Electronic Supplementary Information (ESI)

Enthalpy-entropy relations in acid-base equilibrium of warfarin and 10-hydroxywarfarin; joint experimental and theoretical studies

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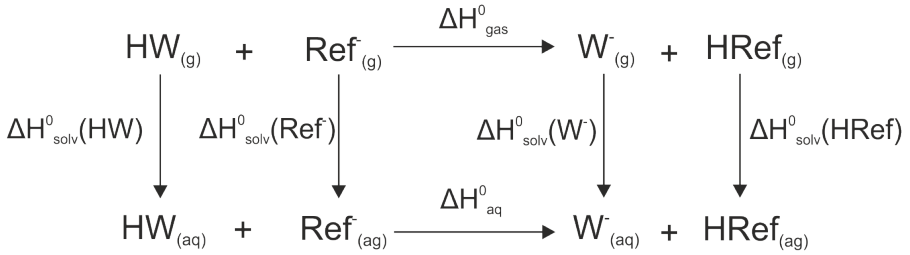
1. The calculated dissociation (deprotonation) enthalpies and entropies.

Table S-1. DFT calculated enthalpies and entropies of deprotonation of WAR and W10 obtained from thermodynamic cycle presented below in Fig.S-1.

	ΔH_{exp} (kJ·mol^{-1})	$\Delta H_{CPCM\text{-}UFF}$ (kJ·mol^{-1})	$\Delta H_{CPCM\text{-}UAKS}$ (kJ·mol^{-1})	ΔS_{exp} (J·mol^{-1}K^{-1})	$\Delta S_{CPCM\text{-}UFF}$ (J·mol^{-1}K^{-1})	$\Delta S_{CPCM\text{-}UAKS}$ (J·mol^{-1}K^{-1})
WAR	16.9	12.45		-4.4	-9.98	-14.24
W10	34.3	33.08	23.88	0.0	-6.50	-6.82



$$\Delta H^0_{aq} = \Delta H^0_{gas} + \Delta H^0_{solv}(HRef) + \Delta H^0_{solv}(W^-) - \Delta H^0_{solv}(HW) - \Delta H^0_{solv}(Ref^-)$$

$$\Delta H = \Delta H^0_{aq} + \Delta H^0_{aq}(Ref)$$

Fig.S-1. The cycle used in the DFT calculations of thermodynamic parameters.

Table S-2. Thermodynamic parameters (enthalpic) calculated based on the solvent model CPCM-UFF.

CPCM-UFF	ΔH°_{gas} (kcal·mol^{-1})	ΔH°_{solv}(HRef) (kcal·mol^{-1})	ΔH°_{solv} (W^-) (kcal·mol^{-1})	ΔH°_{solv}(HW) (kcal·mol^{-1})	ΔH°_{solv}(Ref^-) (kcal·mol^{-1})	ΔH°_{aq}(Ref) (kcal·mol^{-1})
WAR	-0.61	-12.06	-46.68	-9.24	-48.69	4.40
W10	7.07	-12.06	-49.87	-12.06	-48.69	4.40

Table S-3. Thermodynamic parameters (enthalpic) calculated based on the solvent model CPCM-UAKS.

CPCM-UAKS	ΔH°_{gas} (kcal·mol^{-1})	ΔH°_{solv}(HRef) (kcal·mol^{-1})	ΔH°_{solv} (W^-) (kcal·mol^{-1})	ΔH°_{solv}(HW) (kcal·mol^{-1})	ΔH°_{solv}(Ref^-) (kcal·mol^{-1})	ΔH°_{aq}(Ref) (kcal·mol^{-1})
WAR	-0.61	-48.46	-70.71	-36.73	-80.98	4.40
W10	7.07	-48.46	-89.81	-51.53	-80.98	4.40

Table S-4. Thermodynamic parameters (entropic) calculated based on the solvent model CPCM-UFF.

CPCM-UFF	ΔS°_{gas} (cal·mol^{-1}K^{-1})	ΔS°_{solv} (HRef) (cal·mol^{-1}K^{-1})	ΔS°_{solv} (W) (cal·mol^{-1}K^{-1})	ΔS°_{solv} (HW) (cal·mol^{-1}K^{-1})	ΔS°_{solv} (Ref^{-}) (cal·mol^{-1}K^{-1})	ΔS°_{aq} (Ref) (cal·mol^{-1}K^{-1})
WAR	2.33	0.867	-11.41	1.07	-3.51	-4.2
W10	0.63	0.867	-5.18	2.13	-3.51	-4.2

Table S-5. Thermodynamic parameters (entropic) calculated based on the solvent model CPCM-UFF.

