Journal of Physical Organic Chemistry

Received: 23 January 2013, Revised: 11 April 2013, Accepted: 17 April 2013, Published online in Wiley Online Library: 10 June 2013

(wileyonlinelibrary.com) DOI: 10.1002/poc.3138

Steric effects and mechanism in the formation of hemi-acetals from aliphatic aldehydes[†]

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Some physical properties (pK_a, log P_{OW}, boiling points) of hexanoic acid 1 (X = COOH) and its seven isomers 2–8 (X = COOH) are reported.
Hexanal 1 (X = CHO) and its seven isomeric aldehydes 2–8 (X = CHO) are shown to equilibrate, in methanol solution, with their hemi-acetals. Logarithms of equilibrium constants correlate with values of E_s for the isomeric C_5H_{11} substituents, and with logs of relative rates for saponification of the corresponding methyl esters with $\rho = 0.52$, reflecting the reduced steric demand of hydrogen compared to oxygen in the quaternization of ester and aldehydic carbonyl groups. Rates of equilibration have also been measured in buffered methanol. For hexanal, with a 2:1 Et_3N:AcOH buffer, the buffer-independent contribution is dominated by the methoxide catalysed pathway. Rates in this medium have been determined for isomers 1 – 8 (X = CHO), and their logarithms do not correlate with logarithms of equilibrium constants for hemi-acetal formation or with substituent steric parameters derived from ester formation or saponification, indicating that the steric changes associated with full quaternization of the carbonyl group are not mirrored in the transition structures for hemi-acetal formation. It is suggested that transition states for hemi-acetal formation are relatively early so that steric interactions are effectively those between the nucleophile and ground state conformations of the aldehydes. A comparison of the entropies of hemi-acetal formation with entropies of activation has provided a basis for a suggested transition structure. Comparisons with acid chloride hydrolyses are made. © 2013 The Authors. *Journal of Physical Organic Chemistry* published by John Wiley & Sons Ltd.

Keywords: aliphatic aldehydes; methyl hemi-acetals; rates and equilibria; steric effects; mechanism

INTRODUCTION

In an earlier paper,[1] we noted that the volumes and surface areas of the saturated hydrocarbon groupings of molecular formula C_5H_{11} were remarkably independent of both connectivity and conformation. Following a suggestion by Charton,[2] we have pursued the possibility that these residues then present a set of eight readily available substituents (see Fig. 1) whose polarity, polarizability and solvation properties show little variation and might be used to probe substituent effects on functional group reactivity which are purely steric in origin, i.e. arising only from interactions between filled orbitals on atoms of the substituent and the reacting set in the functional group and reagent.

We have already compared relative reactivities in acid-catalysed methyl esterification of hexanoic acid and its isomers, **1 – 8** (X = COOH) with those for saponification of the same set of esters. In devising his set of group steric parameters, Taft,[3,4] suggested these reactions might have similar sensitivities to steric interaction with the substituent and pointed out that similar experiments applied to *m*- or *p*-substituted benzoic acids or benzoates demonstrated the very different sensitivities of these reactions to polar effects, with $\rho = -0.23$ for the acid-catalysed esterification[3] and $\rho = +2.26$ for saponification[5] in Hammett treatments. The plot of logarithms of relative rates, k_{HO^-}, for the saponification reactions against those, k_{H^+}, for the acid-catalysed esterifications for isomers, **1 – 8** (X = COOMe or COOH), Fig. 2, yielded a good linear correlation (see Eqn 1, $R^2 = 0.988$) with a slope close to one, with reactivities decreasing 130-fold from **1** (X = COOR) to **8** (X = COOR). The correlation excludes any major variation of electronic properties within the series; the minor deviation from unit slope might reasonably be assigned to a small difference in steric demand in the transition states for acid- and base-catalysed ester reactions.

$$\mathit{Log}\ k_{HO^-} = 0.963(\pm 0.044)\ \mathit{log}\ k_{H^+} + 0.022(\pm 0.060) \qquad (1)$$

Logarithms of relative rates for the acid-catalysed esterifications provide the traditional steric substituent parameters, E_s, and we have tabulated those for the C_5H_{11} isomers in our earlier paper.[1] It is clear that relative rates for the ester saponifications might equally be used to compare steric demand within this series.

As a preliminary to the study of reactivity presented in this paper, we report some physical measurements on the set of carboxylic acids. Many of these are already available in the literature, and we have found no significant disagreement with earlier measurements, but the collection presented here (Table 1) offers, at least, an internal consistency in terms of operator, reagents and apparatus. Within the set, refractive indices show

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[†] This article is published in Journal of Physical Organic Chemistry as a Special issue: In Memoriam edited by Michael Page (University of Huddersfield, Chemistry, Queensgate, Huddersfield, HD1 3DH, United Kingdom).

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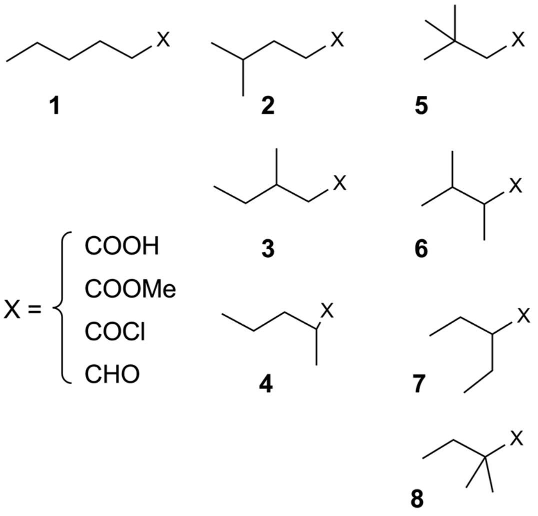

Figure 1. Structures of the eight isomers of $C_5H_{11}X$

little variation, 1.413 (±0.002) at 21 °C, with no indication of trend with structure, at least supportive of constant polarizability. Other properties (octanol/water distribution coefficient, boiling point) show some variation but with no obvious relationship to structure. The variation, however, is considerably less than that associated with addition or removal of a single CH_2 group. For example, $1.55 < \log P_{ow} < 1.98$ for the set, while for the homologues, pentanoic, hexanoic and heptanoic acid values are 1.39, 1.98 and 2.49, respectively. For the boiling points, 186 < BP 204 °C within the isomer set, while those for pentanoic, hexanoic and heptanoic acid are 184, 204 and 223 °C respectively.

Over the set, $4.67 < pK_a < 5.00$, with 2,2-dimethylbutanoic acid, **8** (X = COOH) being the weakest acid with $pK_a = 5.00$. This reduced acidity might be associated with a small inductive electron donation from methyl substituents at the α-position, but that suggestion is difficult to reconcile with the finding that 3,3-dimethylbutanoic acid, **5** (X = COOH), with the methyl substitution at the β-position, has almost equal acidity with $pK_a = 4.97$. We suggest that the more plausible explanation for the slightly reduced acidities of **8** and **5** (X = COOH) is steric hindrance to solvation by hydrogen bonding, tighter in the negatively charged carboxylate anion than in the neutral carboxylic acid. If the effect of these substituents on reactivity was purely electronic in origin, and the saponification of methyl esters had ρ = 2.23 (against Hammett constants), then the pK_a spread could account for a factor of only 6.9 in the reactivity across the eight isomers, rather than the observed 130-fold.

