Hydrogen Isotope Effects in Hydride Transfer Reactions of Formaldehyde and Glyoxal. An *Ab initio* and MNDO SCF-M.O. Study

Indira H. Rajyaguru and Henry S. Rzepa*

Department of Chemistry, Imperial College, London SW7 2AY, U.K.

Ab initio and MNDO calculations predict the hydroxide anion-catalysed intramolecular hydride transfer reaction of glyoxal to exhibit a larger kinetic hydrogen isotope effect than the intermolecular Cannizzaro reaction of formaldehyde.

In contrast to proton transfer reactions between carbon atoms, the properties of simple hydride transfers are less well established, particularly with regard to the importance of tunnelling and the relationship between the transition state structure and the magnitude of the primary kinetic isotope effect.[1] Two apparently simple reactions which are thought to involve a hydride transfer as the rate limiting step are the hydroxide ion-catalysed Cannizzaro reaction of formaldehyde[2] (reaction 1) and the benzilic acid type rearrangement of glyoxal to glycolic acid[3] (reaction 2). The former involves an intermolecular hydride transfer, whereas the latter is thought to involve an intramolecular[4] [1,2] hydride shift *via* a highly bent transition state. Neither reaction has been the subject of published theoretical studies at the *ab initio* SCF-M.O. level.[5] We report such calculations[6] which suggest that both reactions will exhibit significant primary isotope effects, with the intramolecular transfer having the larger values.

$$\mathrm{H_2CO + OH^-} \overset{K_{\mathrm{eq}}}{\rightleftharpoons} \underset{(\mathbf{1})}{\mathrm{H_2C(OH)O^-}} \xrightarrow{k_2} \mathrm{HCO_2H + MeOH} \quad (1)$$

$$\mathrm{OHC{-}CHO + OH^-} \rightleftharpoons \underset{(\mathbf{2})}{\mathrm{OHC{-}CH(OH)O^-}} \longrightarrow \mathrm{CH_2(OH)CO_2H} \quad (2)$$

$$\mathrm{ODC{-}^{13}CHO + OH^-} \longrightarrow \mathrm{CHD(OH)^{13}CO_2H + {}^{13}CHD(OH)CO_2H} \quad (3)$$

$$\mathrm{OD^{13}C{-}CHO + OH^-} \longrightarrow \mathrm{CHD(OH)^{13}CO_2H + {}^{13}CHD(OH)CO_2H} \quad (4)$$

Each mechanism involves the reversible addition of hydroxide anion to one carbonyl group to form a tetrahedral intermediate (**1**) or (**2**), followed by rate limiting hydride transfer to a second carbonyl group to give the products. We have shown previously that alternative mechanisms involving, *e.g.* single electron transfers are unlikely for the reaction of formaldehyde[5a] or glyoxal.[5b] The observed rate for these reactions ($k_{\mathrm{obs.}}$) is the product of the rate constant for the second step (k_2) and the equilibrium constant for the pre-equilibrium step (K_{eq}). It follows that the observed isotope effect ($k_{\mathrm{obs.}}{}^{\mathrm{H}}/k_{\mathrm{obs.}}{}^{\mathrm{D}}$) is the product of the two ratios $K_{\mathrm{eq}}{}^{\mathrm{H}}/K_{\mathrm{eq}}{}^{\mathrm{D}}$ and $k_2{}^{\mathrm{H}}/k_2{}^{\mathrm{D}}$. These are both readily calculated from the normal vibrational frequencies, of reactant and intermediate for the equilibrium isotope effect[7] and of the reactant and the transition state for the kinetic isotope effect.[8]

The calculated transition state for reaction (1) (Figure 1) shows pronounced asymmetry in the C–H bond lengths at the 3-21G basis level, but not at the higher 6-31+G level, or indeed with MNDO. Houk and Wu reported a similarly asymmetric geometry for hydride transfer between methoxide anion and formaldehyde at the *ab initio* 3-21G level.[9] We also find that the linearity of the transition state for reaction (1) shows a large basis set dependence (176.8°//MNDO, 136.5°//3-21G, 148.2°//6-31G, 162.2°//6-31+G, Figure 1).[10]

Table 1. Barriers to hydride transfer for glyoxal and formaldehyde in kcal mol^{-1} (1 cal = 4.184 J).

