Hydride shift in substituted phenyl glyoxals: Interpretation of experimental rate data using electronic structure and variational transition state theory calculations[†]

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Experimental rate data for hydride transfer in some *p*-substituted phenyl glyoxals in 80 : 20 dioxan : water are presented including kinetic hydrogen isotope effects. The roles of different substituents are discussed using electronic structure calculations of the potential energy surfaces at the SM5.4/PM3 level together with calculations employing variational transition state theory and multidimensional tunneling. *p*-NO₂ substitution has the most pronounced effect on the rate parameters, which can be understood in terms of the relative destabilisation of the reactant *and* reduced quantum mechanical tunneling through the barrier. The use of different models for tunneling suggests that when coupled with the SM5.4/PM3 method, the higher level of theories tend to overestimate the degree of tunneling.

Introduction

Hydrogen transfer is a common process in many organic systems. Both protic and hydridic motions can be important steps in many biological redox processes.¹ It is also observed in industrially important reactions involving inter- and intramolecular transfer in hydrocarbons² and combustion processes.³ The light mass of the transferring particle can facilitate quantum mechanical tunneling, which is reflected in measured kinetic isotope effects. Several recent experimental studies have implicated tunneling in enzymatic systems,⁴⁻⁶ although it is often difficult to quantify this effect, particularly the role of the motion of the enzyme, which has been suggested to enhance the tunneling.^{4,7}

We here report a combined experimental and theoretical study of the hydride transfer in phenyl glyoxal hydrate, which occurs in aqueous solution. The aim has been to study the effect of different substituent groups located at the *para*position of the phenyl ring and to see if current computational methods can predict the subtle changes in the reactivity which we observe. In particular we shall explore the suitability of variational transition state theory (VTST) and multidimensional tunneling methods for the study of this system. Although the phenyl glyoxal hydrate system does not directly represent any particular biological scheme, it is an aqueous phase organic hydride transfer similar in many respects to those observed in enzymatic reactions.

Various theoretical methods have been used to model tunneling, and hydrogen transfer in general. In particular classical molecular dynamics,^{8,9} and VTST, both with hybrid quantum mechanical and molecular mechanical (QM/MM) potential energy calculations^{10–12} and with wholly quantum mechanical or semi-empirical potential energy surfaces have been used.^{13–17} In the work described here canonical variational transition state theory (CVT)¹⁸ has been used to calculate the overbarrier contribution to the rate. A multiplicative transmission coefficient is then included which accounts for tunneling through the barrier and is evaluated by different methods.

The reaction studied here is the aqueous base induced rearrangement of phenyl glyoxal hydrate to mandelate. The process has been shown to involve migration of the hydratedformyl hydrogen to the adjacent carbonyl carbon¹⁹ and is best formalised as the transfer of a hydride from electron-rich to electron-deficient carbon (Fig. 1). This hydride shift can occur either in the mono-anion or the di-anion of the hydrate. The shift in the di-anion is expected to be significantly faster than that in the mono-anion and its contribution is thought to dominate except at low pH.²⁰ At high pH the mono-anion form is dominant but the reaction occurs via a small concentration of rapid and reversibly formed di-anion. The experimental barrier must therefore be partitioned between the free energy for the formation of an equilibrium concentration of the di-anion and the barrier for the subsequent hydride transfer step.20

We here describe calculations of energetic and rate data with kinetic isotope effects for the four substituted phenyl glyoxal hydrates (Fig. 1) and compare these to experiment. In addition to the unsubstituted species (1) we have studied electron withdrawing ($-NO_2$, 4), Hammett $\sigma = 0.778$, and electron donating (-OMe, 3), $\sigma = -0.286$, groups at the *para* (*p*-) position, as well as methyl substitution (2). Our results provide more insight into the mechanism of the phenyl glyoxal hydride transfer rearrangement and also identify the role of tunneling in such processes. Although the highest levels of theory cannot be used to model this reaction in the aqueous phase, the work presented here does, however, show that calculations using VTST and multidimensional tunneling methods can be an extremely useful tool for understanding organic and biological mechanisms.



Fig. 1 General reaction for the rearrangement involving the 1,2-hydride shift, the *p*-group, X = H(1), Me (2), OMe (3), NO₂ (4).