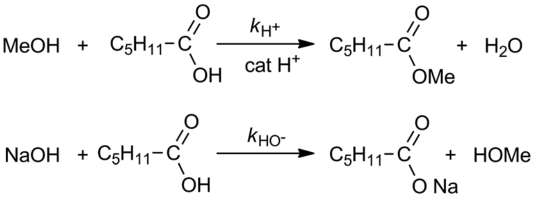

Figure 2. Comparison of relative reactivities in acid-catalysed esterification and in ester saponification

Table 1. Some physical properties of the isomeric acids

Acid 1–8 (X = COOH)	BP °C	^{a}Log $P_{(OW)}$	${}^{b}pK_a$
Hexanoic **1**	204.2–204.8	1.98	4.81
4-methylpentanoic **2**	198.6–198.9	1.75	4.78
3-methylpentanoic **3**	198.4–198.5	1.68	4.68
2-methylpentanoic **4**	195.9–196.1	1.74	4.75
3,3-dimethylbutanoic **5**	186.0–186.4	1.64	4.97
2,3-dimethylbutanoic **6**	191.4–191.8	1.55	4.75
2-ethylbutanoic **7**	190.8–191.0	1.74	4.67
2,2-dimethylbutanoic **8**	192.9–193.3	1.63	5.00

[a] P_{OW} against dil. HCl to suppress any effect of dissociation of the carboxylic acid group

[b] Means of three separate determinations agreeing to ± .005

The major portion of this work is a study of the addition of methanol to the corresponding aldehydes, **1 – 8** (X = CHO) in dilute methanol solution, yielding the hemi-acetals (see Fig. 3), selected because it offered the possibility of measurement of both rates and equilibria, a situation remarkably rare in organic chemistry. This then permits the informative testing of the relationship between $\Delta G_{reaction}$ and $\Delta G^{\ddagger}$ for the same reaction (a possible Type 1 linear free energy relationship[6]) as well as of correlation of those measurements with substituent parameters defined through other reactions.

RESULTS

Preparative chemistry

Hexanal **1** (X = CHO), 2-methylpentanal **4** (X = CHO) and 2-ethylbutanal **7** (X = CHO) were commercially available. All other aldehydes were prepared by oxidation of the corresponding primary alcohols, themselves available by lithium aluminium hydride reduction of methyl esters of the corresponding acids. A number of oxidation methods were investigated, but, in our hands, a minor modification of the method of Anelli *et al.*[7] (oxidation by bleach, catalysed by TEMPO and potassium bromide) was most effective, routinely giving "GC yields" of over 75%. Isolated yields of analytically pure material, however, were usually *ca* 30%, with the losses arising mainly in ensuring that the material produced was free from contamination by solvent or hydrate. A representative procedure is given in the experimental section, but we note that there were particular difficulties in preparing aldehyde **8** (X = CHO) which, on standing in impure form, deposited a white solid, yet to be identified, but which was not the oxidation product. Distilled material was much more stable, but was stored under an inert atmosphere and distilled immediately before use.

Initial observations

The behaviour of solutions of the aldehydes in d_4-methanol was first examined by ^{1}H-NMR spectroscopy. Figure 4 shows the

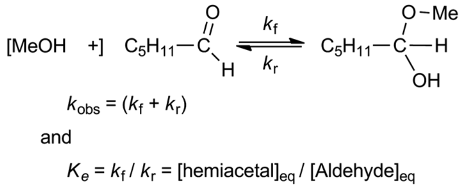

Figure 3. Hemi-acetal formation by addition of methanol to aldehydes **1–8** (X = CHO)

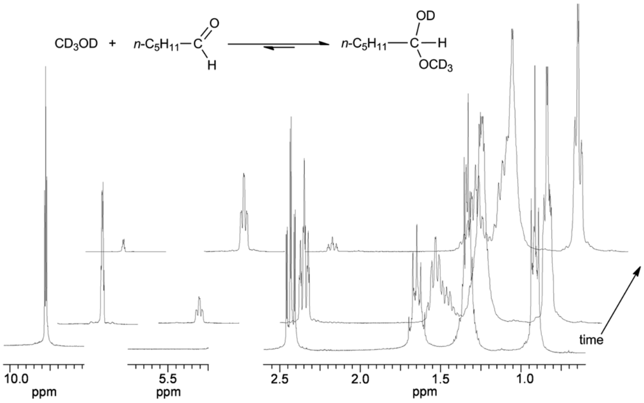

Figure 4. The equilibration of hexanal (initially *ca* 0.06 M) and its hemi-acetal in d_4-methanol, observed by ^{1}H-NMR spectroscopy over approximately 6 h

behaviour of hexanal itself, **1** (X = CHO) with the most obvious indicators of reaction being the diminution of the signals from the aldehydic hydrogen (at δ9.70) and adjacent CH_2 group (at δ2.47) and the matching appearance of a new triplet at higher field. The times over which these changes occurred were variable from about an hour to several days, with strong sensitivity to traces of acid or base, even in carefully cleaned NMR tubes. This irreproducibility of time scale could be eliminated by buffering with 0.05 M Et_3N:HOAc in 1:2 molar ratio, with times for equilibration at 30 °C then conveniently reduced, reproducibly, to a matter of minutes. The changes in spectra associated with the aldehyde chemistry were unaffected by presence of the buffer.

The appearance of the new triplet might be associated either with hemi-acetal formation as shown in the figure, or with formation of the full dimethyl acetal. This latter possibility was tested by comparison with an authentic sample of 1,1-dimethoxyhexane, whose ^{1}H-NMR spectrum, separately and in addition to the equilibrated mixture, presents a one-hydrogen triplet well resolved, 0.2 ppm upfield from that observed in the equilibration mixture, showing clearly that the product of equilibration observed under these conditions is not the full acetal. Experiments with the other isomers similarly indicated that the products of equilibration with methanol under these very mild conditions were not full acetals.

For equilibrations of aldehydes **1**, **2**, **5**, **7** and **8** (X = CHO), the new methine signals appeared at δ4.373 (t, *J* = 5.5Hz), 4.351 (t, *J* = 5.5Hz), 4.470 (t, 5.0Hz), 4.291 (d, *J* = 5.3 Hz) and 4.048 (s), respectively. The hydrocarbon portions of aldehydes **3**, **4** and **6** (X = CHO) each contain a stereogenic centre, and the more complex methine signals, shown in Fig. 5, are believed to reflect the introduction of the new stereogenic centre in formation of hemi-acetals, but with no indication of any strong diastereoselectivity.

