Geometrical preferences for general acid-catalysed hydride transfer: comparative theoretical study of transition structures for reduction of formaldehyde

John Wilkie and Ian H. Williams *
School of Chemistry, University of Bath, Bath, UK BA2 7AY

The geometries of transition structures (TSs) for acid-catalysed hydride reduction of formaldehyde have been determined using several different theoretical methods. In each case hydride transfer (HT) and proton transfer (PT) occur in roughly perpendicular planes. The TS for the simplest system, with methylamine as the hydride donor and ammonium as the proton donor, exists in three conformations differing in the orientation of methylamine about the axis for HT; the preferred conformer has been studied using the AM1, PM3, HF/3-21G, HF/6-31G** and MP2/6-31G** methods. TSs with dihydropyridine as the hydride donor and with imidazolium as the proton donor have been studied using the AM1, PM3 and HF/3-21G methods, and show very similar overall structural features. Most of the TSs are for concerted HT and PT, but the PM3 method predicts some reactions to be stepwise with rate-determining HT. All the TSs show PT to be very much more advanced than HT. The preferred distance between the donor and acceptor carbon atoms for HT is about 2.6 Å for a system bearing an overall positive charge in the HT moiety. As compared with more sophisticated models for the mechanism of reduction by lactate dehydrogenase, the use of very simple models does not materially alter the nature of the TS, which seems to be a rather structurally robust entity.

Introduction

Site-directed mutagenesis has afforded mutants of the enzyme lactate dehydrogenase (LHD) in which individual active-site residues have been substituted, and a wealth of kinetic, thermodynamic and structural data now exists[1] which has led to mechanistic hypotheses concerning the catalytic roles of several amino-acid side-chain groups; these now invite complementary investigation by computational modelling methods. As part of a larger programme of modelling studies, we have performed quantum-chemical calculations upon the uncatalysed model reaction (1) whose essential components are a hydride donor (dihydropyridine), a carbonyl substrate (formaldehyde), and a proton donor (imidazolium cation). We have reported[2] a transition structure (TS) for this reaction, obtained by complete optimization of all geometrical degrees of freedom *in vacuo*, using the AM1 semiempirical molecular-orbital (MO) method,[3] which suggests that the hydride-transfer (HT) and proton-transfer (PT) components of the process are kinetically coupled (the mechanism is concerted) but dynamically uncoupled (PT is significantly more advanced than HT in the TS). Increasing the basicity of the imidazole moiety, by means of a suitably placed dipole of variable magnitude, leads to essentially no change in the degree of PT in the TS but to a substantial increase in the degree of HT, in accord with predictions made using a More O'Ferrall–Jencks (MOFJ) diagram.† Correspondingly, the primary kinetic isotope effect (KIE) calculated for replacement of the transferring proton by a deuteron shows little change, but there is a significant increase in the magnitude of the calculated primary KIE for replacement of the transferring protide by a deuteride as the TS structure changes with increasing basicity of the imidazole moiety. These theoretical findings have since received support from an experimental study[4] of benzoquinone reduction by an NADH analogue, which found evidence for a mechanism in which hydride transfer is concerted with proton transfer from a general-acid catalyst, and which showed KIEs of similar magnitudes to those calculated for our model reaction.

Our previous AM1 theoretical study was concerned with *changes* in the geometry of the TS rather than with the absolute values of the various geometrical parameters, but nonetheless it is pertinent to enquire as to the reliability of this semi-empirical MO method for studies of this nature. The purpose of the present work is to compare the important geometrical features of the TS for reaction (1) as predicted not only by AM1 but also by the PM3 semiempirical MO method[5] and by the HF/3-21G *ab initio* MO method. Furthermore, we present analogous results for the very similar reaction (2), in which ammonium replaces imidazolium as the proton donor, and for the simpler reaction (3), in which methylamine replaces dihydropyridine as the hydride donor; the smaller size of the latter system permits the comparison to be extended also to the HF/6-31G** and MP2/6-31G** *ab initio* MO methods.

