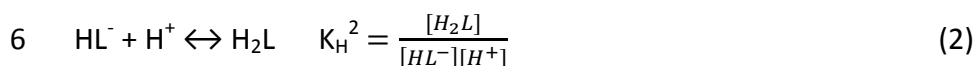


1 **Supplementary information:**

2 **I. Calculation of protonation constants of DO2A²⁻ and ODO2A²⁻ using the TC**
 3 **method.**

4 Thermodynamic Cycle:



7 $L = DO2A^{2-}$ or $ODO2A^{2-}$

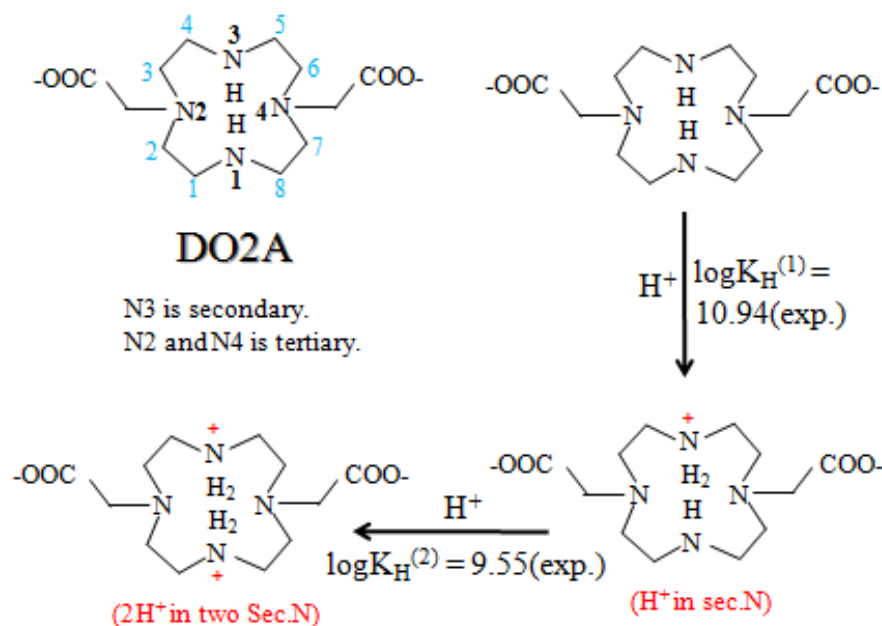
8 $\Delta G_{gas} = \sum G_{gas}(products) - \sum G_{gas}(reactants)$ (3)

9 $\Delta \Delta G_{sol} = \sum \Delta G_{sol}(products) - \sum \Delta G_{sol}(reactants)$ (4)

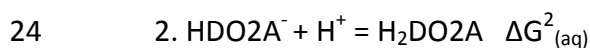
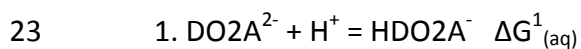
10 $\Delta G_{aq} = \Delta G_{gas} + \Delta \Delta G_{sol}$ (5)

11 $\Delta G_{aq}^n = -RT \ln K_a^n \quad (n=1, 2)$ (6)

12



22 In Water:



25 $\Delta G_{DO2A^1(aq)} = \Delta G_{gas}^1 + \Delta \Delta G_{sol}^1 = -2.303 \times RT \times \log K_H^1 = -2.303 \times 1.987 \times 298.1 \times \log K_H^1$

$$1 \quad \Delta G_{\text{DO2A}^{2-}(\text{aq})}^2 = \Delta G_{\text{gas}}^2 + \Delta \Delta G_{\text{sol}}^2 = -2.303 \times RT \times \log K_{\text{H}}^2 = -2.303 \times 1.987 \times 298.1 \times \log K_{\text{H}}^2$$

species	G_{gas}^a	G_{aq}^a	ΔG_{sol}^b
DO2A^{2-}	-990.096957	-990.342199	-153.89
HDO2A^-	-990.726343	-990.826212	-62.67
$\text{H}_2\text{DO2A}$	-991.266863	-991.287563	-12.99

2 ^a In atomic unit, hartree (1 hartree = 627.5 kcal/mol). ^b In kcal/mol.

3 * G_{gas} is the Gibbs free energy calculated by B3LYP/6-31G* in gas phase, G_{sol} is the
 4 Gibbs free energy calculated by B3LYP/6-31G* in aqueous solution (PCM/UFF), ΔG_{sol}
 5 = $G_{\text{aq}} - G_{\text{gas}}$.