[†] Electronic supplementary information available. See http:// www.rsc.org/suppdata/cp/b1/b102330f/

Experimental details

Phenyl glyoxal is a yellow oil that forms a stable crystalline hydrate, PGOH. A dissociation constant $K_D = 3.5 \times 10^{-4}$ has been quoted.²¹ The hydrate is a weak acid and Letellier *et al.* also report a $pK_a = 10.85$ at 298 K. In solution at $pH \ge 12$, it exists mainly as its mono-anion, PGO⁻.



Conversion of the mono-anion, PGO^- , to mandelate, MA^- , was monitored by the changes in UV absorbance of solutions at 252 nm, the reaction being found to be first order in PGO^- .



The dependence of k_{obs} on base concentration shows that the reaction requires a second hydroxide ion. We therefore believe that there is then a second deprotonation and the hydride shift occurs in the di-anion. There is no experimental measurement of the second acidity constant, but many dibasic acids of the form $RX(OH)_2$ show first and second acidity constants differing by 4 to 5 pK_a units.

Rates for the conversion of PGO⁻ to MA⁻ were measured in aqueous phosphate buffer (pH 12 at 298 K) at four different temperatures between 289 and 325 K. The results are summarised in Table 1.

Substituents on the phenyl ring were not expected to alter the acidity of the phenyl glyoxal greatly. Reasonable extrapolations suggest that the p-NO₂ compound should be more acidic than PGOH by 0.3 pK_a units at one extreme, and that p-OMe should be less acidic by just 0.1 pK_a. At pH 12 all should be mostly ionised in solution. Not all compounds were sufficiently soluble in pure water so, for comparability, all

 Table 1
 Temperature dependence of rates for rearrangement of PGH (1)

T/K	$k_{\rm obs(H)}/{\rm s}^{-1}$	Activation parameters
289.9 304.8 312.2 324.7	$\begin{array}{c} 1.94 \times 10^{-4} \\ 1.01 \times 10^{-3} \\ 2.09 \times 10^{-3} \\ 6.75 \times 10^{-3} \end{array}$	$\begin{aligned} A &= 4.27(\pm 1.1) \times 10^{10} \text{ s}^{-1};\\ E_{a} &= 79.5(\pm 0.4) \text{ kJ mol}^{-1}\\ \Delta H^{\ddagger} &= 77.0(\pm 0.4) \text{ kJ mol}^{-1}\\ \Delta S^{\ddagger} &= -49.8(\pm 21.0) \text{ J K}^{-1} \text{ mol}^{-1} \end{aligned}$

Table 2 Rate data for the rearrangement of substituted phenyl glyoxal hydrates. Experimental rates and kinetic isotope effects. Errors $\pm 5\%$ for rates and $\pm 10\%$ for the KIEs apply, all measured at 305 K in 80 : 20 dioxan : water, pH 12.57

X	$k_{\mathrm{obs(H)}}/\mathrm{s^{-1}}$	$k_{\mathrm{obs(H)}}/k_{\mathrm{obs(D)}}$
H (1) ^a	1.13×10^{-3}	3.52
p-Me (2)	4.62×10^{-4}	3.55
p-OMe (3)	3.86×10^{-4}	2.56
$p-NO_2(4)$	1.48×10^{-2}	2.27

^a The data in Tables 1 and 2 are from separate studies, so that the rate constants for 1 differ slightly.

rates were measured using 80: 20 dioxan : water. At this level, the acid base properties of the solvent are similar to pure water and ionisation equilibria are unaffected.²²



Reactions for a series of p-substituted phenyl glyoxals were again buffered with phosphate at pH 12.57, and the temperature was held constant at 305 K. The rate data are presented in Table 2.