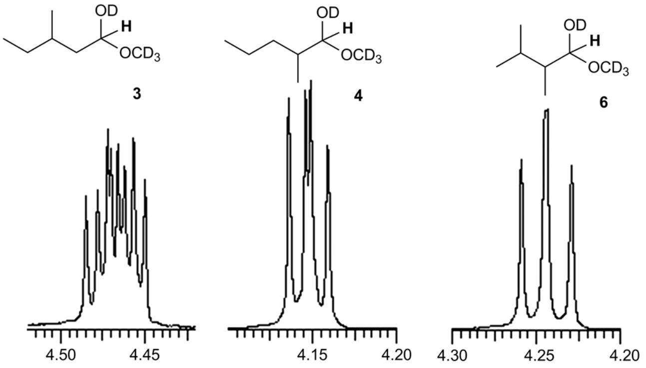

Figure 5. Methine signals (400 MHz H-NMR spectra) from the hemi-acetals formed from aldehydes **3, 4** and **6** (X = CHO)

Measurements of rates and equilibria

The NMR observations described above allow measurements of equilibrium constants for hemi-acetal formation by signal integration and, in principle at least, also rates of approach to equilibrium. In practice, the timescales for equilibration in the buffered solutions were inconveniently short for this method, and we reverted to use of UV–vis spectroscopy. Solutions of all these aldehydes in methanol show an n → π* absorption band with $\lambda_{max} = 287(\pm 5)$ nm and $\varepsilon_{max} \approx 55$. Dimethyl acetals of saturated aldehydes are transparent at these wavelengths, and we assume that the hemi-acetals show the same behaviour in their UV–vis spectra as the full acetals. Absorbances at λ_{max}, after rapid addition of the aldehydes to buffered methanol mixtures and mixing, showed first-order decay to new equilibrium values, yielding a rate constant, k_{obs}, for the approach to equilibrium, which is the sum of forward and reverse rate constants, $(k_f + k_r)$, where the constant methanol concentration is subsumed into k_f. Initial and final values of the absorbances, A_o and A_{eq} yield values for the equilibrium constant with $K_e = (A_o - A_{eq})/A_{eq}$ and the relationships between rates and equilibrium then allow extraction of separate values for both k_f and k_r.

In view of the sensitivity of rates to solution acidity, we first examined the behaviour of hexanal itself in a series of buffer mixtures to identify conditions under which the mechanism of acetal formation was likely to be the same for all isomers. Table 2 collects rate constants for equilibrations of hexanal in methanol containing four different triethylamine:acetic acid buffers and one triethylamine:citric acid buffer. Plots of rate constant against total buffer concentration are linear (Fig. 6A), allowing estimates of buffer-independent contributions, k_o, which are included in the table.

The buffer-independent rate constants may contain contributions from spontaneous reaction, k_s, and from lyate and lyonium catalysed reactions, i.e. Eqn 2.

$$k_o = k_s + k_{MeO^-}[MeO^-] + k_{MeOH2^+}[MeOH_2^+] \qquad (2)$$

Methanol is a well-characterised solvent,[8,9] with a reliable measurement of its autoprotolysis constant (1.995×10^{-17} at 25 °C). Constants are also available for dissociation of acetic acid (2.69×10^{-10} M), citric acid (7.41×10^{-9} M) and triethylammonium ion (2.19×10^{-11} M) in methanol, so that concentrations of MeO^- and $MeOH_2^+$ can be calculated for buffers used in this study, and Table 2 includes calculated values of *pH* (= − log[$MeOH_2^+$]).

Figure 6B plots values of log k_o against p*H* and shows increasing rate as the buffers become more basic with a reasonable fit to limiting lines of slope zero and one (dashed lines). The solid curve in this plot is the best fit of Eqn 3 to the data (R = 0.978) yielding values for $k_s = 1.84(\pm 0.51) \times 10^{-3}\,s^{-1}$ and $k_{MeO^-} = 4.15 (\pm 0.62) \times 10^4\,M^{-1}\,s^{-1}$ for the rate constants.

$$\log k_o = \log\,(k_s + k_{MeO^-}[MeO^-]) \qquad (3)$$

Values here are comparable with those obtained by Pocker *et al.*[10] for additions of water to propanal, *iso*-butyraldehyde and pivaldehyde (values for k_{HO^-} were, respectively, 2.35×10^3, 1.77×10^3 and $6.33 \times 10^3\,M^{-1}\,s^{-1}$ at 0 °C). Even with

Table 2. Rate constants for equilibrations of hexanal in methanolic buffers at 25 °C

Buffer	Et_3N: AcOH	Et_3N: AcOH	Et_3N: AcOH	Et_3N: AcOH	Et_3N:Citric
[c]ratio	1:2	2:3	3:2	2:1	3.5:4.0
-log[$MeOH_2^+$]	9.51	9.74	10.49	10.72	8.92
[a]**[Buffer]$_{tot}$** /M	[b]k_{obs} /s^{-1}				
0.075	19.2×10^{-3}	2.20×10^{-2}	8.95×10^{-2}	16.2×10^{-2}	4.22×10^{-2}
0.050	14.1×10^{-3}	1.68×10^{-2}	6.91×10^{-2}	12.9×10^{-2}	2.92×10^{-2}
0.025	9.34×10^{-3}	1.10×10^{-2}	4.45×10^{-2}	9.37×10^{-2}	1.58×10^{-2}
[d]0.000	4.35×10^{-3}	0.56×10^{-2}	2.27×10^{-2}	5.99×10^{-2}	0.27×10^{-2}

[a] Concentrations are sums of the separate base and acid concentrations.
[b] Reactions were run in duplicate, and individual values of k_{obs} were reproducible to ±2%.
[c] Molar ratios of triethylamine and either acetic acid or citric acid.
[d] Extrapolated values (k_o)

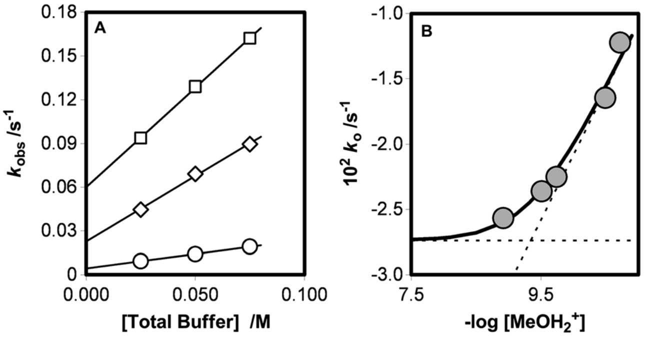

Figure 6. Dependences of rates of hemi-acetal formation for hexanal in methanol at 25 °C with Et_3N:HOAc buffers in 2:1 (□), 1.5:1(◇) and 1:2(○) molar ratios (plot A), and of log k_o on *pH* (plot B)

the uncertainties, because of the balance of concentrations, it is clear that in all the Et_3N:AcOH buffers used, k_o is dominated by the methoxide-catalysed contribution (k_{MeO^-}[MeO^-]). In the case of the 2:1 molar ratio Et_3N:HOAc buffer (calcd. p$H = 10.72$), the fraction is greater than 99.9%. We have not been able to carry out similar full examinations of dependences on buffer composition on rates for the remaining aldehydes, but in view of the demonstrated absence of large electronic factors in the reactivity with the set, we assume a similar pattern.

For each aldehyde, rates have been determined by UV–vis spectroscopy at three different buffer concentrations. In all cases, rates were linearly dependent on buffer concentration yielding values for the rate constant for the buffer catalysed reaction, k_{buff}, and extrapolation to zero buffer concentration to yielding k_o. Since equilibrium constants are also available for each aldehyde, we have extracted values of the rate constants for formation of hemi-acetal, k_{buff}(f) and k_o(f) in this medium.

Table 3 collects those rate constants and the equilibrium constants, K_{eq}, for hemi-acetal formation, which were, as expected, independent of buffer concentration. The span in reactivities is 47 for the buffer-independent reaction (k_o) and 29 for the buffer-catalysed process (k_{buff}), both much reduced from the *ca* 130-fold spread for the ester reactions. The span of equilibrium constants is notably less again ($0.69 < K_{eq} < 10.6$), so that the sensitivity to substituents effects is larger in the progress to transition than to product state.