6

$$7 \quad G_{\text{H}^+(\text{g})} = -6.28 \text{ kcal/mol} ; \Delta G_{\text{H}^+(\text{sol})} = -264.61 \text{ kcal/mol}$$

$$8 \quad \Delta G_{\text{gas}}^1 = G_{\text{HDO2A}^-(\text{g})} - G_{\text{DO2A}^{2-}(\text{g})} - G_{\text{H}^+(\text{g})} = -388.66 \text{ kcal/mol}$$

$$9 \quad \Delta \Delta G_{\text{sol}}^1 = \Delta G_{\text{HDO2A}^-(\text{sol})} - \Delta G_{\text{DO2A}^{2-}(\text{sol})} - \Delta G_{\text{H}^+(\text{sol})}$$

$$10 \quad = -62.67 + 153.89 + 264.61 = 355.83 \text{ kcal/mol}$$

$$11 \quad \Delta G_{(\text{aq})}^1 = -388.66 + 355.83 = -32.83 \text{ kcal/mol}$$

$$12 \quad \Delta G_{\text{DO2A}^{2-}(\text{aq})}^1 = \Delta G_{\text{gas}}^1 + \Delta \Delta G_{\text{sol}}^1 = -32.83 \text{ kcal/mol} = -2.303 \times 1.987 \times 298.1 \times \log K_{\text{H}}^1$$

$$13 \quad \log K_{\text{H}}^1 = 24.07 \text{ (cal.) v.s } \log K_{\text{H}}^1 = 10.94 \text{ (exp.)}$$

$$14 \quad \delta^1 = \log K_{\text{H}}^1(\text{cal.}) - \log K_{\text{H}}^1(\text{exp.}) = 13.13$$

15

$$16 \quad \Delta G_{\text{gas}}^2 = G_{\text{H}_2\text{DO2A}(\text{g})} - G_{\text{HDO2A}^-(\text{g})} - G_{\text{H}^+(\text{g})} = -332.90 \text{ kcal/mol}$$

$$17 \quad \Delta \Delta G_{\text{sol}}^2 = \Delta G_{\text{H}_2\text{DO2A}(\text{sol})} - \Delta G_{\text{HDO2A}^-(\text{sol})} - \Delta G_{\text{H}^+(\text{sol})}$$

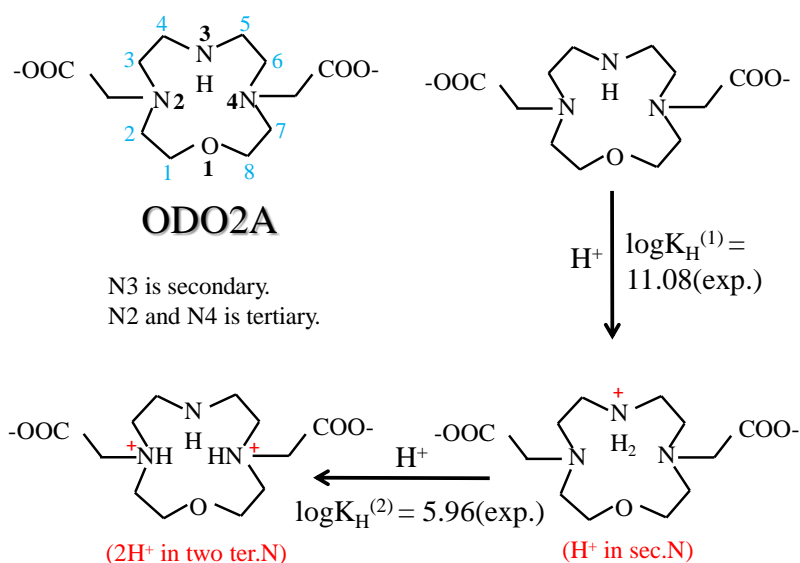
$$18 \quad = -12.99 + 62.67 + 264.61 = 314.29 \text{ kcal/mol}$$

$$19 \quad \Delta G_{(\text{aq})}^2 = -332.90 + 314.29 = -18.61 \text{ kcal/mol}$$

$$20 \quad \Delta G_{\text{DO2A}^{2-}(\text{aq})}^2 = \Delta G_{\text{gas}}^2 + \Delta \Delta G_{\text{sol}}^2 = -18.61 \text{ kcal/mol} = -2.303 \times 1.987 \times 298.1 \times \log K_{\text{H}}^2$$