CPCM-UAKS	ΔS°_{gas} (cal·mol^{-1}K^{-1})	ΔS°_{solv} (HRef) (cal·mol^{-1}K^{-1})	ΔS°_{solv} (W^{-}) (cal·mol^{-1}K^{-1})	ΔS°_{solv} (HW) (cal·mol^{-1}K^{-1})	ΔS°_{solv} (Ref^{-}) (cal·mol^{-1}K^{-1})	ΔS°_{aq} (Ref) (cal·mol^{-1}K^{-1})
WAR	2.33	-11.84	-12.48	-4.19	-7.76	-4.2
W10	0.63	-11.84	-7.737	-8.70	-7.76	-4.2

2. The Hirshfeld atomic charges and electrostatic potentials of WAR and W10.

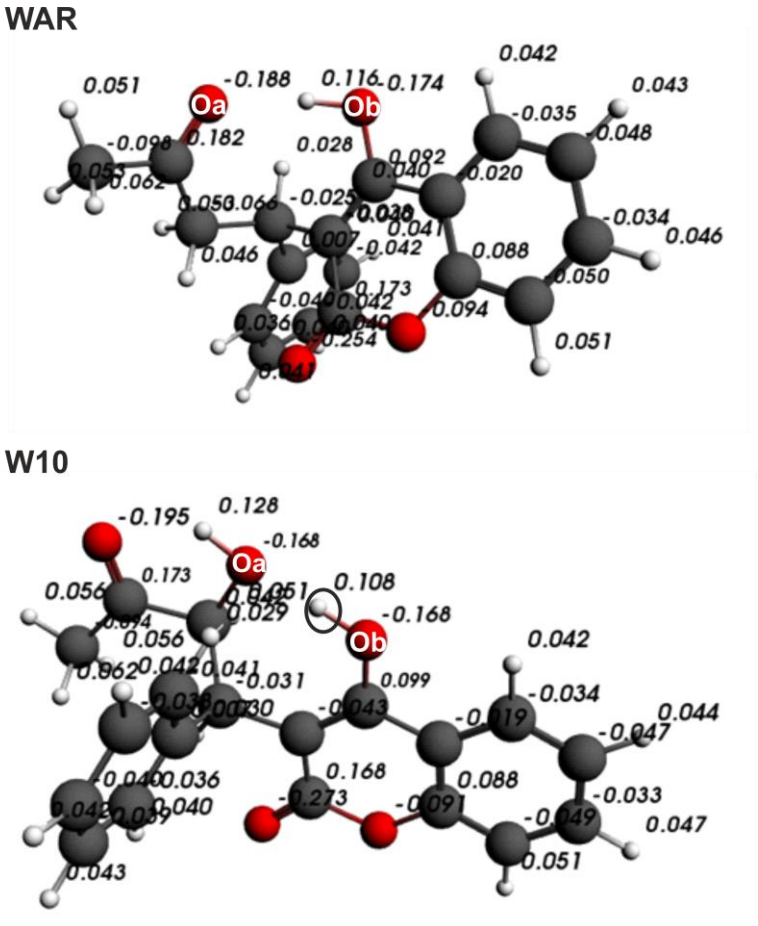


Fig.S-2. The Hirshfeld atomic charges of WAR and W10. Red color – oxygen atoms; grey/black-carbon atoms, white – hydrogen atoms.