Computational details

Electronic structure calculations have been carried out on the four phenyl glyoxals, which differ only in the substituent present at the para position. Our strategy is to evaluate rate constants using semiclassical variational transition state theory (SC-VTST), which requires generalised Gibbs energies of activation, $\Delta_{act}G_T$, along the reaction path. Such calculations are computationally expensive, since Hessians are needed to evaluate the required vibrational partition functions. These calculations are generally feasible for quite large systems with semi-empirical Hamiltonians such as AM1 or PM3, but may be prohibitive for even quite small systems when high levels of theory are employed. For this reason the so-called dual level approach is often used, where information on full pathways computed at a lower level of theory is corrected by more limited information from higher level calculations such as that relating to stationary points. We have previously adopted such an approach in a study of hydride transfer in polycyclic hydroxy ketones in the condensed phase.¹⁷ This latter study involved a dual level calculation on a single molecule of a size comparable to those to be studied here and was at the limit of computational feasibility. We adopt a different strategy for the four molecules studied here since initial ab initio calculations on reactant structure (1) at the B3LYP/6-311++ $G^{**23,24}$ level could not locate a reactant minimum, due to cleavage of the C7-C8 bond (Fig. 2). Such a problem may not exist if solvation effects were to be included. However, in view of this problem, as well as the number of molecules to be studied and the success of semi-empirical methods that include solvation, we have chosen to use the latter approach for our study.

We employ the SM5.4/PM3 solvation model developed by Truhlar and Cramer,²⁵ which has been shown to successfully reproduce vapour pressures as a test of the calculated solvation energies.²⁶ This is a continuum model, employing the PM3 Hamiltonian for the electronic structure calculation and a Gibbs energy of solvation that involves two terms. A Born approximation contribution accounts for the electric polarisation of the continuum-dielectric solvent. Charge Model 1 $(CM1)^{27}$ class IV partial charges are used for this and are



Fig. 2 Atom labelling of 1.

obtained from the fitting of charges from NDDO Mulliken population analyses such that they more accurately represent experimental dipole moments. The second term, a solvent accessible surface area (SASA) term, accounts for the Gibbs energy of cavity formation, dispersion interactions, and various effects arising from the first solvation shell. Water solvent was used for the calculations, which differs from the experimental, non-polar, dioxan : water 80 : 20 mixture. Using parameters for pure dioxan led to difficulty in finding stable reactant structures. It is possible that experimentally, the counter cation has a role to play in stabilising the reactant.²⁸ For simplicity this effect was not included in the calculation and the stabilisation was instead the result of the larger relative permittivity of water.

VTST calculations of the rate of hydride transfer in the dianion were carried out for all four molecules. This was accomplished by using AMSOLRATE,²⁹ interfacing SC-VTST in the POLYRATE³⁰ code and the SM5.4/PM3 solvation model from AMSOL.³¹ Optimisation was carried out using the eigenvector following method in AMSOL, with semianalytical methods to evaluate the gradients and derivatives and with an SCF energy convergence criterion of 10^{-9} eV. Stationary structures were characterised by calculation of harmonic frequencies. The solvated reaction path was calculated using the Page-McIver³² method in mass scaled co-ordinates with a reduced mass of 1. Calculation of the Gibbs energy of activation at all the points along the path requires the generalised normal modes. These were calculated by the harmonic approximation using curvilinear internal coordinates³³ as opposed to rectilinear Cartesians. This was found to give a more realistic representation of the frequencies along the path. The maximum in the Gibbs energy was then found and the rate constant calculated by CVT for that point. The rate was then combined with a multiplicative transmission coefficient that accounts for tunneling by either the Wigner (W),³⁴ zero curvature tunneling $(ZCT)^{18,35}$ or small curvature tunneling (SCT)^{14,36} methods. The Wigner method depends only on the curvature at the top of the barrier. The ZCT method calculates the effect of tunneling through the minimum energy path and the SCT method allows for tunneling through the adiabatic curve. The ZCT and SCT models differ by the use of an effective reduced mass in the SCT case as opposed to a more simple reduced mass for ZCT. The effective reduced mass includes the effects of turning points and reaction path curvature thereby including the effects of corner cutting.

All calculations employed the re-orientation of the dividing surface (RODS)³⁷ algorithm which maximises the Gibbs energy of the generalised transition state at every point. This was found to eliminate dips which arose when the minimum energy path was followed by conventional methods, an effect similar to that seen in previous work.³⁸ The resultant minimum energy pathway (MEP) and adiabatic curves were much smoother and allowed for more accurate rate constants and transmission coefficients to be calculated.

Computational results

We first describe the structural and energetic features of the stationary structures that we have located. We will then

describe the use of the associated potential energy surfaces in VTST calculations of rate constants.

