *peri*-dihydroxy-9,10-anthraquinones and their deprotonated forms

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The natural bonding orbitals (NBO) approach is employed to gain a deeper insight into the nature of intramolecular interactions in a series of *peri*-hydroxyderivatives of 9,10-anthraquinones and their deprotonated forms. The intuitive predictions of relative energies of these species and the strength of hydrogen bonding were confirmed by the NBO analysis, whereas intuitive evaluation of the role of steric effects in the stability of deprotonated hydroxyanthraquinones seemed to be exaggerated.

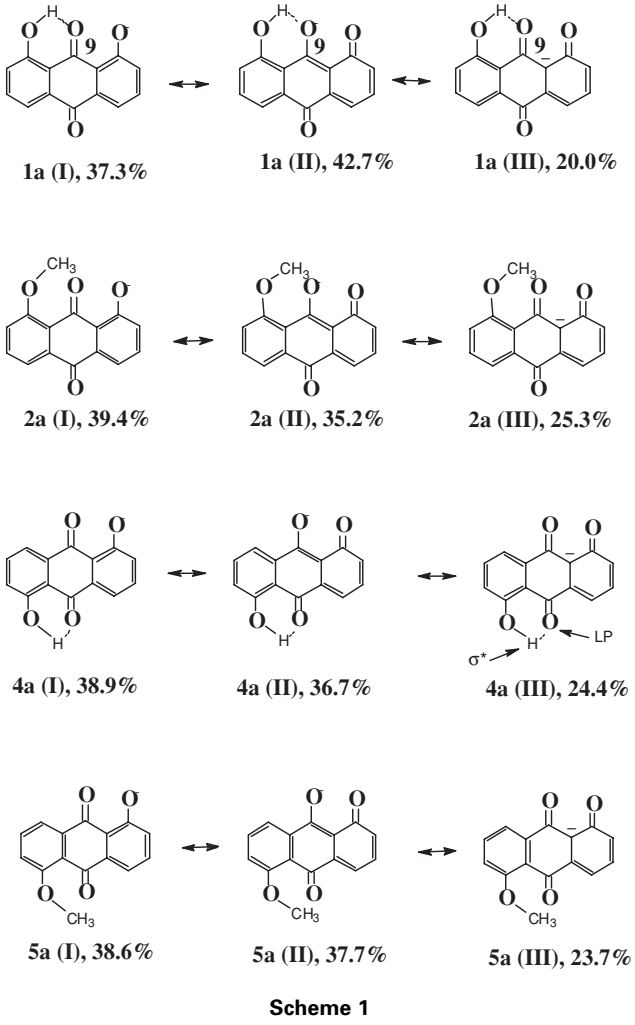
Keywords natural orbitals, acidity, computational chemistry, hydrogen bonding

During our current research we have found a highly selective procedure for monomethylation of 1,8-dihydroxy-9, 10-anthraquinone **1**[1] and observed little or no selectivity for its 1,5-counterpart **4**[1]. As opposed to fully methylated 1-hydroxy-8-methoxy-9,10-anthraquinone **2** and 1-hydroxy-5-methoxy-9,10-anthraquinone **6**, monomethylated *peri*-dihydroxy-9,10-anthraquinones **2** and **5** are key intermediates in the synthesis of anthraquinone antibiotics[2]. Therefore, the reason for such selectivity seems to be of general practical interest. Later we found[3] that methylation of *peri*-dihydroxy-9,10-anthraquinones is controlled by the acidity of the starting phenol as opposed to the nucleophilicity of the deprotonated form. The aim of our study is to reveal factors accounting for the relative acidity of *peri*-dihydroxy-9,10-anthraquinones with the emphasis on the NBO analysis of hydrogen bonding.

Methods

We employed the NBO 3.0 program as a part of the GAUSSIAN 98W computational package[4] to assess the contribution of hydrogen bonding to the energies of monodeprotonated forms of **1** and **4**. Strong hydrogen bonds can be efficiently described in terms of the charge transfer from the nonbonding orbital of the proton acceptor to the σ* - NBO of the OH-bond[5]. If the proton donor and the proton acceptor are connected with a conjugated *p*-system, the "Resonance-assisted hydrogen bonding" should also be taken into account[6]. The natural resonance theory (NRT), implemented to the GENNBOW 5.0 standalone application[7], allowed us to compare relative contributions of resonance structures that may account for the stability of deprotonated forms **1a, 2a, 4a, 5a** and the effectiveness of hydrogen bonding. We also evaluated the contribution of steric repulsions between occupied natural bonding orbitals (NBO) and lone electron pairs to the total energy of the studied species for the Lewis structures **I** (Scheme 1). The species of interest were geometry optimised at the B3LYP/6-31G** level of theory, implemented into the GAUSSIAN 98W package. The energies were calculated at the 6-31+G** basis set with the tight criterion for the SCF convergence. The NBO analyses were performed at the 6-31G** basis set to avoid linear dependence of the basis functions which would be difficult for the NBO 3.0 program to handle. The computed energies of deprotonation for the species **1, 2, 4** and **5** were nearly the same with and without the diffuse functions. Additionally, the general trend observed at the 3-21G* basis set was kept at the selected 6-31G** basis set, which confirmed the adequacy of the latter for the NBO analysis.