Tests for internal free energy relationships are shown in Fig. 7A and Fig. 7B, with the dashed line providing a reference of unit slope. Figure 7A shows that there is a reasonable linear correlation ($R^2 = 0.984$, Eqn 4) between logarithms of rates, relative to hexanal,

Table 3. Rates and equilibrium constants for hemi-acetal formation from aliphatic aldehydes **1–8** (X = CHO) in methanol at 25 °C with 2:1 Et_3N:HOAc buffer

Aldehyde **1 – 8** (X = CHO)	**10^3 k_o(f)**[a] /s^{-1}	**10^1 k_{buff} (f)**[a] /M^{-1} s^{-1}	[b]K_{eq}
Hexanal **1**	57.4 (±1.7)	20.6 (±0.5)	10.5
4-methylpentanal **2**	69.2 (±3.1)	20.0 (±0.1)	10.6
3-methylpentanal **3**	48.5 (±2.9)	13.3 (±0.1)	5.62
2-methylpentanal **4**	9.92 (±0.34)	5.90 (±0.09)	4.03
3,3-dimethylbutanal **5**	56.3 (±4.8)	16.3 (±1.3)	2.49
2,3-dimethylbutanal **6**	12.2.(±0.4)	3.06 (±1.3)	1.15
2-ethylbutanal **7**	5.77 (±3.6)	2.11 (±.0.10)	1.17
2,2-dimethylbutanal **8**	1.45 (±0.8)	0.69 (±0.02)	0.95

[a] Uncertainties in rate constants are standard errors based on the linear regression analysis for three buffer concentrations. Reactions were run in duplicate, and individual values of k_{obs} were reproducible to ±2%.
[b] Uncertainties in the values of the equilibrium constants arise almost wholly from that in the initial absorbance (see experimental section) and are estimated to be less than ±10%.

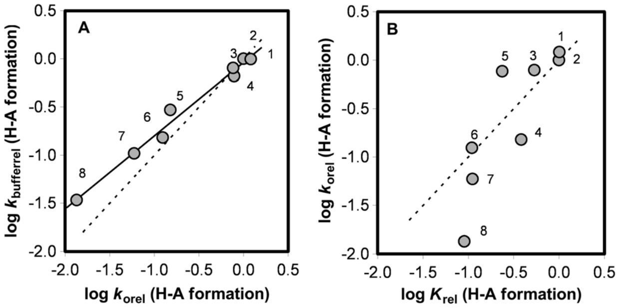

Figure 7. Internal correlations between rates and equilibria for formation of hemi-acetals (H-As) from aldehydes **1–8** (X = CHO). Graph A plots logarithms of relative rates for buffer-catalysed reaction against those for buffer-independent reaction. Graph B plots logs of relative rates for the buffer-independent reaction against the logarithms of the equilibrium constants

of the buffer-catalysed ($k_{\text{buff rel}}$) and buffer-independent ($k_{\text{o rel}}$) reactions, with the buffer-catalysed reaction being less sensitive to the effects of substituent variation.

$$\log k_{\text{buff rel}} = 0.726\ (\pm 0.040)\ \log k_{o\,rel} - 0.037(\pm 0.036) \qquad (4)$$

Figure 7B, in contrast, shows that the correlation between logarithms of rate and equilibrium constants is poor.

For external correlation with steric parameters, we have used logarithms of relative rates of saponification of the corresponding methyl esters as our reference points. Figure 8A shows a reasonable linear relationship between logarithms of equilibrium constants for formation of hemi-acetals and logarithms of rates constants for ester saponification (see Eqn 5, $R^2 = 0.986$)

$$\log K_{rel} = 0.520\ (\pm 0.025)\ \log k_{rel(\text{sapn})} + 0.010\ (\pm 0.033) \qquad (5)$$

Figure 8B plots logarithms of relative rate constants for the buffer-independent formation of the hemi-acetals against the same reference points, and it is clear that no simple relationship exists between reactivities in the reactions. Use of the more traditional E_s-values (based on relative rates of acid-catalysed esterification) does not alter the picture.

For these reactions, also, the availability of both rates and equilibria offers the possibility of an informative comparison of enthalpy and entropy changes in progress to transition and product states, and the temperature dependences of rates and equilibria were examined for aldehydes **1**, **5**, **7** and **8** (X = CHO). Because reactions of **1** and **5** in the 2:1 Et_3N:HOAc buffer were too fast for observation at T ≥ 30 °C with available apparatus, reactions were compared in the less basic 1:2 Et_3N:HOAc buffer, but one in which buffer-independent reactivity remains dominated by the methoxide-catalysed pathway. Table 4 collects the equilibrium constants, K_e, and first-order rate constants k_o(f) for the buffer-independent formation of the hemi-acetals over 20 < T < 40 °C, and the values for the enthalpy, entropy and free energy changes derived from the temperature dependences.

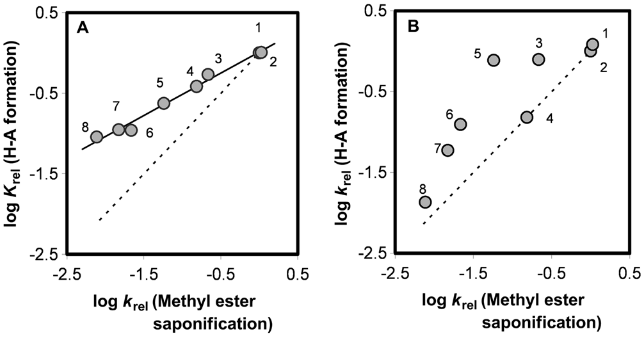

Figure 8. Plot of log K_{rel} for hemi-acetal formation against log k_{rel} for saponification of methyl esters (graph **A**) and plot of logs of relative rate constants of hemi-acetal formation (log k_{rel}) against logs of relative rates of methyl ester saponification (graph **B**). Saponification rates are taken from reference 1

For the variation of equilibrium constants ($[\text{Hemi-acetal}]_{eq}/[\text{Aldehyde}]_{eq}$), Van't Hoff treatment yields enthalpy changes between $-33.5 < \Delta H < -31.4\ \text{kJ mol}^{-1}$, rather less than the value calculated for the reaction ($-41.4\ \text{kJ mol}^{-1}$) in the gas phase using Benson's[11] group increments for conversion of the double bond of a general aliphatic aldehydic carbonyl group to a hemi-acetal. The entropy changes are large and negative ($-92.6 > \Delta S > 110.0\ \text{J.K}^{-1}\ \text{mol}^{-1}$) and comparable with that ($-76\ \text{J.K}^{-1}\ \text{mol}^{-1}$) found by Pocker[10] for hydration of propanal. Entropic contributions ($27.6 > -T\Delta S > 32.8\ \text{kJ mol}^{-1}$) to the free energy change almost cancel the enthalpic change. If the concentration of methanol (for liquid methanol, [MeOH] = 24.59 M at 25 °C) is taken into account in the equilibrium expression (i.e. $K_e = [\text{Hemi-acetal}]_{eq}/[\text{MeOH}][\text{Aldehyde}]_{eq}$), all entropies become more negative by $23.4\ \text{J.K}^{-1}\ \text{mol}^{-1}$ so that the range is ($-126.0 > \Delta S > -134.4\ \text{J.K}^{-1}\ \text{mol}^{-1}$). Since liquid methanol[12] has S (298) = 128 J.K. mol^{-1} of which the major contribution is translational,[13] the entropy changes found for the equilibrium processes correspond closely with those expected from the reaction stoichiometry.

Eyring treatment of the rate constants (pseudo-first order, k_o (f)) yields entropies of activation which are significantly more negative ($-160.8 > \Delta S^{\ddagger} > -211.0\ \text{J K mol}^{-1}$) than those for the equilibration by factors between 1.62 and 1.92, so that entropic contributions ($47.9 > -T\Delta S > 62.9\ \text{kJ mol}^{-1}$) dominate the free energies of activation.

