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Communications

Comparisons of N–H, C–H, O–H, and S–H Heterolytic and Homolytic Bond Strengths in Aqueous and Dimethyl Sulfoxide Solution

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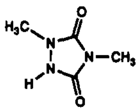
Summary: Analysis of relative homolytic bond dissociation energy (ΔBDE) data for 16 different molecules, obtained via incorporation of aqueous and dimethyl sulfoxide (DMSO) solution acid–base and redox data into thermochemical cycles, indicates that DMSO and water as solvent have minimal differential effects on the homolytic strengths of labile N–H, C–H, O–H, and S–H bonds for the species in this study.

The solvent dependence of kinetic[1] and thermodynamic[2] parameters for reactions involving organic ions, reactions in which covalent bonds are formed and/or destroyed in a heterolytic sense, has long been recognized. For example, aqueous and DMSO solution pK_a's of 5.3[3] and 11.4[4] for 1,4-dimethylurazole (1) suggest that the conjugate base derived from 1 (i.e., 1 − H^+) is stabilized via hydrogen-bonding interactions (largely absent in the nonhydroxylic DMSO) afforded it by water. Similar interactions account for the difference between the aqueous (pK_a = 4.8) and DMSO (pK_a = 7.4) acidities for Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione).[5]



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It has been demonstrated that the *rates* of reactions that involve the homolytic cleavage of bonds[6] present in closed shell neutral organic species (resulting in the initial formation of two organic radicals) are insensitive to solvent changes. There have been a few comparisons of the homolytic strengths of bonds present in solution-phase species, from a thermodynamic perspective. With the aid of photoacoustic techniques, O–H BDEs for five substituted phenols (in isooctane)[7] and C–H BDEs for five alcohols, acetonitrile, and the acetate anion (in water) have been determined.[8] Other solution-phase homolytic bond strength data have resulted from utilization of thermochemical cycles for organic species dissolved in water[9] and in DMSO.[10] To our knowledge, there are no published

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[9] (a) $BDE_{(aq)} = 1.37\ pK_a + 23.06E_{ox} + 56.8$ kcal/mol.[9b] (b) Friedrich, L. E. *J. Org. Chem.* **1983**, *48*, 3851–3852.

[10] (a) $BDE_{(DMSO)} = 1.37pK_a + 23.06E_{ox} + 55.4\text{–}55.9$ kcal/mol.[10b] (b) Bordwell, F. G.; Cheng, J.-P.; Harrelson, J. A., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 1229–1231.

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Table I. Aqueous Acidity (pK_a and ΔpK_a[17]) and Relative Homolytic Bond Dissociation Energy (ΔBDE$_{aq}$)[18] Data for N–H, C–H, O–H, and S–H Bonds in Substrates H–A (n) and Aqueous Oxidation Potentials[19] and Relative Oxidation Potentials[20] for the Conjugate Bases (n – H$^+$) Derived from H–A

substrate (**n**)	p$K_{a(n)}$	ΔpK_a (kcal/mol)	$E_{ox(n\text{-}H^+)}{}^a$ (V)	ΔE_{ox} (kcal/mol)	ΔBDE$_{aq}$ (kcal/mol)
1,4-dimethylurazole (**1**)	5.3^b	(0.0)	0.78	(0.0)	(0.0)
1,2-dimethylurazole (**2**)	7.5^b	3.0	1.24	10.6	13.6
succinimide (**3**)	9.5^b	5.8	1.11	7.6	13.4
hydrazoic acid (**4**)	4.7^c	–0.8	1.31	12.2	11.4
4,4-dimethylpyrazolidine-3,5-dione (**5**)	6.0^b	1.4	0.75	–0.7	0.7
1-methylhydantoin (**6**)	9.1^b	5.2	1.14	8.3	13.5
1-methyl-2-phenylurazole (**7**)	6.97^d	2.3	1.30	12.0	14.3
1-phenyl-3-methoxyurazole (**8**)	6.93^d	2.2	1.05	6.2	8.4
3-methylhydantoin (**9**)	11.4^e	8.4	1.42	14.8	23.2
malononitrile (**10**)	11.0^c	8.2	0.89	2.5	10.7
Meldrum's acid (**11**)	4.85^f	–0.6	1.33^f	12.7	12.5
2,4-pentanedione (**12**)	8.9^f	5.3	1.07^f	6.7	12.0
dimedone (**13**)	5.2^f	0.3	1.22^f	10.1	10.4
phenol (**14**)	10.0^c	6.4	0.72	–1.4	5.0
4-chloro-2,6-dinitrophenol (**15**)	3.0^c	–3.2	1.43	15.0	11.8
thiophenol (**16**)	6.5^c	1.6	0.50	–6.5	–4.9

