

Correlation analysis between equilibria for addition of semicarbazide and hydroxylamine to several carbonyl compounds and their equilibria for addition of water

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Received 25 April 2002; revised 15 October 2002; accepted 12 November 2002

ABSTRACT: Equilibrium constants for semicarbazide and hydroxylamine addition to several carbonyl compounds are reported and compared with those for addition of water. The results are correlated by the linear free relationship $\log K_{\text{add}} = Sw + B$, where w is a measure of the reactivity of a given compound to water addition, S is a measure of the sensitivity of the examined reactions compared with the model of hydration equilibrium constants and B is a constant for a given reaction series. Copyright © 2003 John Wiley & Sons, Ltd.

KEYWORDS: equilibria; semicarbazide; hydroxylamine; water; carbonyl compounds; correlation analysis

INTRODUCTION

There is a general consensus that the most reactive carbonyl compounds to addition of nitrogen nucleophiles are also the most hydrated in aqueous solutions. This work was intended to establish a quantitative relationship between equilibrium constants for addition of semicarbazide and hydroxylamine to a series of carbonyl compounds and their degree of hydration. This relationship is expressed by $\log K_{\text{add}} = Sw + B$, where w is defined as $\log K_{\text{hyd}}^*/K_{\text{hyd}}$, K_{hyd}^* and K_{hyd} being the values of the equilibrium constants of water addition to a given compound and of benzaldehyde respectively, S is a measure of the sensitivity of the examined series compared with the model of hydration equilibrium constants and B is a constant for a given reaction series.

EXPERIMENTAL

Most of the values of the equilibrium constants for semicarbazide, hydroxylamine and water have been taken from the literature. Here we describe the evaluation of the equilibrium constant for the addition of semicarbazide to 4-trimethylammoniumbenzaldehyde iodide and the same constant for the equilibrium between hydroxylamine and 3-nitrobenzaldehyde, data not found in the literature.

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Materials. 4-Trimethylammoniumbenzaldehyde iodide was prepared by refluxing 4-dimethylaminobenzaldehyde with methyl iodide. The product was carefully recrystallized to a constant melting-point, 157–158 °C (lit.:¹ 156–157 °C). 3-Nitrobenzaldehyde was obtained commercially. Semicarbazide and hydroxylamine hydrochlorides were obtained commercially and purified by crystallization from ethanol. Solutions of these reagents were prepared just prior to use to minimize the possibility of decomposition. Distilled water was used throughout.

Equilibrium constant for addition of semicarbazide to 4-trimethylammoniumbenzaldehyde iodide. This constant was determined spectrophotometrically at 283 nm, 30 °C, ionic strength 0.5 (KCl), pH 8.13 in 0.125 M phosphate buffer. An average of 30 determinations were made. The equilibrium constant was obtained from the negative intercept of a plot of $1/\Delta A_{\text{eq}}^{\circ}$ vs $1/[\text{amine}]_{\text{fb}}$. A value of 15 ± 0.2 was obtained.

Equilibrium constant for addition of hydroxylamine to 3-nitrobenzaldehyde. This constant was determined kinetically in 0.125 M phosphate buffer, at pH 6.52, ionic strength 0.5 (KCl), 30 °C, at 253 nm, from the dependence of pseudo-first-order rate constants for oxime formation, k_{obs} , on the concentration of hydroxylamine free base, at concentrations between 3.16×10^{-3} and 5.07×10^{-2} M. A plot of $1/k_{\text{obs}}$ against $1/[\text{amine}]_{\text{fb}}$ yields an excellent straight line. The equilibrium constant, K_{add} , was determined from the negative intercept on the abscissa. A value of $96 \pm 6 \text{ M}^{-1}$ was obtained.