DISCUSSION

The esterification and hemi-acetal reactions are compared in Fig. 9. Saponification of the methyl esters is first order in both ester and hydroxide, reflecting their union in an activated complex often modelled by the tetrahedral intermediate arising from full addition of hydroxide to the carbonyl. Hemi-acetal formation also involves quaternization of a carbonyl group, but differs in replacement of the ester alkoxy residue by a smaller hydrogen atom (Van der Waals radii for O and for H are 1.72 Å and 1.44 Å, respectively[14]), with corresponding reduced steric demand. The proportionality and the reduced slope of the correlation line, seen in Fig. 8A and Eqn 5, seem entirely consistent with the original Taft proposition that the steric effects in the transition states of the ester reactions are well modelled by those in the familiar tetrahedral intermediates.

The absence of correlation between rates and equilibria in hemi-acetal formation (Fig. 7B) and the similar absence of correlation between rates of hemi-acetal formation and rates of ester saponification (Fig. 8B) signals that the changes in steric interaction in progress to transition structures for hemi-acetal formation are not modelled by those associated with full quaternization of the carbonyl group. This work has shown already

Table 4. Temperature dependences of rate and equilibrium constants for hemi-acetal formation for aldehydes **1**, **5**, **7** and **8** (C = CHO)

T /°C	$^{a}k_{o}(f)$ /s^{-1}	$^{a}K_{eq}$	Equilibrium and activation parameters
Hexanal **1** (X = CHO)			
20.0	2.44×10^{-3}	13.6	$\Delta H_r = -33.5\ (\pm 1.1)$kJ mol^{-1} $\Delta S_r = -92.6\ (\pm 5.5)$ J K^{-1} mol^{-1}
25.0	3.94×10^{-3}	10.4	$\Delta G_r(298) = -5.9\ (\pm 2.1)$ kJ mol^{-1}
30.0	4.39×10^{-3}	8.60	$\Delta H^{\ddagger} = 39.1\ (\pm 4.5)$ kJ mol^{-1} $\Delta S^{\ddagger} = -160.8\ (\pm 18.1)$ J K^{-1} mol^{-1}
40.0	7.72×10^{-3}	5.59	$\Delta G^{\ddagger}(298) = 87.0\ (\pm 10.9)$ kJ mol^{-1}
3,3-dimethylbutanal **5**(X = CHO)			
20.0	1.57×10^{-3}	3.23	$\Delta H_r = -32.0\ (\pm 0.4)$ kJ mol^{-1} $\Delta S_r = -99.5\ (\pm 1.4)$ J K^{-1} mol^{-1}
25.0	2.15×10^{-3}	2.49	$\Delta G_r(298) = -2.4\ (\pm\ 0.9)$ kJ mol^{-1}
30.0	2.82×10^{-3}	2.08	$\Delta H^{\ddagger} = 37.2\ (\pm\ 1.5)$ kJ mol^{-1} $\Delta S^{\ddagger} = -171.3\ (\pm\ 4.9)$J K^{-1} mol^{-1}
40.0	4.49×10^{-3}	1.39	$\Delta G^{\ddagger}(298) = 88.3\ (\pm\ 2.9)$ kJ mol^{-1}
2-ethylbutanal **7**(X = CHO)			
20.0	1.62×10^{-4}	1.46	$\Delta H_r = -31.4\ (\pm 0.3)$ kJ mol^{-1} $\Delta S_r = -103.9\ (\pm 1.0)$ J K mol^{-1}
25.0	2.42×10^{-4}	1.17	$\Delta G_r(298) = -0.4\ (\pm 0.6)$ kJ mol^{-1}
30.0	3.04×10^{-4}	0.96	$\Delta H^{\ddagger} = 43.7\ (\pm 2.4)$ kJ mol^{-1} $\Delta S^{\ddagger} = -168.2\ (\pm 7.9)$ J K^{-1} mol^{-1}
40.0	5.88×10^{-4}	0.64	$\Delta G^{\ddagger}(298) = 93.8\ (\pm 4.8)$ kJ mol^{-1}
2,2-dimethylbutanal **8**(X = CHO)			
20.0	5.37×10^{-5}	1.16	$\Delta H_r = -32.6\ (\pm 1.7)$ kJ mol^{-1} $\Delta S_r = -110.0\ (\pm 5.5)$ J K^{-1} mol^{-1}
25.0	5.85×10^{-5}	0.95	$\Delta G_r(298) = 0.2\ (\pm 3.3)$ kJ mol^{-1}
30.0	8.77×10^{-5}	0.75	$\Delta H^{\ddagger} = 34.0\ (\pm 4.5)$ kJ mol^{-1} $\Delta S^{\ddagger} = -211.0\ (\pm 14.0)$ J K^{-1} mol^{-1}
40.0	1.33×10^{-4}	0.50	$\Delta G^{\ddagger}(298) = 96.6\ (\pm 8.9)$ kJ mol^{-1}

[a] For uncertainties, see footnotes to Table 3.

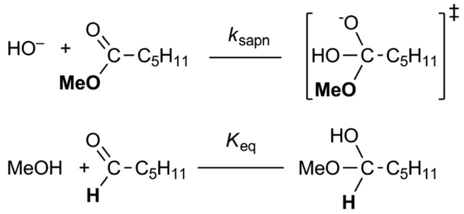

Figure 9. Relationships between rates of saponification of esters and equilibria in hemi-acetal formation

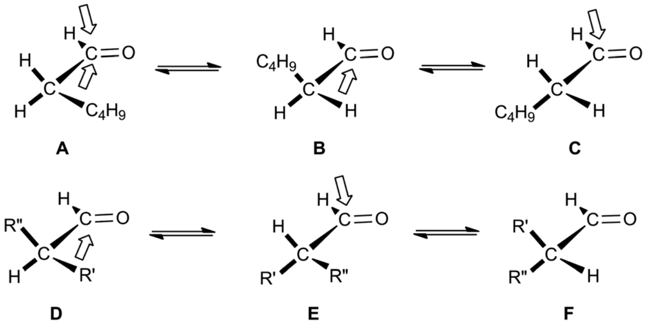

Figure 10. Conformations of simple aliphatic aldehydes and vectors for approach of nucleophile to carbonyl carbon

that energy changes in hemi-acetal formations for this set of aldehydes are small (based on $K_e = [\text{Hemi-acetal}]_{eq}/[\text{MeOH}][\text{Aldehyde}]_{eq}$, $4.1 < \Delta G_{298} < 8.7$ kJ mol^{-1}) compared to those for tetrahedral intermediate formation for esters, which should be close to activation energies for saponification of methyl esters of aliphatic esters,[15–17] typically with $\Delta G^{\ddagger} > 85$ kJ mol^{-1}. Bema–Hapothle[18] considerations would then suggest that the transition structures for the addition to aldehyde should be more reactant-like with relatively small development of bonding between the incoming nucleophile and the carbonyl carbon, and correspondingly small displacements of the central carbon from the plane of its original three ligands. Our measurements (graphed in Fig. 7B and Fig. 8B) show that aldehydes, **1**, **2**, **3** and **5** react at closely similar rates. These isomers are all are mono-substituted at the α-carbon, i.e. C_4H_9–CH_2–CHO. The remaining four isomers, all branched at the α-position, are significantly less reactive, and we suggest that this pattern is consistent with reactivity reflecting steric interaction of the incoming nucleophile with the ground state conformations accessible to the aldehydes.