System	MNDO	3-21G	6-31G	RMP4// 6-31G	6-31+G	RMP4// 6-31+G
ΔH^{a}	28.81	27.36	34.98	28.78	38.61	34.92
ΔH^{b}	17.58	7.24	13.78	4.10	17.01	7.86

[a] Barrier to hydride migration for glyoxal. [b] Barrier to hydride migration for formaldehyde.

Table 2. Kinetic isotope effects at 373 K.

Reaction	Method	HRR	Tunn. corr.[e]	K_{eq}^{H}/K_{eq}^{D}	$k_{obs.}^{H}/k_{obs.}^{D}$	$k_{obs.}^{H}/k_{obs.}^{D}$ × tunn. corr.
(1)	MNDO	2.980	1.450	0.940	2.801	4.062
	3-21G	2.652	1.494	0.967	2.565[a]	3.832
	6-31+G	2.480	1.940	0.892	2.212[a]	4.292
(2)	MNDO	3.453	1.998	0.896	3.095[b]	6.183
	3-21G	4.737	1.172	0.885	4.192[b]	4.913
	6-31+G	4.771	1.534	0.844	4.026[b]	6.176
(3)	MNDO	3.871	1.894	0.867	3.356[c]	6.357
	3-21G	5.786	1.154	0.797	4.612[c]	5.322
	6-31+G	5.410	1.476	0.810	4.380[c]	6.464
(4)	MNDO	3.808	1.917	0.858	3.268[d]	6.264
	3-21G	5.615	1.162	0.818	4.593[d]	5.338
	6-31+G	5.222	1.489	0.832	4.343[d]	6.466

For T = 373—700 K: [a] $k_{obs.}^{H}/k_{obs.}^{D} = 1.1011 \times \exp(317.64/T)$ (3-21G), $1.1334 \times \exp(251.70/T)$ (6-31+G). [b] $k_{obs.}^{H}/k_{obs.}^{D} = 1.0654 \times \exp(399.32/T)$ (MNDO), $0.9412 \times \exp(556.98/T)$ (3-21G), $0.9651 \times \exp(532.07/T)$ (6-31+G). [c] $k_{obs.}^{H}/k_{obs.}^{D} = 1.0139 \times \exp(447.23/T)$ (MNDO), $0.8782 \times \exp(619.12/T)$ (3-21G), $0.9072 \times \exp(587.82/T)$ (6-31+G). [d] $k_{obs.}^{H}/k_{obs.}^{D} = 1.0324 \times \exp(430.68/T)$ (MNDO), $0.8939 \times \exp(611.18/T)$ (3-21G), $0.9196 \times \exp(579.77/T)$ (6-31+G). [e] Tunnelling correction.

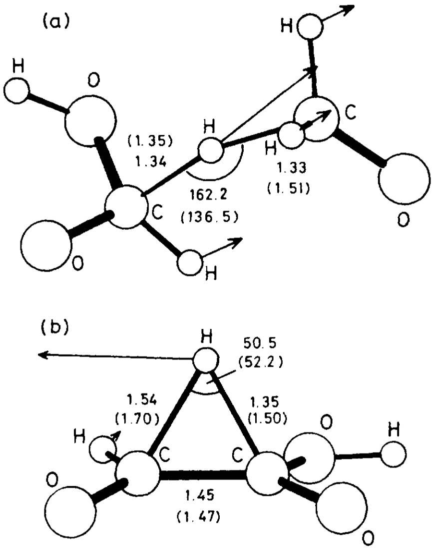

Figure 1. Calculated transition state structures (a) for the hydride transfer step in reaction (1) and (b) for reaction (2). Bond lengths are in Å at the 6-31+G basis set level; those in parentheses are at the 3-21G level.