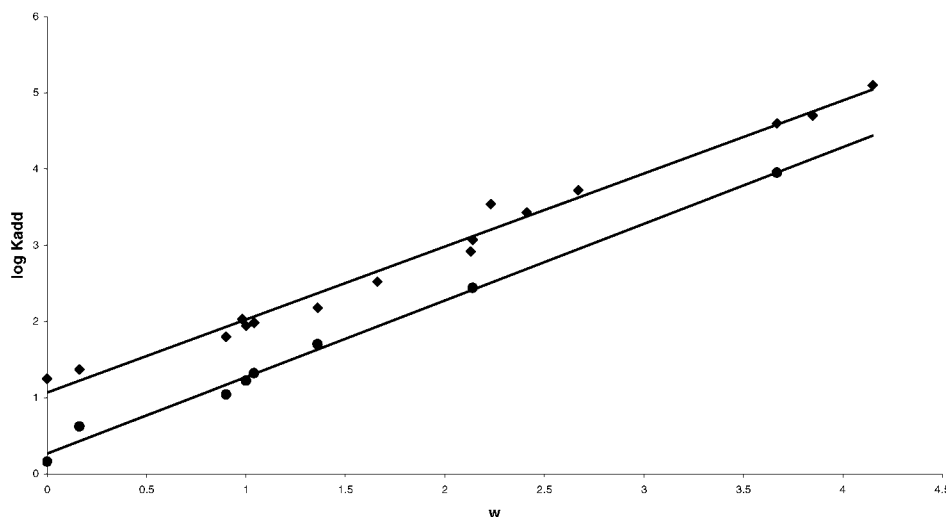


Figure 1. Logarithmic relationship between equilibrium constants for the addition of hydroxylamine and semicarbazide to a series of carbonyl compounds and w , the ratio of the equilibrium constants for hydration $K^*_{\text{hyd}}/K_{\text{hyd}}$. ●, Semicarbazide; ◆, hydroxylamine

RESULTS AND DISCUSSION

Figure 1 shows plots of the logarithms of the addition constants for the addition of semicarbazide and hydroxylamine to several carbonyl compounds against w , defined as $\log K^*_{\text{hyd}}/K_{\text{hyd}}$, where K^*_{hyd} and K_{hyd} are the values of the equilibrium constants of water addition to a given carbonyl compound and of benzaldehyde respectively. Equilibrium constants for the addition to the unhydrated forms of the series of carbonyl compounds from this work and the literature are summarized in Table 1. These equilibrium constants, K_{add} , were calculated from the equilibrium constants for addition to hydrated plus unhydrated substrates, K^{app} , according to the equation,

$$K_{\text{add}} = K^{\text{app}}(1 + K^*_{\text{hyd}}) \quad (1)$$

where K^*_{hyd} is the equilibrium constant for hydration.

Note in Fig. 1 the good correlation of the experimental points in both series of reactions ($r = 0.99$ for both lines), and also the modest difference that the addition constants show with the large change in amine basicity. This is in accord with previous findings² and indicates that the equilibrium constants for addition of amines to the carbonyl group are not strongly dependent on the basicity of the amine. These good correlations have a practical value, as they permit the evaluation of addition constants for the addition of semicarbazide or hydroxylamine to carbonyl compounds when their degrees of hydration, measured under similar conditions, are known.

The fact that both series of the reactions examined have S values near 1 (semicarbazide = 0.96 and hydroxylamine = 1.00) means that they show the same sensitivity to the substituent effects as do the hydration

equilibria, which is not surprising and is the expected behavior when a model reaction, in this case hydration, is very similar to the examined reactions. In all equilibria, an sp^2 carbon in the reactants is converted to an sp^3 carbon connected to two electronegative atoms in the product, hence the energy difference between the products should be small, and it is the energy content of the reactants that principally is responsible for the value of K_{add} ; since the carbonyl compounds examined are common with those of hydration reactions, the values of the K_{add} are only a consequence of the nucleophilicity of the amines, and as this factor is constant along the series it therefore determines the slopes of the lines. With this argument it is easy to understand that both series of reactions show the same sensitivity.

In an earlier study, Sanders and Jencks² noted that the addition of several nitrogen nucleophiles to formaldehyde, 4-pyridinecarboxaldehyde and 4-chlorobenzaldehyde showed the same sensitivity to the affinity of amines towards the carbonyl group. The relationship was expressed by $\log K_{\text{add}} = \Delta\gamma + A$, where γ was defined as a measure of the ability of a given nucleophile to add to the carbonyl group, and its values were calculated from $\log K_{\text{HX}}/K_{\text{H}_2\text{NCH}_3}$, where K_{HX} and $K_{\text{H}_2\text{NCH}_3}$ represent the values of the addition constants of a given amine to 4-pyridinecarboxaldehyde and of methylamine, respectively, Δ is a measure of the sensitivity of a particular carbonyl compound to the affinity of amines toward the carbonyl group and A is a constant for a given reaction series. Note that the chosen model is again a reaction of addition to the carbonyl group: constants of addition of a given amine to 4-pyridinecarboxaldehyde. The difference between the study presented here and the relationship proposed by Sanders and Jencks² is that γ is a measure of the affinity of a given amine to add the

Table 1. Values of equilibrium constants for the addition of water, semicarbazide and hydroxylamine to carbonyl compounds