NMR observations,[19,20] supported by computational studies,[21] on simple aliphatic aldehydes suggest that conformations predominate in which the carbonyl oxygen is eclipsed either by hydrogen or alkyl at the α-position as shown in Fig. 10. Barriers for rotation about the bond between carbonyl carbon and α-carbon are less than 10 kJ mol^{-1} and energy differences are less than 5 kJ mol^{-1}, so that all conformations should be populated at room temperature.

For aldehydes with a single α-alkyl substituent (other than *t*-butyl), the alkyl group eclipses the oxygen in lowest energy conformation (A in Fig. 10) with the other rotamers (B and C in Fig. 10) being slightly higher in energy. The substituent eclipsing the $>C=O$ bond seems unlikely to have major steric interaction with a nucleophile approaching the carbonyl group along the Burgi–Dunitz angle,[22,23] but the others certainly do, with the steric demand of an alkyl group being the larger. When both are hydrogen as in conformation A, the interaction is minimal so that approach may occur equally from either face of the carbonyl group, while in conformations B and C an alkyl group closes one face. All conformations thus possess at least one open face. For aldehydes with two alkyl substituents at the α-position, steric interactions are unfavourable for the conformation in which the remaining α-hydrogen eclipses the > C = O bond (conformation F) and one face only is open in the remaining two (conformations D and E). If the relative reactivities of open and closed faces, as defined above, are similar in all isomers, then while total reactivities must reflect conformational population distributions,[24] aldehydes with branching at the α-position can never be more reactive than isomers with a single α-alkyl group. Isomer **8** (X = CHO), with full substitution at the α-carbon, may be taken to give an estimate of the reactivity of a closed face and comparing this with the reactivities of **1**, **2**, **3** and **5** (X = CHO) provides a very crude estimate that open faces are between 30- and 90-fold more reactive than closed faces.

Our interpretation thus requires that the transition states in these additions are 'early', with relatively little perturbation of geometry and bonding in the transition structure. We believe the picture presented is internally consistent but must draw attention to the measurements of Hill and Milosevich[25] of secondary α-deuterium isotope effects on hydrate and ethyl hemi-acetal formation from pentanal, $C_4H_9CO.L$ (L = H or D). The *equilibrium* α-deuterium isotope effects reported for both hydrate and ethyl hemi-acetal formation are large and inverse, $K^H/K^D = 0.72$ and 0.73, respectively, and consistent with the change of the attachment of the isotopically labelled hydron from trigonal to tetrahedral carbon. The secondary *kinetic* α-deuterium isotope effect for formation of the ethyl hemi-acetal, for the buffer-catalysed reaction using a acidic buffer (1:1 HOAc;AcO$^-$) is similar, $k^H/k^D = 0.74$, suggesting that force constants changes in product and transition state formations are alike, i.e. that the transition state is late.[26] The discrepancy between the indications from variation of alkyl substituents in our work and the isotopic substitution reported by Hill and Milosevic is challenging, and at this stage, we can only note the different reaction conditions and suggest that there are important differences in transition structures for acid- and base-catalysed reactions of oxygen nucleophiles to aldehydes.

We have not yet considered the detailed nature of the nucleophile for the methoxide-catalysed additions, but this must be consistent with the very large negative entropies of activation found. Isotopic fraction factors for methoxide in methanol have been interpreted,[27–29] in terms of the existence of a tri-solvate, with the anion strongly hydrogen bonded to three molecules of methanol. For reactions in which methoxide behaves as a base towards carbon acids,[30–32] this fully solvated anion is apparently not the active species. Rather, desolvation, releasing solvating methanol molecules into bulk solvent to provide more reactive forms, precedes proton abstraction. Solvent isotope effects for methanolysis of phenyl carbonates[33] and of phenyl esters[34,35] have similarly been interpreted in terms of release of at least one of the solvating methanols prior to the nucleophilic attack at carbonyl carbon. We have not been able to measure solvent isotope effects in this work, but suggest that release of solvating methanol should increase rather than decrease entropy of activation and so is difficult to reconcile with the very large negative entropies of activation we have found in our kinetic measurements for hemi-acetal formation. We suggest that these require, not only that the aldehyde carbonyl groups are sufficiently reactive to engage a fully solvated methoxide, but that achievement of transition state calls for involvement of an additional molecule of methanol. The exact organisation of such an assembly must be speculative, but it seems reasonable that the additional molecule of methanol hydrogen bonds to the developing negative charge on the carbonyl oxygen. A possible arrangement is shown below (Fig. 11), in which the methoxide functions as a general base, catalysing addition of one of its solvating methanol molecules, with the additional molecule of methanol placed to minimise nuclear motion in the eventual collapse to neutral product hemi-acetal ($pK_a \approx 13.3$)[36] with regeneration of a fully solvated methoxide anion. Similar cyclic arrays have already been considered for hydrations of aliphatic aldehydes.[10,37,38]

To conclude this discussion, we make comparison between the kinetics of formation of the hemi-acetals from aldehydes and of hydrolyses of the corresponding set of acid chlorides **1 – 8** (X = COCl). In our earlier work,[1] we found that the logarithms of rates of hydrolyses of the acid chlorides did not correlate with logs of rates of methyl ester formation, or of ester saponification. The behaviour is shown in Fig. 12A, and we took that as evidence against mechanisms for acid chloride involving rate-limiting formation of a tetrahedral intermediate by addition of water to the acid chloride carbonyl, but did suggest that the reactivity of aldehydic carbonyls might offer a better model for the behaviour of acid chlorides than that of esters. In the event, Fig. 12A, bears a remarkable qualitative resemblance to Fig. 8B, with both showing the close grouping in reactivity of isomers with no α-branching.

Figure 12B now plots logs of rates of acid chloride hydrolyses against those for hemi-acetal formation and, despite the relative small span of reactivities in both cases (27-fold for the acid

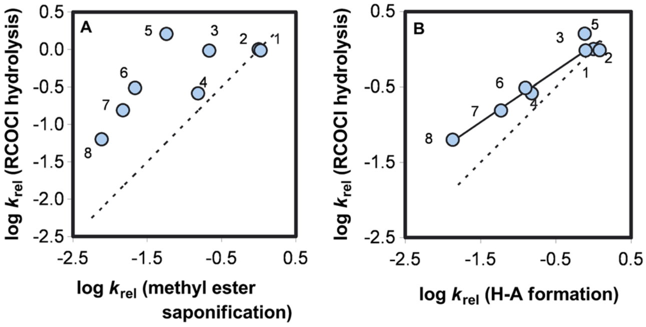

Figure 12. Plot A, logs of relative rates for hydrolysis of acid chlorides against logs of relative rates for ester saponification. Plot B, of plot of logs of relative rates for hydrolysis of acid chlorides against logs of relative rates hemi-acetal formation

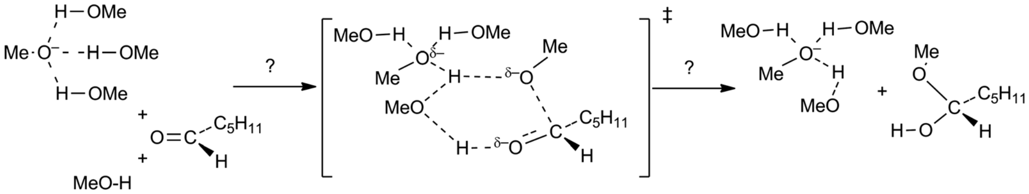

Figure 11. A possible mechanism and transition structure to account for the large negative entropies of activation

chlorides and 47-fold for the aldehydes), a reasonable correlation exists (Eqn 6, $R^2 = 0.951$).

$$\begin{aligned} logk_{rel}(RCOCl) = 0.670(\pm 0.063)\ logk_{rel}(H\text{-}A) \\ +0.054(\pm 0.057) \end{aligned} \qquad (6)$$

On this basis it is clear that, provided transition states are early, mechanisms involving rate-limiting formation of tetrahedral intermediates, or activated complexes, are not excluded by the behaviour of these aliphatic acid chlorides.