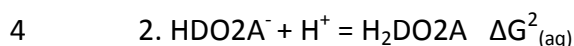
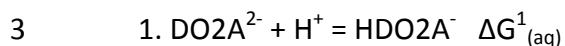
$$21 \quad \log K_{\text{H}}^2 = 13.64 \text{ (cal.) v.s } \log K_{\text{H}}^1 = 9.55 \text{ (exp.)}$$

$$22 \quad \delta^2 = \log K_{\text{H}}^2(\text{cal.}) - \log K_{\text{H}}^2(\text{exp.}) = 4.09$$



1

2 In Water:



5 $\Delta G_{\text{ODO2A}^{2-}}^{1(\text{aq})} = \Delta G_{\text{gas}}^1 + \Delta \Delta G_{\text{sol}}^1 = -2.303 \times RT \times \log K_{\text{H}}^1 = -2.303 \times 1.987 \times 298.1 \times \log K_{\text{H}}^1$

6 $\Delta G_{\text{ODO2A}^{2-}}^{2(\text{aq})} = \Delta G_{\text{gas}}^2 + \Delta \Delta G_{\text{sol}}^2 = -2.303 \times RT \times \log K_{\text{H}}^2 = -2.303 \times 1.987 \times 298.1 \times \log K_{\text{H}}^2$

species	G_{gas}^a	G_{aq}^a	ΔG_{sol}^b
ODO2A ²⁻	-1009.967321	-1010.212968	-154.14
HODO2A ⁻	-1010.619126	-1010.711448	-57.93
H ₂ ODO2A	-1011.087590	-1011.160575	-45.80

7 ^a In atomic unit, hartree (1 hartree = 627.5 kcal/mol). ^b In kcal/mol.

8 * G_{gas} is the Gibbs free energy calculated by B3LYP/6-31G* in gas phase, G_{sol} is

9 the Gibbs free energy calculated by B3LYP/6-31G* in aqueous solution

10 (PCM/UFF), $\Delta G_{\text{sol}} = G_{\text{aq}} - G_{\text{gas}}$.

11

12 $G_{\text{H}^+(\text{g})} = -6.28 \text{ kcal/mole} ; \Delta G_{\text{H}^+(\text{sol})} = -264.61 \text{ kcal/mol}$

13 $\Delta G_{\text{gas}}^1 = G_{\text{HODO2A}^-(\text{g})} - G_{\text{ODO2A}^{2-}(\text{g})} - G_{\text{H}^+(\text{g})} = -402.73 \text{ kcal/mol}$

14 $\Delta \Delta G_{\text{sol}}^1 = \Delta G_{\text{HODO2A}^-(\text{sol})} - \Delta G_{\text{ODO2A}^{2-}(\text{sol})} - \Delta G_{\text{H}^+(\text{sol})}$

1
$$= -57.93 + 154.14 + 264.61 = 360.82 \text{ kcal/mol}$$

2
$$\Delta G_{(aq)}^1 = -402.73 + 360.82 = -41.91 \text{ kcal/mol}$$

3
$$\Delta G_{(aq)}^1 = \Delta G_{gas}^1 + \Delta \Delta G_{sol}^1 = -41.91 \text{ kcal/mole} = -2.303 \times 1.987 \times 298.1 \times \log K_H^1$$

4
$$\log K_H^1 = 30.72 \text{ (cal.) v.s } \log K_H^1 = 11.08 \text{ (exp.)}$$

5
$$\delta^1 = \log K_H^1 \text{ (cal.)} - \log K_H^1 \text{ (exp.)} = 19.72$$

6

7
$$\Delta G_{gas}^2 = G_{H_2ODO_2A(g)} - G_{HODO_2A-(g)} - G_{H+(g)} = -287.68 \text{ kcal/mol}$$

8
$$\Delta \Delta G_{sol}^2 = \Delta G_{H_2ODO_2A(sol)} - \Delta G_{HODO_2A-(sol)} - \Delta G_{H+(sol)}$$

9
$$= -45.80 + 57.93 + 264.61 = 276.74 \text{ kcal/mol}$$

10
$$\Delta G_{(aq)}^2 = -287.68 + 276.74 = -10.94 \text{ kcal/mol}$$

11
$$\Delta G_{(aq)}^2 = \Delta G_{gas}^2 + \Delta \Delta G_{sol}^2 = -10.94 \text{ kcal/mol} = -2.303 \times 1.987 \times 298.1 \times \log K_H^2$$