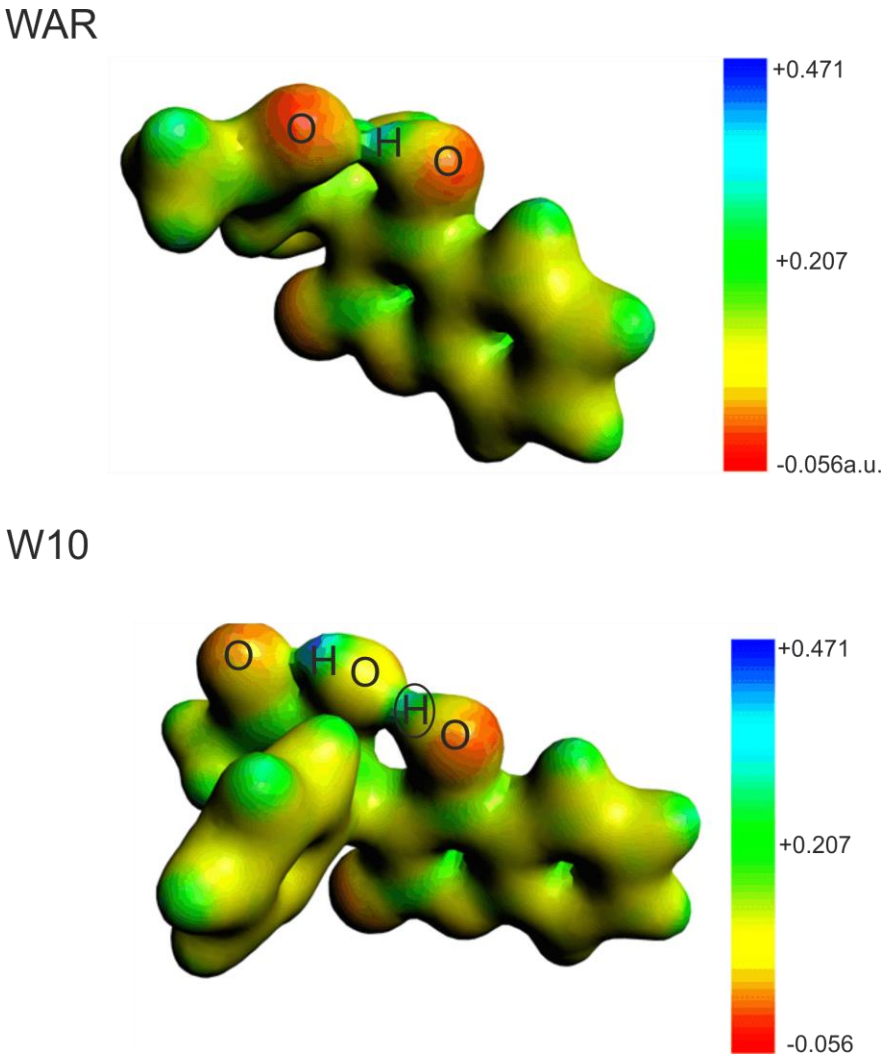


Fig.S-3. The molecular electrostatic potentials (MEP) calculated for WAR and W10. The values of MEP are in atomic units (a.u.). The dissociating proton is marked by the circle. For more information on MEP, see the paragraph below. Plots of MEP were prepared by ADF-GUI interface.

Molecular Electrostatic Potential (MEP)

The electrostatic potential *V*(r) of molecule at coordinate point '*r* (x, y, z)', due to nuclei and electrons, is given by:

$$V(r) = \sum_A \frac{Z_A}{|R_A - r|} - \int \frac{\rho(r')dr'}{|r - r'|} \qquad (1)$$

where Z_A is the charge of nucleus at position R_A and $\rho(r)$ is the total electronic density. The sign of *V(r)* depends upon whether the positive contribution of the nuclei or negative from the electrons is dominant. Negative values of *V(r)* correspond to nucleophilic areas of molecule, whereas the positive to electrophilic regions.

In order to further characterize WAR and W10 we have analyzed the Hirshfeld charges and the electrostatic potentials (Eq.1). The results are collected in Fig.S-2 and Fig. S-3. It is seen that both WAR and W10 exhibit similar characteristics of the intramolecular hydrogen bonding bridges OH···O; namely, the oxygen atoms (marked by Oa) that interact with the dissociating proton carry ~ -0.17e, the hydrogen atom ~ +0.11e and the oxygen atoms of covalent O-H bond (marked by Ob) ~ -0.17e. The same trend is visible from the molecular electrostatic potentials (Fig.S-3) – i.e. the regions of the OH···O bridge (involving dissociating proton) are similarly colored, what indicates similar overall charge distribution around OH···O. These results demonstrate that the electrostatic contribution within the hydrogen bonding bridges can likely be similar in WAR and W10. Given the fact that W10 shows significantly shorter OH···O bridge with respect to WAR and W7, one can infer that the electronic factor, related to the charge donation from the lone oxygen pair to the empty σ^*(O-H), might be superior in the case of W10. Also the dispersion contribution can be of importance. In order to obtain full quantitative knowledge on various contributions to overall stabilization of these bonds, future specialized bonding studies would be necessary.