CONCLUSION

We have found, like others before us, that structure–reactivity correlations using substituent parameters intended to quantify their steric interaction with the reacting site can be very poor, even when the functionality and the bonding changes are closely related to those in the reference reaction. Such failures have often been ascribed to variable and unquantified electronic contributions to the substituent parameters, but this work has confirmed that poor correlations may persist even when the substituent set is chosen very carefully to ensure electronic homogeneity. We have suggested here that poor correlations then signal markedly different extents of bonding change at the transition states of the reference reaction and the reaction under examination. The corollary is, that while substituent steric parameters should be used with caution as predictors of reactivity, those for a substituent set such as the isomeric saturated C_5H_{11} hydrocarbon residues have value as a probe for variation of extent of bonding changes in the transition state in similar reactions.

EXPERIMENTAL SECTION

The compounds

The carboxylic acids **1 – 8** (X = COOH) were available from our earlier studies.[1] Hexanal, 2-ethylbutanal, 2-methylpentanal and 3,3-dimethylbutanal were purchased from Sigma-Aldrich. All other aldehydes were prepared by oxidation of the corresponding primary alcohol, using an adaptation of the method of Anelli *et al.*,[7] and one example is detailed below. Of the precursor primary alcohols, hexanol, 4-methylpentanol, 2-methylpentanol and 3,3-dimethylbutanol were commercially available. All others were prepared by reduction of the methyl esters of the corresponding carboxylic acids with lithium aluminium hydride. Exemplary methods are described below. All aldehydes were distilled shortly before use in kinetic or equilibrium measurements and shown to be >99.95% by GLC analysis on a 30 m × 0.25 mm polydimethylsiloxane capillary column (*Restek* RTX-1). ^{1}H- and ^{13}C-NMR spectra showed no extraneous peaks (see below) and were consistent with structures and literature data where available.

Measurements of acid dissociation constants (pK_a)

A 0.05 M aqueous sample solution of each carboxylic acid was prepared, except in the case of 2,2-dimethylbutanoic acid **8** (X = COOH), which was only 0.03 M, being restricted by its lower aqueous solubility. Each carboxylic acid (15 ml of solution was then titrated, at 20 °C against aqueous NaOH solution (0.750 M), using a Radiometer Copenhagen TitraLab VIT 90 video titrator (ABU91 auto burette and a SAM90 sample station) adding 0.3 ml aliquots and allowing each 20 s between each addition before recording solution p*H*, using a glass electrode calibrated against standard buffers at p*H* 4 and p*H* 10 (Hydrion buffer capsules). Non-linear regression of calculated p*H* to the experimental values using pK_a as variable yielded values for pK_as at $\mu = 0.047$ M for acids **1**, **2**, **3**, **4**, **5**, **6**, **7** (X = COOH) and $\mu = 0.029$ M for **8** (X = COOH). Tabulated values are the means of three titrations agreeing to ±0.005.

Measurements of partition coefficients (Log P_{OW})

A sample of the carboxylic acid (*ca* 0.025 g) was weighed out (±0.0001 g) into a screw-capped polypropylene centrifuge tube. Octanol (1 ml) and 0.001 M aqueous HCl solution (5 ml) were then added and the tube shaken vigorously for 10 min forming a cloudy suspension. The tube was then centrifuged at 3600 rpm for 30 minutes at 20 °C resulting in complete separation of the two layers, and samples were taken from the water layer using a syringe. Air was blown out from the air-filled syringe while the needle passing through the organic phase and only when in the water layer was a sample of the lower aqueous layer taken in to the syringe. Some of this was expelled as the needle was withdrawn through the organic layer, and the needle was wiped dry thoroughly before transferring a sample of the aqueous layer to a GC vial. This complete aqueous layer was analysed by GLC on a 30 m × 0.25 mm polydimethylsiloxane capillary column (Restek RTX-1). The method used held the oven at 50 °C for 5 min before a ramp of 3 °C a minute until 95 °C and then a second ramp of 20 °C per minute, until 320 °C where it was held for 2 min. Peaks were identified for the carboxylic acid, and octanol, and the ratio of areas of the octanol (solubility in water at 20 °C, 0.042 g in 100 g),[39] and carboxylic acid peaks used to compare relative amounts carboxylic acid in the aqueous layer, assuming that the response factors of the flame ionisation detector for octanol and the acid were in the ratio of 8 to 6 (i.e. the carbon numbers in the molecular formulae[40]). Each measurement was run in triplicate. This procedure yielded log $P_{ow} = 1.98$ for hexanoic acid, slightly larger than the published value (log $P_{ow} = 1.92$).[41]

Esterification of the acids and reduction of methyl esters (representative procedure)

A round-bottom flask was charged with 2,2-dimethylbutyric acid (60.0 g, 520 mmol) which was warmed to 40 °C. Thionyl chloride (75.0 ml, 1040 mmol) was added dropwise, and the resultant solution was heated under reflux for 30 min. The acid chloride product was distilled from the reaction mixture using a Vigreux column, and the residue added dropwise to an ice-cooled solution of methanol (30 ml, 780 mmol) in CH_2Cl_2 (50 ml). This mixture was then left to stir overnight at room temperature, before being washed with saturated sodium bicarbonate solution (50 ml) and distilled water (50 ml). The organic phase was separated, then dried over magnesium sulfate before distillation at atmospheric pressure yielded methyl 2,2-dimethylbutanoate as a colourless liquid (40.0 g., 60 %, bp 124–128 °C).

Methyl 2,2-dimethylbutanoate (10.0 g, 76.9 mmol) was added dropwise down the condenser of a reflux apparatus to a stirred suspension of lithium aluminium hydride (1.75 g, 46.0 mmol) in diethyl ether (40 ml). The resultant mixture was then stirred at room temperature for 1 h before careful addition of a saturated solution of aqueous sodium sulphate to form a white granular precipitate from which the organic layer could be decanted. The organic layer, and further ethereal washings were combined, and the ether removed by distillation at atmospheric pressure through a Vigreux column. The residue was then finally subjected to bulb-to-bulb distillation to afford 2,2-dimethylbutan-1-ol (6.0 g, 76 %, bp 132–135 °C) as a colourless oil.