12
$$\log K_H^2 = 8.02 \text{ (cal.) v.s } \log K_H^2 = 5.96 \text{ (exp.)}$$

13
$$\delta^2 = \log K_H^2 \text{ (cal.)} - \log K_H^2 \text{ (exp.)} = 2.06$$

14 **TABLE S1:** Comparison of experimental ($\log K_{H,exp}$) and calculated ($\log K_{H,calc}$)
 15 protonation constants using the TC method. (All free energy in kcal/mol). (1-13)

Reaction	ΔG_{aq}	ΔG_{gas}	$\Delta \Delta G_{sol}$	$\log K_{H,exp}^a$	$\log K_{H,calc}^b$	δ
$DO_2A^{2-} + H^+ = HDO_2A^-$	-32.83	-388.66	355.83	10.94	24.07	13.13
$HDO_2A^- + H^+ = H_2DO_2A$	-18.61	-332.90	314.29	9.55	13.64	4.09
$ODO_2A^{2-} + H^+ = HODO_2A^-$	-41.91	-402.73	360.82	11.08	30.72	19.72
$HODO_2A^- + H^+ = H_2ODO_2A$	-10.94	-287.68	276.74	5.96	8.02	2.06

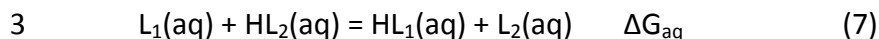
16 ^aExperimental protonation constants at 25°C. For DO_2A^{2-} , ref. 8a; for ODO_2A^{2-} , ref. 9.

17 ^bThermodynamic cycle method was used by B3LYP/6-31G* and PCM-UFF model for
 18 Gibb's Free Energy.

19

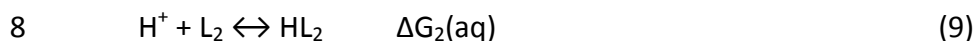
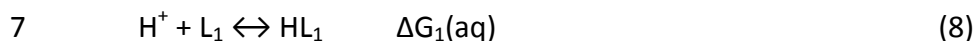
20

1 **II. Calculation of protonation constants using the Isodesmic Reactions IRn**
2 **method.**



4 $L_{(2)}$ is the reference molecule

5 ✦ The main challenge associated with the use of isodesmic reaction is the
6 selection of the appropriate reference molecule.



9 $\Delta G_1(aq)$ (planned to computed molecule)

10 $\Delta G_2(aq)$ (experimental value of the reference molecule)

11 *Two molecules (L_1 & L_2) must be in the same ionic strength and temperature.

12

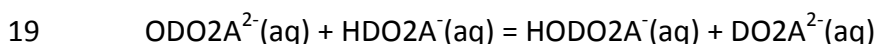
13 $\Delta G_1(aq) = G_{aq}(HL_1) - G_{aq}(H^+) - G_{aq}(L_1) \quad (10)$

14 $\Delta G_2(aq) = G_{aq}(HL_2) - G_{aq}(H^+) - G_{aq}(L_2) \quad (11)$

15 $\Delta G_{aq} = \Delta G_1(aq) - \Delta G_2(aq) = G_{aq}(HL_1) - G_{aq}(L_1) - G_{aq}(HL_2) + G_{aq}(L_2) \quad (12)$

16 ✦ Where the uncertainty related to $G_{aq}(H^+)$ is no more applicable as this term
17 cancels.

18 $L_1 = ODO_2A^{2-}$; $L_2 = DO_2A^{2-}$ (as reference molecule)



20 $\Delta G_{aq}^1 = \Delta G_{ODO_2A^{2-}}^1(aq) - \Delta G_{DO_2A^{2-}}^1(aq)$

21 $= G_{aq}(HODO_2A^-) - G_{aq}(ODO_2A^{2-}) - G_{aq}(HDO_2A^-) + G_{aq}(DO_2A^{2-})$

22 ✦ $\Delta G_{ODO_2A^{2-}}^1(aq) = \Delta G_{DO_2A^{2-}}^1(aq)$ (exp.)