^{a} All redox data from this work except where noted. ^{b} Reference 21. ^{c} Reference 2b. ^{d} Reference 22. ^{e} This work. ^{f} Reference 14.

Table II. DMSO Acidity (pK_a and ΔpK_a[17]) and Relative Homolytic Bond Dissociation Energy (ΔBDE$_{DMSO}$[18]) Data for N–H, C–H, O–H, and S–H Bonds in Substrates H–A (n) and DMSO Oxidation Potentials[23] and Relative Oxidation Potentials[20] for the Conjugate Bases (n – H$^+$) Derived from H–A

substrate (**n**)	p$K_{a(n)}$	ΔpK_a (kcal/mol)	$E_{ox(n\text{-}H^+)}{}^a$ (V)	ΔE_{ox} (kcal/mol)	ΔBDE$_{DMSO}$ (kcal/mol)
1,4-dimethylurazole (**1**)	11.4^b	(0.0)	0.45	(0.0)	(0.0)
1,2-dimethylurazole (**2**)	12.35^b	1.3	0.96	11.8	13.1
succinimide (**3**)	14.75^b	4.6	0.74	6.7	11.3
hydrazoic acid (**4**)	7.9^c	–4.8	1.14	15.9	11.1
4,4-dimethylpyrazolidine-3,5-dione (**5**)	13.5^b	3.3	0.36	–2.1	1.2
1-methylhydantoin (**6**)	14.7^b	4.5	0.73	6.5	11.0
1-methyl-2-phenylurazole (**7**)	10.8^d	–2.2	1.15	16.1	13.9
1-phenyl-3-methoxyurazole (**8**)	10.65^d	–1.0	0.90	10.4	9.4
3-methylhydantoin (**9**)	19.0^d	10.4	1.05	13.8	24.2
malononitrile (**10**)	11.0^c	–0.1	0.79	7.8	7.7
Meldrum's acid (**11**)	7.4^e	–5.1	1.25^f	18.4	13.3
2,4-pentanedione (**12**)	13.6^e	3.4	0.77^f	7.4	10.8
dimedone (**13**)	11.2^e	0.1	0.94^f	11.3	11.4
phenol (**14**)	18.0^c	9.0	0.42^g	–0.7	8.3
4-chloro-2,6-dinitrophenol (**15**)	3.6^c	–10.7	1.44	22.8	12.1
thiophenol (**16**)	10.3^c	–1.5	0.39^g	–1.4	–2.9

^{a} All redox data from this work except where noted. ^{b} Reference 21. ^{c} Reference 2b. ^{d} This work. ^{e} Reference 5. ^{f} Reference 14. ^{g} Reference 10b.

thorough examinations of the effect(s) of solvents on the homolytic strengths of various bonds contained in organic species. Presented in this communication are results that summarize our investigations of the relative strengths of various N–H, C–H, O–H, and S–H bonds present in 16 organic molecules dissolved in aqueous and DMSO solution.