Oxidation of primary alcohols (representative procedure)

A round-bottom flask was charged with 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) (0.08 g 0.50 mmol), 4-methylpentanol (5.11 g, 50 mmol) and CH_2Cl_2 (20 ml). Potassium bromide (1.20 g, 10.1 mmol in 2.5 ml water) was added to this solution, and the resulting mixture was stirred vigorously while being cooled to −10 °C in a NaCl-ice bath. A mixture of aqueous sodium hypochlorite solution (66 ml of 1.5 M, 0.10 mmol) and sodium bicarbonate (0.91 g, 10.8 mmol) was added over a period of 20–30 min, keeping the temperature below 15 °C. The mixture was left to stir for a further 5 min at room temperature before the organic phase was separated and diluted in pentane (20 ml). This solution was then washed with 1 M HCl (10 ml) in KI (0.16 g, 0.96 mmol), 10 % aqueous sodium thiosulphate solution (20 ml), sodium bicarbonate solution (10 ml) and water (10 ml). The organic phase was dried over sodium sulfate and distilled at atmospheric pressure first through a Vigreux column, to remove the majority of the solvent, and finally by bulb-to-bulb distillation to afford 4-methylpentanal (1.50 g, 30%) as a colourless liquid.

Hexanal[42] δH (300 MHz, $CDCl_3$) 9.78 (1H, t, $J = 1.8$ Hz), 2.43 (2H, dt, $J = 7.2$ and 1.8 Hz), 1.65 (2H, q, $J = 7.2$ Hz), 1.36–1.29 (4H, m) and 0.91 (3H, t, $J = 6.9$ Hz); δC (300 MHz, $CDCl_3$) 202.9, 43.9, 31.3, 22.4, 21.8, 13.8.

4-Methylpentanal[43] δH (300 MHz, $CDCl_3$) 9.79 (1H, t, $J = 2.1$ Hz), 2.48–2.42 (2H, m), 1.68–1.51 (3H, m), 0.93 (6H, d, $J = 6.3$ Hz); δC (300 MHz, $CDCl_3$) 203.0, 42.0, 30.8, 27.7, 22.3.

3-Methylpentanal[44] δH (500 MHz, $CDCl_3$) 9.70 (1H, t, $J = 2.5$ Hz), 2.34 (1H, ddd, $J = 16.0$, 5.5 and 2.0 Hz), 2.16 (1H, ddd, $J = 16.0$, 8 and 2.5 Hz), 1.92 (1H, oct, $J = 7.0$ Hz), 1.35–1.27 (1H, m), 1.23–1.17 (1H, m), 0.89 (3H, d, $J = 6.5$ Hz) and 0.84 (3H, t, $J = 7.5$ Hz); δC (300 MHz, $CDCl_3$) 203.2, 50.7, 29.8, 29.5, 19.5, 11.3.

2-Methylpentanal[45] δH (300 MHz, $CDCl_3$) 9.64 (1H, d, J = 2.1), 2.37 (1H, dhx, $J = 6.9$ and 2.1 Hz), 1.76–1.63 (1H, m), 1.47–1.27 (3H, m), 1.11 (3H, d, $J = 6.9$ Hz), 0.95 (3H, t, $J = 6.9$ Hz); δC (400 MHz, $CDCl_3$) 205.5, 46.1, 31.6, 20.1, 13.9, 13.3.

3,3-Dimethylbutanal[46] δH (300 MHz, $CDCl_3$) 9.86 (1H, d, $J = 3.0$ Hz), 2.28 (2H, d, J = 3.0 Hz), 1.09 (9H, s); δC (300 MHz, $CDCl_3$) 203.6, 56.6, 30.9, 29.8.

2,3-Dimethylbutanal[47] δH (200 MHz, $CDCl_3$) 9.67 (1H, d, $J = 3.0$ Hz), 2.30–2.00 (2H, m) 1.04 (3H, d, $J = 10.2$ Hz), 1.00 (3H, d, $J = 10.2$ Hz), 0.92 (3H, d, $J = 10.2$ Hz); δC (400 MHz, $CDCl_3$) 205.8, 52.4, 28.4, 20.6, 18.7, 9.5.

2-Ethylbutanal[48] δH (300 MHz, $CDCl_3$) 9.59 (1H, d, $J = 3$ Hz), 2.18–2.08 (1H, m), 1.75–1.46 (4H, m), 0.93 (6H, t, $J = 7.5$ Hz); δC (300 MHz, $CDCl_3$) 205.6, 54.9, 21.4, 11.4.

2,2-Dimethylbutanal[49] δH (300 MHz, $CDCl_3$) 9.47 (1H, s), 1.54 (2H, q, $J = 7.5$ Hz), 1.06 (6H, s), 0.86 (3H, t, $J = 7.5$ Hz); δC (300 MHz, $CDCl_3$) 206.7, 46.0, 29.8, 20.8, 8.6.

Behaviour of solutions observed by NMR

A stock buffer solution of deuterated methanol containing 0.050 M deuterated acetic acid and 0.025 M triethylamine was initially prepared. Eight vials were prepared each containing a hexanal (10 μl) isomer and 1 ml of the stock solution. The samples were left overnight before being transferred to a Bruker 400 MHz NMR spectrometer and allowed to equilibrate at 25 °C for at least 20 min. A ^{1}H NMR spectrum of each isomer was then acquired, recording accurate integration values for the aldehyde (≈ 9.5 ppm) and hemi-acetal (4.5–4 ppm) resonances, and the equilibrium constant, $K = [\text{Hemi-acetal}]_{eq}/[\text{Aldehyde}]_{eq}$ was evaluated as the ratio of integrals.

Kinetics of reactions of aldehydes with methanol

Methanol was taken from a 2.5 l bottle of anhydrous methanol (Aldrich 0.005% water), which was freshly opened and then stored under nitrogen atmosphere. Triethylamine was distilled from KOH pellets through a 20 cm Vigreux column and stored under nitrogen. Acetic acid was redistilled through a 20 cm Vigreux column before taking a centre cut which was stored under nitrogen.

A buffer solution of methanol containing 0.050 M acetic acid and 0.025 M triethylamine was initially prepared. This stock solution was then further diluted in methanol to produce two new acetic acid solutions of 0.0333 M and 0.0166 M giving a total of three different concentrations of buffer.

In a typical kinetic experiment, aliquots of methanolic buffer (3 ml) were pipetted into stoppered quartz 1 cm UV cells, which were placed in the thermostatted block of the UV spectrometer and allowed to equilibrate to the set temperature for at least 20 min. Spectra were recorded on a Varian Cary Bio-50 single beam spectrometer using a multiblock whose temperature was controlled by a Varian Cary PCB 150 water Peltier system. Initially, the spectrum of the appropriate hexanal isomer was recorded by scanning between 400 and 200 nm to identify the maximum of the n-π^* carbonyl excitation ($\lambda_{max} = 287$ nm). Reaction kinetics were then monitored by adding 10 μl of the appropriate hexanal to a fresh buffer solution, with agitation by a Teflon paddle (to make them *ca* 0.03 M in aldehyde) while monitoring absorbance at 287 nm. Mixing was complete in less than 2 s, and initial absorbances, *ca* 1.3, were obtained by extrapolating curves back to initial addition. The changes in absorbance were first order and monitored for at least five half-lives. Rate constants were extracted by non-linear least squares fitting of $A_{calc} = A_{inf} - \Delta A\ e^{-kt}$ to the data. A plot of the rate constant at different concentrations of buffer against concentration of acetic acid produced a straight line, which could be extrapolated back to determine the rate constant at zero buffer concentration (see main text)

Experiments were repeated with a second buffer mixture containing initially 0.045 M Et_3N and 0.03 M in HOAc.

Acknowledgements

This work was supported by a grant from EPSRC (UK). We thank Dr Paul Christian (University of Manchester) for the use of his centrifuge. This work arose from enjoyable and useful conversations with Professor Peter Guthrie (University of Western Ontario), and we thank him and Dr T.W. Bentley (University of Swansea) for prepublication comment on the MS.

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