23 $+ G_{aq}(HODO_2A^-) - G_{aq}(ODO_2A^{2-}) - G_{aq}(HDO_2A^-) + G_{aq}(DO_2A^{2-})$

24

25 Part 1: $\Delta G_{DO_2A^{2-}}^1(aq) = -2.303 \times 1.987 \times 298.1 \times 10.94 = -14.92$ kcal/mol

26 Part 2: $\Delta G_{aq} = G_{aq}(HODO_2A^-) - G_{aq}(ODO_2A^{2-}) - G_{aq}(HDO_2A^-) + G_{aq}(DO_2A^{2-})$

27 $= -1010.711448 + 1010.212968 + 990.826212 - 990.342199$

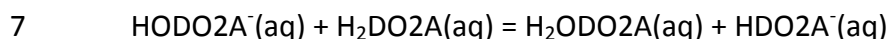
1 = - 0.014467 (a.u.) = - 9.08 kcal/mol

2 $\Delta G_{\text{ODO2A2}^{-1}(\text{aq})} = - 14.9235 - 9.0780 = -24.00 \text{ kcal/mol} = -$
 3 $2.303 \times 1.987 \times 298.1 \times \log K_{\text{H}}^1$

4 $(\text{ODO2A}) \log K_{\text{H}}^1 = 17.59 \text{ (cal.)}$

5 $\Delta \delta^1 = \log K_{\text{H}}^1(\text{cal.}) - \log K_{\text{H}}^1(\text{exp.}) = 17.59 - 11.08 = 6.51$

6



8 $\Delta G_{\text{aq}}^2 = \Delta G_{\text{ODO2A2}^{-2}(\text{aq})} - \Delta G_{\text{DO2A2}^{-2}(\text{aq})}$

9 $= G_{\text{aq}}(\text{H}_2\text{ODO2A}) - G_{\text{aq}}(\text{HODO2A}^{-}) - G_{\text{aq}}(\text{H}_2\text{DO2A}) + G_{\text{aq}}(\text{HDO2A}^{-})$

10 $\star \Delta G_{\text{ODO2A}^2(\text{aq})} = \Delta G_{\text{DO2A}^2(\text{aq})}(\text{exp.})$

11 $+ G_{\text{aq}}(\text{H}_2\text{ODO2A}) - G_{\text{aq}}(\text{HODO2A}^{-}) - G_{\text{aq}}(\text{H}_2\text{DO2A}) + G_{\text{aq}}(\text{HDO2A}^{-})$

12

13 Part 1: $\Delta G_{\text{DO2A}^2(\text{aq})} = -2.303 \times 1.987 \times 298.1 \times 9.55 = - 13.03 \text{ kcal/mol}$

14 Part 2: $\Delta G_{\text{aq}} = G_{\text{aq}}(\text{H}_2\text{ODO2A}) - G_{\text{aq}}(\text{HODO2A}^{-}) - G_{\text{aq}}(\text{H}_2\text{DO2A}) + G_{\text{aq}}(\text{HDO2A}^{-})$

15 $= -1011.160575 + 1010.711448 + 991.287563 - 990.826212$

16 $= 0.012224 \text{ (a.u.)} = 7.6706 \text{ kcal/mol}$

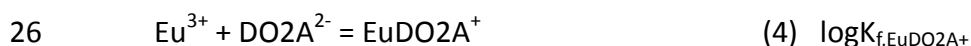
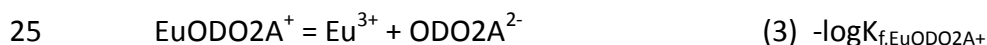
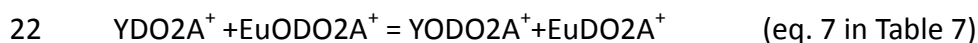
17 $\Delta G_{\text{ODO2A}^2(\text{aq})} = - 13.0274 + 7.6706 = - 5.36 \text{ kcal/mol} = -2.303 \times 1.987 \times 298.1 \times \log K_{\text{H}}^2$

18 $(\text{ODO2A}^{2-}) \log K_{\text{H}}^2 = 3.93 \text{ (cal.)}$

19 $\Delta \delta^2 = \log K_{\text{H}}(\text{cal.}) - \log K_{\text{H}}(\text{exp.}) = 3.93 - 5.96 = -2.03$

20

21 **III. Calculation of $\Delta \log K = \log K_{\text{f},\text{YDO2A}} - \log K_{\text{f},\text{YODO2A}}$ values:**



1 (1)+(2)+(3)+(4) : $\Delta G = -2.303 \times RT \log K_f$

2 $\Delta G = -2.303RT(\log K_{f, YODO2A+} - \log K_{f, YDO2A+} + \log K_{f, EuDO2A+} - \log K_{f, EuODO2A+})$

3 $0.02 \times 1000 = -2.303 \times 1.987 \times 298.15(\log K_{f, YODO2A+} - \log K_{f, YDO2A+} + 12.99 - 12.27)$

4 $\Delta \log K_f = \log K_{f, YDO2A+} - \log K_{f, YODO2A+} = +0.71$