Carbonyl Compound	K_{hyd}^* ^a (water)	K_{add}^b (M^{-1}) (semicarbazide)	K_{add}^b (M^{-1}) (hydroxylamine)	w^c
2-Quinolincarboxaldehyde ^d	154 ^e		1.27×10^{5f}	4.15
2-Pyridinecarboxaldehyde ^d	77 ^g		5×10^{4h}	3.85
4-Pyridinecarboxaldehyde ^d	52 ^g	9×10^{3i}	4×10^{4h}	3.67
3-Pyridinecarboxaldehyde ^d	5.1 ^g		5.2×10^{3h}	2.67
Pyruvic acid	1.86 ^j		3.5×10^{3k}	2.23
Methyl pyruvate	2.8 ^l		2.7×10^{3m}	2.41
4-Pyridinecarboxaldehyde	1.53 ^g	2.78×10^{2n}	1.2×10^{3h}	2.14
2-Quinolincarboxaldehyde	1.47 ^e		8.25×10^{2f}	2.13
2-Pyridinecarboxaldehyde	0.501 ^g		3.30×10^{2h}	1.66
4-Nitrobenzaldehyde	0.25 ^o	5.01×10^p	1.53×10^{2q}	1.36
3-Pyridinecarboxaldehyde	0.104 ^g		1.06×10^{2h}	0.98
3-Nitrobenzaldehyde	0.08 ^r	2.1×10^p	10.37×10	0.86
4-Trimethylammoniobenzaldehyde iodide	0.11 ^s	1.67×10	8.72×10^q	1.00
Pyruvate anion	0.087 ^j	1.09×10^t	6.3×10^k	0.90
4-Chlorobenzaldehyde	0.016 ⁿ	4.21 ^p	2.4×10^q	0.16
Benzaldehyde	0.011 ^s	1.45 ^p	1.76×10^q	0.00

^a $K_{\text{hyd}}^* = [\text{hydrate}]/[\text{aldehyde}]$.

^b All K_{add} values have been corrected by the equation $K_{\text{add}} = K_{\text{add}}^{\text{app}} (1 + K_{\text{hyd}}^*)$.

^c $w = \log K_{\text{hyd}}^*/K_{\text{hyd}}$ (K_{hyd}^* and K_{hyd} are the values of water addition to a given compound and benzaldehyde, respectively).

^d Conjugate acid.

^e Ref. 5.

^f Ref. 6.

^g Ref. 7.

^h Ref. 8.

ⁱ Taking as a model 4-formyl-1-methylpyridinium ion.⁹

^j Ref. 10.

^k Ref. 11.

^l This value was calculated at 30° from Ref. 12.

^m Ref. 13.

ⁿ Ref. 2.

^o Ref. 14.

^p Ref. 3.

^q Ref. 4.

^r Ref. 15.

^s Ref. 1.

^t Ref. 16.

carbonyl group and w is a measure of the affinity of a given carbonyl compound to water addition. The results in both studies indicate that there is no difference in sensitivity to the carbonyl compound or amine used.

The advantages of using values of w instead of Hammett σ values are that they permit a comparison of addition constants of carbonyl compounds not structurally related to benzenoid molecules and they avoid the unwanted negative deviation observed in Hammett plots when resonance effects on substrate stabilization are present.^{3,4}

REFERENCES

- Greenzaid P. *J. Org. Chem.* 1973; **38**: 3164–3167.
- Sander EG, Jencks WP. *J. Am. Chem. Soc.* 1968; **90**: 6154–6162.
- Anderson BM, Jencks WP. *J. Am. Chem. Soc.* 1960; **82**: 1773–1777.
- Calzadilla M, Malpica A, Cordova T. *J. Phys. Org. Chem.* 1999; **12**: 708–712.
- Abe K, Hirota M, Takeuchi I, Hamada Y. *Bull. Chem. Soc. Jpn.* 1977; **50**: 2028–2032.
- Calzadilla M, Malpica A, Diaz PM. *Int. J. Chem. Kinet.* 1996; **28**: 687–691.
- Cabani S, Gianni P, Matteoli E. *J. Phys. Chem.* 1972; **76**: 2959–2966.
- Malpica A, Calzadilla M, Baumrucker J, Jiménez J, Lopez L, Escobar G, Montes C. *J. Org. Chem.* 1994; **59**: 3398–3401.
- Sojo P, Vilorio F, Malave L, Possamai R, Calzadilla M, Baumrucker J, Malpica A, Moscovi R, Do Amaral L. *J. Am. Chem. Soc.* 1976; **98**: 4519–4525.
- Cooper AJL, Redfield AG. *J. Biol. Chem.* 1975; **250**: 527–532.
- Malpica A, Calzadilla M, Cordova T. *J. Phys. Org. Chem.* 2000; **13**: 162–166.
- Pocker Y, Meany JE, Zadorojny C. *J. Phys. Chem.* 1971; **75**: 792–799.
- Cordova T, Peraza AJ, Calzadilla M, Malpica A. *J. Phys. Org. Chem.* 2002; **15**: 48–51.
- Sayer JM. *J. Org. Chem.* 1975; **40**: 2545–2547.
- Bell RP. *J. Chem. Soc., Perkin Trans. 2* 1976; 1594–1598.
- Jencks WP. *J. Am. Chem. Soc.* 1959; **81**: 475–481.