Computational methods

Semiempirical MO calculations with either the AM1 or PM3 Hamiltonian were performed using the MOPAC version 6.0 program[6] on a Hewlett-Packard 720 workstation. *Ab initio* MO calculations were performed using the GAUSSIAN92 program[7] on a Convex C3480 supercomputer. All TSs were determined by gradient search techniques, without any constraints, and using the default gradient norm criterion for geometry optimization, unless otherwise stated. These structures were shown to be first-order saddle points by virtue of possessing a single imaginary vibrational frequency for the reaction coordinate mode, and in each case the intrinsic reaction coordinate path was followed forwards and backwards in order to establish the identity of the species in the adjacent energy minima.

† More O'Ferrall[27]–Jencks[18b] diagrams are two-dimensional 'maps of alternative routes'[28] with an implied third dimension of energy assumed to have the form of a saddle, thus representing the TS region of a potential-energy surface for a reacting system. The use of these popular empirical constructs for predictions of TS structural change and mechanistic change has been well described in at least two texts.[29,30]

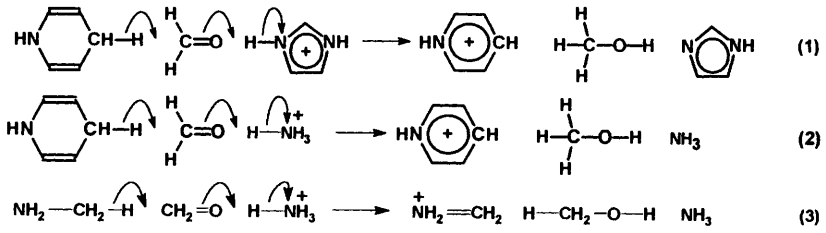

Table 1 Calculated bond lengths (in Å) and derived constants c for use with the Pauling relation for bond order, $n = \exp[(r_1 - r_n)/c]$

	CH_4	$(CH_3 \cdots H \cdots CH_3)^+$		$(H \cdots CH_3 \cdots H)^-$		CH_3OH	
Method	n(CH) = 1.0	n(C ··· H) = 0.5	c	n(C ··· H) = 0.5	c	n(H_hC) = 1.0	n(OH_p) = 1.0
AM1	1.1116	1.2714	0.23	1.2948	0.26	1.1190	0.9641
PM3	1.0870	1.2605	0.25	1.2769	0.27	1.0936	0.9487
HF/3-21G	1.0829	1.2339	0.22	1.7016	0.89	1.0849	0.9659
HF/6-31G**	1.0836	1.2361	0.22	1.7071	0.90	1.0861	0.9419
MP2/6-31G**	1.0854	1.2153	0.19	1.6569	0.82	1.0906	0.9622

Results and discussion

Pauling bond orders

To facilitate comparison of the transition structures between different theoretical methods it is convenient to use the Pauling bond orders[8] n(H_hC) and n(OH_p) to measure the extent of bond formation, respectively, between the transferring hydride and the carbonyl carbon and between the carbonyl oxygen and the transferring proton. These are defined as $n = \exp[(r_1 - r_n)/c]$, where r_1 and r_n are lengths for bonds of order 1 and n, respectively. A value of 0.3 for the constant c was determined empirically by Sims and co-workers[9] and has been widely employed in conjunction with the BEBOVIB method for empirical modelling of transition-state structure.

Pauling commented[8] that 'there is some evidence that the constant varies with the kind of atom and with the type of bond', although he was unable to determine the nature of the variation. We note that the experimental bond lengths used to derive the generalized value $c = 0.3$ all corresponded to bond orders of unity or greater (*e.g.*, the series ethane, benzene, ethene and ethyne) in which the variation is due to changes in hybridization and in the degree of π-bonding. In contrast, variation in lengths of partial bonds of order less than unity, as occurs in TSs, is always due to changes in the degree of σ-bonding. There is no reason why the same value of c should apply in these instances, but of course there are no experimental data available from which to derive appropriate values.