Previous articles have shown that acidity data for a given family of organic acids (H–A), when combined with oxidative data for their respective conjugate bases (A$^-$), as shown in eq 1, (all parameters in kcal/mol) enables accurate comparisons of the homolytic strengths of the bonds connecting hydrogen atoms H$^\bullet$ to fragments A$^\bullet$.[11] Listed in Table I are the aqueous solution acid–base and redox data necessary to determine the relative homolytic strengths for labile H–A bonds present in **1–16**. Listed in Table II are the analogous data for **1–16**, when dissolved in DMSO. The resulting ΔBDE(H–A) data enable comparisons of the effects of structural changes on homolytic bond strengths for substrates dissolved in aqueous and DMSO solution, from a free energy perspective. Since, at 0.1 V/s scan rates, the CV oxidations of the anion derived from 1,4-dimethylurazole (**1** – H$^+$) are reversible in DMSO and water,[12] the redox couple

$$\Delta\mathrm{BDE(H{-}A)} = \Delta\mathrm{p}K_a\mathrm{(H{-}A)} + \Delta E_{ox}(\mathrm{A}^-) \qquad (1)$$

$$[\mathbf{1} - \mathrm{H}^+ \underset{+e^-}{\overset{-e^-}{\rightleftharpoons}} \mathbf{1} - \mathrm{H}^\bullet]$$

has been chosen as the reference upon which the ΔE_{ox} values for the anions derived from **2–16** are based, in both Tables I and II. It follows that the ΔBDE values in Tables I and II for **2–16** are relative to the N–H bond strength in 1,4-dimethylurazole (**1**).

Inspection of the ΔpK_a, ΔE_{ox}(A$^-$), and ΔBDE$_{aq}$ data in Table I reveals that the aqueous solution acidities, anion

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oxidation potentials, and homolytic bond strengths for **1**–**16** vary by ca. 12, 22, and 28 kcal/mol, respectively. In DMSO, the ΔpK_a, $\Delta E_{ox}(A^-)$, and ΔBDE_{DMSO} data (Table II) vary by ca. 21, 25, and 27 kcal/mol, respectively. There is no apparent relationship between heterolytic and homolytic H–A bond strengths for these species, since the least-squares correlation coefficients (r) are 0.37 (in water) and 0.21 (in DMSO) when, in either solvent ΔpK_a is plotted vs ΔBDE(H–A). As expected from the varying degrees of hydrogen-bonding, stabilization afforded anions derived from **1**–**16** (in the hydroxylic solvent water), a rather poor least-squares line results when the $\Delta pK_{a(DMSO)}$ values in Table II are plotted vs the $\Delta pK_{a(aq)}$ values in Table I (r = 0.84 and slope = 1.3).

On the other hand, when, for **1**–**16**, $\Delta BDE_{(DMSO)}$ (Table II) is plotted vs $\Delta BDE_{(aq)}$ (Table I), the least-squares line has a near unit slope (0.91) and a correlation coefficient of 0.96. Stated differently, for a given substrate, there is remarkably good agreement between the $\Delta BDE_{(DMSO)}$ values in Table II and the corresponding $\Delta BDE_{(aq)}$ values in Table I. Consider some of the N–H bond data first. In a homolytic sense, the N–H bond in 3-methylhydantoin (**9**, a surprisingly acidic species; in DMSO, its $pK_a = 19.0$ while the pK_a of 1,3-dimethylurea is 27.5[13]), compared to the N–H bond in **1**, is 23 kcal/mol stronger when both **9** and **1** are dissolved in water and 24 kcal/mol stronger when both are dissolved in DMSO. Similarly, the imide N–H bond in 1,2-dimethylurazole (**2**), again compared to the N–H bond in **1**, is 14 kcal/mol stronger when both are dissolved in water and 13 kcal/mol when both are dissolved in DMSO. The N–H bond in hydrazoic acid (**4**) is 11 kcal/mol stronger than the N–H bond in **1**, in both aqueous and DMSO solutions, while the N–H bond in 1-phenyl-3-methoxyurazole (**8**) is 8 and 9 kcal/mol (in aqueous and DMSO solutions, respectively) stronger than the N–H bond in **1**.