Structures and energetics

As far as the reactants (di-anion) are concerned, a number of different minimum energy conformers were located and properly characterised for all four systems studied. These differed mainly in the orientation of the hydrated-formyl group. Two are of particular importance. These are the lowest energy reactant conformer (R1) and the reactant structure (R2) obtained by an intrinsic reaction co-ordinate calculation starting from the transition state. Harmonic vibrational frequencies (cm^{-1}) for the structures R1, R2 and the four transition states are shown in Table S1. The latter structure (R2) is approximately 22 kJ mol⁻¹ higher in energy than the most stable reactant structure. These two different structures may be characterised by the different values of the O10-C7-C8-H12 dihedral angle (Fig. 2). In structures R1 and R2 these values are -170° and -142° respectively, showing that in the reactant structure R2, H12 is more favourably positioned for attack at C7.

The origin of the difference in energies between the structures R1 and R2 can be seen from Table 3. Whereas the internal energy favours R2, which is the structure that connects directly to the transition state, the greater solvation energy of R1 results in this structure being favoured overall, by $\sim 22 \text{ kJ}$ mol⁻¹. This increase in solvation arises from the differing orientation of the hydrated-formyl group in the two structures. In R2, in contrast to R1, the close proximity of H13 to O11 restricts the solvation around the negatively charged O11 and this leads to a reduced solvation energy for R2. This feature is confirmed as the origin of the energy difference by consideration of O9, which is fully solvated in both structures.

Thus, the reaction proceeds first by deprotonation of the mono-anion, to give structure R1, followed by a conformational change to give R2, from which hydride transfer occurs. These steps are shown schematically in Fig. 3, the energy difference between the mono-anion and di-anion being estimated using a $\Delta p K_a$ of 4.5.



Fig. 3 Energy profile $(kJ mol^{-1})$ for the reaction involving 1.

Table 3Contribution to the energies $(kJ mol^{-1})$ of reactant structures (R1, R2) of 1

	TIDDS ZEIO	
O9 H13 O11 Total of solute en	nergy energ	y Energy ^a
R1 -656.9 38.6 -659.4 -1264.0 235.6 -	-1028.4 321.3	-707.1
R2 -653.5 69.5 -570.7 -1184.9 182.4 -	-1002.5 317.6	-684.9

^a Gibbs energy including zero point energy.

Table 4 Selected bond lengths (Å) and energies $(kJ \text{ mol}^{-1})$ of reactant (R), transition state (TS) and product (P). Selected bond lengths (Å) for different species studied are shown in Table S2[†]

	<i>p</i> -H (1)			<i>p</i> -Me (2)			<i>p</i> -OMe (3)			p-NO ₂ (4)		
	R	TS	Р	R	TS	Р	R	TS	Р	R	TS	Р
C ₈ –O ₉	1.39	1.32	1.27	1.39	1.32	1.27	1.39	1.32	1.27	1.39	1.33	1.27
$C_{8} - O_{11}$	1.39	1.33	1.28	1.39	1.33	1.28	1.39	1.33	1.28	1.39	1.33	1.28
$C_{8} - C_{7}$	1.57	1.52	1.56	1.57	1.52	1.56	1.57	1.52	1.56	1.57	1.52	1.56
$C_{8} - H_{1}$	1.14	1.42	2.16	1.14	1.43	2.16	1.14	1.43	2.16	1.13	1.41	2.19
$C_{7} - H_{12}$	2.14	1.69	1.12	2.14	1.68	1.13	2.15	1.68	1.12	2.15	1.69	1.12
$C_{7} - O_{10}^{12}$	1.23	1.26	1.38	1.23	1.26	1.38	1.23	1.26	1.38	1.23	1.26	1.38
$C_7 - C_3$	1.49	1.50	1.52	1.49	1.50	1.52	1.49	1.50	1.52	1.50	1.50	1.52
$C_6 - X$	1.10	1.10	1.10	1.49	1.49	1.49	1.40	1.40	1.40	1.48	1.48	1.47
Relative	(-1002.5)	48.1	-160.9	(-1040.7)	47.7	-160.7	(-1162.7)	48.3	-159.3	(-1043.4)	45.8	-169.2
energy ^a	Ò			Ò			Ò			Ò		
Relative energy ^b	0	36.8	-160.1	0	36.9	- 198.7	0	35.9	-160.6	0	34.9	-171.1

Energies are given relative to the di-anion reactant, "excluding and bincluding zero point energy. Absolute energies for reactants in parentheses.