First, we computed energies of 1,8- and 1,5-dihydroxy-derivatives **1** and **4**, monomethylated products **2** and **5**, and intermediate anions **1a, 2a, 4a** and **5a** in vacuum. The strength



Scheme 1

of hydrogen bonds was characterised by the hydrogen bond lengths, extent of the charge transfer, and hybridisation of the orbital of the hydrogen bond donor, directed toward hydrogen (Table 1).

Based on computed energies of starting and intermediate species for successive methylation, we computed relative energies of deprotonation for phenols **1, 2, 4** and **5** (2). The relative energy of deprotonation of 1,8-dihydroxy-9,10-anthraquinone 1, computed as ($E_{1a} - E_1$) was set to zero as a reference.

Therefore, computed acidities of hydroxyanthraquinones decrease in the following order: **1>4>5>2**.

Acidities of monophenols **2** and **5**, calculated in vacuum, are close as are their acidities observed in an alcohol solvent. The acidity of the *anti*-diphenol **4**, calculated in vacuum, is

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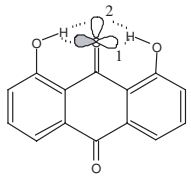
Table 1 Computations of starting and intermediate species for successive methylation of 1,8- and 1,5-dihydroxy-9, 10-anthraquinones

Entry	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Species	**1**	**1a**	**2**	**2a**	**4**	**4a**	**5**	**5a**
Energy au	–839.2904	–838.7433	–878.5735	–878.0086	–839.2922	–838.7400	–878.5733	–878.0128
H-bond length Å	1.68	1.49	1.63	–	1.66	1.60	1.67	–
2nd Order perturbation between LPs and σ*(OH), kcal/mol*	15.84 10.85	55.36 7.33	30.36 6.10	–	25.98 5.67	35.59 6.04	25.66 5.59	–
Steric Repulsion between LPs and σ(OH), kcal/mol*	11.32 5.22	29.44 0.78	18.74 1.32	–	16.11 1.40	20.62 1.08	15.94 1.38	–
s-Character of the OH- oxygen orbital, directed toward H, %	25.85	26.75	26.16	–	25.94	26.36	25.90	–

*The first figure indicates interaction with the *p*-lone electron pair on the carbonyl oxygen; the second figure indicates interaction with the hybridised lone electron pair

Table 2 Relative energy changes for deprotonation of 1, 8-dihydroxy-9,10-anthraquinone 1, 1-hydroxy-8-methoxy-9, 10-anthaquinone 2, 1,5-dihydroxy-9,10-anthraquinone 4 and 1-hydroxy-5-methoxy-9,10-anthraquinone **5**

Phenol	1	2	4	5
Relative energy of deprotonation, kcal/mol	0	11.2	3.2	8.4



Scheme 2

still lower that the acidity of **1**, which is consistent with the experiment. However, the calculated acidity is somewhat higher than would be expected, due to the fact, that the effect of solvation by a protic solvent was ignored in a computation in vacuum. However, the influence of the solvent can be qualitatively rationalised. As opposed to anions **2a** and **5a**, the anion **4a** is stabilised with a hydrogen bond, which is apparently stronger in vacuum, than in a protic solvent, competing for hydrogen bonding.

According to the results of the NBO analysis (Table 1), the computed energies of the second order perturbation between the lone electron pair of the carbonyl oxygen and the natural antibonding σ*-orbital of the OH-bond as well as the steric repulsion of the same electron pair and the natural bonding σ-orbital of the OH-bond are in an excellent agreement with the OH-bond length. This pair of orbital interactions seems to be a better, more sensitive tool, than the OH-bond length for estimation of the energy of hydrogen bonding.

The hydrogen bonding in the anion **1a** does seem to be the strongest (Table 1) as might be expected because of the contribution of the resonance structure **1a (II)** (Scheme 1) to the anion **1a**. This prediction agrees with the NRT analysis, which suggests that this resonance structure has a significant contribution (42.2%) and this contribution is larger, than for all other anions (**2a, 4a** and **5a**). Additionally, the OH-bond is substantially elongated in the anion **1a** (1.03 Å), comparing with all other studied species with weaker hydrogen bonds (0.99-1.01 Å).