C–H bonds present in carbon acids behave similarly: the C–H bond in malononitrile (**10**) is 11 and 8 kcal/mol stronger (in aqueous and DMSO solutions, respectively) than the N–H bond in **1**, in each solvent. These C–H ΔBDE data complement those previously reported for Meldrum's acid (**11**), 2,4-pentanedione (**12**), and dimedone (**13**), in that the relative strengths of the bonds in these species are not substantially affected by changing the medium in which they are dissolved from water to DMSO.[14] Further inspection of the data in Tables I and II reveals that the homolytic strengths of the O–H bonds in phenol (**14**) and 4-chloro-2,6-dinitrophenol (**15**), as well as the S–H bonds in thiophenol (**16**), are also largely insensitive to DMSO/aqueous medium effects. When the data in Tables I and II are evaluated in their totality, they point to minimal differential solvent effects on the homolytic strengths of the labile N–H, C–H, O–H, and S–H bonds present in **1**–**16**. The ΔBDE data in both solvents are therefore consistent with published (kinetic) research[6] in suggesting that solvent effects on radical ($A^\bullet$) stabilities, relative to H–A stabilities, are small in magnitude.

Published articles have outlined cycles that attempt to convert relative aqueous and DMSO (free energy) BDE data such as those in Tables I and II into absolute BDEs comparable to gas-phase (enthalpic) data.[9,10] Inserting the raw data from Tables I and II into the appropriate equations[9b,10b] yields estimates for the absolute BDEs that generally agree within 1–2 kcal/mol. However, the "absolute" nature of BDEs determined in this way is questionable, in part because they depend on the assumption that $\Delta G°_{[H\bullet_{(g)} \rightleftharpoons H\bullet_{(aq)}]}$ is equal to zero.[9] Additionally, the published cycle that describes determinations of absolute enthalpic BDEs (using DMSO data) is flawed in that the estimated value for $\Delta G°_{[H\bullet_{(g)} \rightleftharpoons H\bullet_{(DMSO)}]}$ (−5.7 kcal/mol) is nearly equal in magnitude but opposite in sign to the actual value of $\Delta G°_{[H_{2(g)} \rightleftharpoons H_{2(DMSO)}]}$ (5.6 kcal/mol[15]), the equilibrium that was used to model the free energy of transfer of a hydrogen atom from the gaseous state to DMSO solution.[10] Finally, the cycles in both DMSO and water depend on assumptions regarding the relative entropies of substrates **1**–**16** and their corresponding radicals **1** − $H^\bullet$ to **16** − $H^\bullet$.[16] We are continuing our investigations of the homolytic and heterolytic strengths of chemical bonds present in various organic molecules.

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Registry No. **1**, 34771-26-1; **2**, 5302-26-1; **3**, 123-56-8; **4**, 7782-79-8; **5**, 29005-43-4; **6**, 616-04-6; **7**, 14500-21-1; **8**, 14500-22-2; **9**, 6843-45-4; **10**, 109-77-3; **11**, 2033-24-1; **12**, 123-54-6; **13**, 126-81-8; **14**, 108-95-2; **15**, 88-87-9; **16**, 108-98-5.

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(12) (a) The reversibility of the oxidation of the anion derived from 1,4-dimethylurazole is not unexpected in light of the kinetic stability (persistence) exhibited by selected urazolyl radicals.[12b] (b) Pirkle, W. H.; Gravel, P. L. *J. Org. Chem.* **1978**, *43*, 808–815.

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(14) Bausch, M. J.; Guadalupe-Fasano, C.; Gostowski, R.; Selmarten, D.; Vaughn, A. *J. Org. Chem.* **1991**, *56*, 5640–5642.