The structure and energetics of the reactants, transition state and the products for the four systems studied are shown in Table 4. The expected geometric changes for this type of hydride transfer are found for all four molecules. During hydride transfer there is a compression of the C7-C8 bond in the transition state with the transferring hydrogen being approximately midway between the two carbons (C7,C8). There is also the associated shortening and lengthening of C8-O9,-O11 and C7-O10 respectively as the reaction proceeds. The effect of the different substituents at the para position of the phenyl ring is rather more subtle but can definitely be identified. The role of such substituents is to modify the conjugation between the phenyl ring and the carbonyl group at which hydride attack occurs. However, such conjugation is absent in the product, so that any effect of the substituent will be manifest in the reactant region of the potential energy surface rather than in the product region. The effect of the p-NO₂ group is to reduce the degree of ring-carbonyl conjugation, so that in the reactant the C3-C7 bond is longer than in the unsubstituted molecule, and the $C6-N(O_2)$ bond shortens as the reaction proceeds and the ring-carbonyl (C3-C7) conjugation disappears. Thus, considering only the ringcarbonyl conjugation, the role of the p-NO₂ group is to destabilise the reactant, and render it somewhat more transition state-like, leading to a lower barrier compared to the unsubstituted species (1). The role of the *p*-OMe group is the opposite, stabilising the reactant, and leading to a slightly greater barrier than for (1). These effects are however, small, with the barriers (in the absence of zero point energy effects)

Table 5Kinetic parameters for 1, 2, 3 and 4 at 305 K

varying by only 2.1 kJ mol⁻¹. When zero point energy effects are included the barrier for the p-NO₂ substituent is still the lowest, but now the p-OMe substituent has a slightly lower barrier than the unsubstituted molecule. The lower activation barrier for the p-NO₂ species parallels an earlier transition state with a shorter C8–H12 bond length (by ~0.02 Å), and a smaller imaginary frequency (by 70–90 cm⁻¹, Table 5) than in the three other systems.

These calculations of the stationary structures on the reaction surfaces allow us to rationalise the reaction rates and the KIEs, which we have reported here. Thus the lower barrier which we find for the p-NO₂ species correlates with the observation that the rate for hydride transfer is greater for this system and the somewhat flatter barrier would explain the smaller measured KIE if tunneling were important.

We now describe the results of the VTST calculations of the hydride transfer reaction to evaluate the contribution that such calculations can make to understanding the effect of the substituent on the reaction rates that we have measured.

Calculation of reaction rates

The experimentally determined rate constant is for the conversion of the phenyl glyoxal mono-anion to the mandelate ion. This proceeds *via* deprotonation to form the di-anion, which, from our computational results undergoes a conformational change, followed by hydride transfer (Fig. 3). The large difference in the magnitude of the experimental and theoretical rates (Table 5) can be understood when one considers that the

	TST	CVT	CVT/W ^a	CVT/ZCT	CVT/SCT	Experimental ^b
Rate constants	/s ⁻¹					
<i>p</i> -Н (1)	3.54×10^{6}	2.61×10^{6}	5.39×10^{6} (1071i)	9.46×10^{6}	13.3×10^{6}	1.13×10^{-3}
<i>p</i> -Me (2)	2.47×10^{6}	1.40×10^{6}	2.96×10^{6} (1099i)	6.44×10^{6}	7.40×10^{6}	4.62×10^{-4}
<i>p</i> -OMe (3)	3.24×10^{6}	3.10×10^{6}	6.43×10^{6} (1077i)	9.93×10^{6}	11.4×10^{6}	3.86×10^{-4}
<i>p</i> -NO ₂ (4)	18.7×10^{6}	15.7×10^{6}	30.4×10^{6} (1005i)	54.0×10^{6}	75.9×10^{6}	1.48×10^{-2}
KIE						
p-H (1)	2.62	2.46	2.92	3.71	4.21	3.52
p-Me (2)	2.64	2.30	2.74	4.03	4.20	3.55
<i>p</i> -OMe (3)	2.63	2.74	3.27	3.96	4.07	2.56
$p-NO_2$ (4)	2.10	2.08	2.40	3.72	4.15	2.27

^{*a*} The imaginary frequencies (cm⁻¹) are given in parentheses. ^{*b*} The large difference between the magnitudes of the calculated and experimental rate constants arises from the reactive structure (R2) being 43.5 kJ mol⁻¹ above the mono-anion (Fig. 3).