The intuitive assumption that the hydrogen bonds in the *peri*-diphenol **1** are weaker than isolated hydrogen bonds in its *anti*-counterpart **4** is also consistent with the calculated bondlengths and NBO interactions (Table 1). Additionally, the NBO analysis revealed a particular reason for the weakening of hydrogen bonds in **1**: both OH-bonds mostly interact with the same lone electron pair **1** (100% p-character) of the carbonyl oxygen (Scheme 1), which significantly decreases the donor-acceptor NBO interaction (Table 1). Interaction of OH-antibonding orbitals with the lone pair 2 (40% *p*-character) is weaker (Table 1), and does not compensate for the overall weakening of the H-bond. However, relative contribution of the lone pair 2 to the charge transfer component of the hydrogen bond in the species **1** is much higher (41%) than in all other studied species (12-18%). See Table 1.

It is worth mentioning that consideration of hydrogen bonding in hydroxyanthraquinones on the basis of orbitals of the maximum occupancy (NBOs) demonstrates the inadequacy of the obsolete "rabbit ears" concept, which suggests that each OH-bond interacts with one of two sp^2-hybridised lone electron pairs on the carbonyl oxygen. However, both sets of nonbonding orbitals are identical for the purpose of construction of molecular orbitals.

According to the NBO analysis, the steric and electrostatic repulsions in the anion **2a** did not make a major contribution to the energy of **2a** (as opposed to "proton sponges"[8]), that one might attribute to the substantially lower acidity of the monophenol **2** vs the diphenol **1**, resulting in the observed high selectivity of methylation of **1**[2]. The calculated steric interactions between lone electron pairs of *peri*-oxygens in the anion **2a** were not substantially larger than all other steric interactions in **2a** and steric interactions between lone electron pairs in anions **1a**, **4a** and **5a** (Scheme 1). The calculated NPA charges on the atoms of oxygen in the *peri*-anion **2a** and its *anti*-counterpart **5a** also turned out to be the same (–0.65), which disagreed with the explanation of different stabilities of **2a** and **5a** by the electrostatic factor. The lack of twist between adjacent aromatic rings in all studied derivatives also distinguishes them from the "proton sponges". The structure of 1,8-dimethylaminonaphtalene (a "proton sponge"), optimised at the same level of theory, has a 9° twist between two aromatic rings, and the two C–N bonds are positioned at the 19° angle.

The additional stability of the intermediate anion **1a** vs **2a, 4a** and **5a** can be intuitively explained by enhanced hydrogen bonding due to a larger negative charge on oxygen at C9, contributed by the resonance structure **1a (II)** (42.7%, Scheme 1). For the 1,5-counterpart **4a**, such resonance contribution (36.7%) does not seem to results in such enhancement of hydrogen bonding with the 5-hydroxy-group.

Comparison of relative stabilisation of anions **2a** and **5a** does not reveal a significant preference for deprotonation of **2** vs **5**, which is consistent with the found[3] similar acidities of **2** and **5**.

To access contribution of the "resonance-assisted hydrogen bonding" to the stability of anions **1a** and **4a,** for each reference resonance structure (Scheme 1), we added a structure with the proton migrated from the donor to the acceptor of the hydrogen bond. The overall contribution of new reference structures for the anion **1a** was 26% as opposed to 18% for its 1, 5-counterpart **2a**, whereas relative contributions of initial resonance structures remained unchanged. Therefore, the "resonance-assisted hydrogen bonding" also favours stability of the mono-deprotonated 1,8-dihydroxy-9,10-anthraquinone **1a**. Hybridisation of the oxygen hybrid orbital, directed toward hydrogen, correlates well with the strength of the hydrogen bond (Table 1). In the species 1a with the strongest hydrogen bond and the strongest electron donation from the lone pair of the hydrogen bond acceptor, this orbital has a slightly larger s-character (26.75%), than the corresponding orbitals in the other studied species (25.85–26.36%). This trend agrees with the Bent's rule[10] and is not surprising.

Conclusion

The NBO analysis is employed to confirm or rule out intuitive explanations of different acidities of *peri*-dihydroxy-9,10-anthra-quinones and their deprotonated forms. For the studied system, the NBO approach is found to be a useful tool for detailed analysis of hydrogen bonding and prediction of relevant synthetic consequences such as selectivity of organic reactions and acidity of intermediate species. Both the second order perturbation approach and less sensitive Natural Resonance Theory seem to be useful tools for the quantitative analysis of different aspects of intramolecular interactions in *peri*-9, 10-anthraquinone derivatives.

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