Houk and Wu in their study[9] reported a similar basis set effect, with angles very similar to ours (*e.g.* 159°/6-31+G). In contrast, Williams and co-workers[11] report that hydride transfer from methylamine to methyleneammonium has an essentially linear C–H–C linkage at the 3-21G basis set level.[10] It has been previously noted that hydride transfers are more easily bent than the equivalent proton transfer.[12]

The calculated barriers for the hydride transfer step in each reaction are shown in Table 1. For reaction (1), both the MNDO and the *ab initio* method give barriers similar to those reported for other hydride transfer reactions.[9—13] The barriers we obtained for reaction (2) are uniformly higher than for reaction (1), with a structure for the transition state which, formally at least, involves a highly bent hydride transfer (Figure 1b).

Calculated isotope effects based on the uncorrected, normal vibrational frequencies obtained at the MNDO, 3-21G, and 6-31+G levels are shown in Table 2. The calculated harmonic rate ratios (HRR) are for k_2^{H}/k_2^{D}, and are all typical of quite large primary effects. The 6-31+G values tend to be intermediate between the MNDO and the 3-21G values, with much less variation observed for the isotope effects than for the Bell tunnelling correction.[14] This is not unexpected since the latter are very sensitive to the magnitude of the calculated imaginary frequency, which is in turn highly basis set dependent.[9,11] The ratio K_{eq}^{H}/K_{eq}^{D} for the pre-equilibrium step is predicted to show an interesting *inverse* effect by all three methods, due we think to the 'oxyanion' effect[15] weakening the C–H bond adjacent to the alkoxide substituent in the intermediate, relative to the same bond in the starting material. The observable isotope effect ($k_{obs.}^{H}/k_{obs.}^{D}$) is therefore somewhat attenuated, but the values obtained are still substantial, and very similar to experimental hydride transfer isotope effects recently reported by Watt and co-workers.[13] Particularly noteworthy is that the semi-classical isotope effects are predicted at all three levels to be larger for reaction (2) than for reaction (1). It has long been accepted for example that non-linearity decreases the expected magnitude of a simple proton transfer,[16] and the present result may indicate that hydride transfers differ radically in this respect from proton transfers. The calculated tunnelling corrections show an opposite trend, being larger for reaction (1) at both the 3-21G and 6-31+G levels. A further striking difference between reactions (1) and (2) is the different predicted temperature dependence of the isotope effects (Table 2), the Cannizzaro reaction showing a much lower effect than the intramolecular hydride shift.

Also included in Table 2 are results for reactions (3) and (4), which involve the use of isotopically labelled glyoxal, and provide one potential means of measuring these effects. Competing reactions such as hydrogen exchange *via* α-proton abstraction are known[3,4] not to occur in either the reactant or the product glycolic acid.† The calculated secondary isotope effects tend to *increase* the predicted magnitude of HRR, but to *decrease* the isotope effect on the pre-equilibrium! The overall effect of the use of ^{13}C labels is to increase slightly the observable isotope effect for the hydride transfer.

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† Abstraction by base of the proton α to the carbonyl group in the intermediate (**2**) would result in formation of the enolate anion H(OH)C=C(OH)O$^-$ (or a tautomer), which could then reprotonate to give glycolic acid. The energy of the most stable enol tautomer relative to (**2**) is predicted to be -16.0 (MNDO) or -9.7 kcal mol^{-1} (3-21G). Since such proton abstraction appears not to occur experimentally, this implies that either the barrier to reaction is a high one [owing to electrostatic repulsion between the negatively charged (**2**) and *e.g.* OH$^-$] or that (**2**) is more effectively solvated than any of the enol tautomers.