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Fig. 4 Eyring plot for the hydride transfer in 1.

VTST calculations were conducted on simply the final step of Fig. 3.

The results of the VTST calculations for hydride transfer in reactant R2 are summarised in Table 5. The rate constant is smaller for the CVT than for the TST model, due to the maximisation of the Gibbs energy that is implicit in the VTST procedure. The Eyring plot (Fig. 4) shows little deviation from linearity over the temperature range (273-373 K). The increase in the rate due to tunneling is clearly evident, where the increased rate with SCT compared to that with ZCT shows the importance of corner cutting. At all levels the rate of hydride transfer for the p-NO₂ species is greater, by a factor of about 5, compared to that of the three other species, in qualitative agreement with experiment. For the other three species the rates are quite close and the relative order is dependent upon the computational method employed.

The prediction of the KIEs presents a greater challenge. Experimentally the values vary by only 1.3 for all four species, and are in the range 2–4. The value for the p-NO₂ species is the smallest, a result predicted using both TST and CVT, and with tunneling described by the Wigner approximation. These methods also predict values for the p-NO₂ species essentially in agreement with experiment. All three methods predict that the KIEs for the other three species (p-H, p-Me, p-OMe) are quite close and larger than that for the p-NO₂ species. This is in accord with experiment except for the value for the p-OMe species which, experimentally, is significantly lower than that for the p-H and p-Me species. We find that all KIEs are increased at the ZCT and SCT levels, compared to the values using the Wigner approximation, reflecting the importance of multidimensional tunneling (ZCT) and corner cutting (SCT). The importance of corner cutting is shown by the increase in the KIEs (by 4-16%) at the SCT compared to the ZCT level. However, at both these levels, the values for all four species are larger than the experimental ones, and the relative values are not as good as that found at the simpler level of theory (TST, CVT, CVT/W), in particular the value for the p-NO₂ species is not always the smallest.

Discussion

We have attempted the prediction of quite subtle variations in the reactivity of substituted glyoxals towards hydride transfer, brought about by substituent effects well removed from the site of transfer itself. Such a substituent will stabilise or destabilise both the mono- and di-anion depending on its σ value. The relative effect of the substituent on the mono- and dianion, needed to estimate the pK_a of the mono-anion, is difficult to quantify accurately, preventing a calculation of the overall reaction rate. Nevertheless, the calculated energy barriers for the hydride transfer process itself do broadly reflect the experimental rates, $p-NO_2 > p-H > p-Me > p-OMe$,

although the barriers for the p-H, p-Me and p-OMe species are quite close, as indeed are the corresponding experimental rates. In line with their similar rates, the p-H and p-Me species have very similar KIEs, which are substantially larger than that for the p-NO₂ species. In the absence of tunneling this qualitative trend is reproduced by the calculations but the spread of the KIEs is smaller than experiment, suggesting tunneling is more important for the p-H and p-Me species than for the p-NO₂ species. We note that the measured KIE of the p-OMe species is definitely smaller than those of the other three species which is not shown by the calculations that do not include tunneling. However, the rate data from Table 2 do give a good Hammett plot ($r^2 = 0.995$) but there is no obvious relationship between the rate and the KIE. When tunneling is included, all three treatments (W, ZCT, SCT) predict increased KIEs, the effect being largest for the SCT model, but no model predicts the actual spread of the experimental KIEs. In general the KIEs predicted using the Wigner correction are too small and those for the ZCT and SCT methods are too large.

The origin of the discrepancy between theory and experiment in the case of the KIEs is unclear at present. It may result from the low level of electronic structure theory used, or may reflect the continuum treatment of the solvent, and shows the need for further studies on well defined systems.

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