(15) *Solubility Data Series: Hydrogen and Deuterium Vol 5/6*; Young, C. L., Ed.; Pergamon: New York, 1981; Vol. 5/6, p xviii, 259–261.

(16) Golden, D. M.; Bierbaum, V. M.; Howard, C. J. *J. Phys. Chem.* **1990**, *93*, 5413–5415.

(17) At 25 °C, 1 pK_a unit is equal to 1.37 kcal/mol. Therefore, in Table I, for a given substrate **n**, ΔpK_a (kcal/mol) = $1.37[pK_{a(n)} - 5.3 + \log X_n]$, while in Table II, $\Delta pK_a = 1.37[pK_{a(n)} - 11.4 + \log X_n]$, where 5.3 and 11.4 are the pK_as for 1,4-dimethylurazole (**1**) in aqueous and DMSO solution, respectively, and X_n is equal to the number of acidic protons in **n**. Positive ΔpK_a values signify that the molecule in question is a weaker acid than 1,4-dimethylurazole.

(18) The ΔBDE values in Tables I and II have been determined with the aid of eq 1. Positive ΔBDE values signify that the bond in question is stronger than the analogous bond in 1,4-dimethylurazole (**1**). The ΔBDE data are believed to be accurate to ±2 kcal/mol.

(19) (a) Aqueous cyclic voltammetry (CV) conditions: 0.1 V/s scan rate; 0.1 M K^+Cl^- electrolyte solution buffered to pH 10 (except for phenol, which was buffered to pH 12); glass carbon working and Ag/AgCl reference electrodes [reference: $Fe(CN)_6^{3-}$-$Fe(CN)_6^{2-}$ = 0.458 V (vs NHE)[19b]]. In the nitrogenated electrochemical cell, the anions were generated by adding the neutral acid H–A to the buffered K^+Cl^- solution. The E_{ox} values are the anodic peak potentials as reported by a BAS 100A electrochemical analyzer, are usually the averages of several runs for each compound, and are reproducible to ≤25 mV. The uncertainties in the aqueous ΔBDE values are estimated to be ±2 kcal/mol. (b) Kolthoff, I. M.; Tomsicek, W. J. *J. Phys. Chem.* **1935**, *39*, 945–954.

(20) At 25 °C, 1 V is equal to 23.06 kcal/mol. In Table I, for the anion derived from a given substrate **n**, ΔE_{ox} (kcal/mol) = $23.06[E_{ox(n-H^+)} - 0.78]$, while in Table II, ΔE_{ox} (kcal/mol) = $23.06[E_{ox(n-H^+)} - 0.45]$, where 0.78 and 0.45 are the E_{ox} values (in V) for the 1,4-dimethylurazolide anion in aqueous and DMSO solution, respectively.

(21) Bausch, M. J.; David, B.; Dobrowolski, P.; Guadalupe-Fasano, C.; Gostowski, R.; Selmarten, D.; Prasad, V.; Vaughn, A.; Wang, L.-H. *J. Org. Chem.* **1991**, *56*, 5643–5651.

(22) Gordon, A. A.; Katritzky, A. R.; Popp, F. D. *Tetrahedron Supplement No. 7*, pp 213–217.

(23) (a) DMSO CV conditions: 0.1 V/s scan rate; 0.1 M $Et_4N^+BF_4^-$ electrolyte; Pt working and Ag/AgI reference electrodes (ferrocene/ferrocenium = +0.875 V reference, values corrected to NHE_{aq} by subtracting 0.125 V). In the argonated electrochemical cell, the anions were present in 1–2 mM concentrations. The E_{ox} values are the anodic peaks potentials as reported by a BAS 100A electrochemical analyzer, are the averages of several runs for each compound, and are reproducible to ≤25 mV (ca. 0.5 kcal/mol). The uncertainties in the DMSO ΔBDE values are estimated to be ±2 kcal/mol.