With theoretically calculated molecular geometries it is possible to use a value determined for each method and calibrated by standard bonds of order 1.0 and 0.5: for this purpose we define the C–H bond in methane to have $n = 1.0$ and the C ··· H bond in D_{3d}-symmetrically protonated ethane $(CH_3 \cdots H \cdots CH_3)^+$ to have $n = 0.5$. The latter provides a suitable definition since this species corresponds to hydride half-transferred from methane to the methyl cation. An alternative definition for $n = 0.5$ might be the C ··· H bond in the D_{3h}-symmetrical transition structure $(H \cdots CH_3 \cdots H)^-$ for the S_N2 reaction of methane within hydride anion. Bond lengths and derived values of the constant c for each of the theoretical methods used in this work are presented in Table 1. It is clear that the value of c is more consistent as between the various methods when the C ··· H bond in $(CH_3 \cdots H \cdots CH_3)^+$ is taken as the standard for $n = 0.5$. Interestingly, both the semiempirical methods yield similar values for c (in the range 0.23–0.27) regardless of which standard is chosen; these are in agreement with the value of 0.26 adopted by Johnston for studies of hydrogen-atom transfer using the BEBO method.[10]

Transition-state structures

Table 2 contains a selection of bond lengths, valence angles and dihedral angles describing the geometry of the HT and PT components of each TS, as optimized using each of the methods and as illustrated in Figs. 1–5. The atomic labelling scheme is shown in the figures. Table 3 contains Pauling bond orders for the making H_hC and OH_p bonds, together with the reaction coordinate vibrational frequency and the energy for each TS. Some geometrical data are presented in Table 4 for TSs of symmetrical hydride-transfer reactions as calculated by several *ab initio* methods, and in Table 5 for the PT and HT TSs and intermediate of the stepwise mechanisms predicted by the PM3 method.

Methylamine–formaldehyde–ammonium

Perhaps the most immediate observation to emerge from inspection of Fig. 1 is the overall similarity of the transition structures determined by each of the theoretical methods. The values of the dihedral angle C_hCON_p (in the range 101–109°) show that HT and PT occur in roughly perpendicular planes. HT follows a Bürgi–Dunitz[11] approach of the nucleophile to the carbonyl π-system (valence angle H_hCO has values in the range 104–111°), and PT takes place along a pre-existing hydrogen bond between the proton donor and an in-plane sp^2 lone pair on the carbonyl oxygen. This accords with expectation for the reverse reaction (dehydrogenation) based upon stereoelectronic considerations:[12] departure of hydride as a leaving group from the alcohol is facilitated by an antiperiplanar lone pair in preference to an antiperiplanar OH bond.

The reaction-coordinate vibrational mode comprises motions of both the hydride and the proton in the expected directions; the HT and PT components are thus kinetically coupled.[13] Geometrically, however, transfer from the hydride donor has progressed to only a small degree in each TS, whereas transfer from the proton donor is very advanced; in this sense HT and PT are dynamically uncoupled.[13] Any experimental kinetics study of a reaction with a TS such as this would lead to the conclusion of a concerted mechanism. All of the theoretical methods predict this reaction to proceed by concerted general acid catalysis.

To generalize, the semiempirical methods tend to predict

Table 2 Calculated geometries of transition structures for acid-catalysed hydride reduction[a]

Method	C_hC	C_hH_h	H_hC	C_hH_hC	ON_p	OH_p	H_pN_p	OH_pN_p	H_hCO	N_hC_hCO	C_hCON_p
Methylamine–formaldehyde–ammonium (*syn*)											
AM1	2.717	1.238	1.524	159.3	2.695	1.045	1.655	173.6	104.5	−3.5	101.7
PM3	2.744	1.331	1.424	169.6	2.687	0.994	1.701	170.5	111.0	−5.6	104.8
HF/3-21G	2.550	1.280	1.376	147.5	2.557	1.071	1.490	173.8	106.7	−6.5	108.4
HF/6-31G**	2.587	1.257	1.422	149.7	2.691	0.991	1.704	173.5	107.6	−8.2	102.8
MP2/6-31G**	2.547	1.229	1.433	146.0	2.542	1.083	1.463	172.5	105.1	−6.4	103.2
Methylamine–formaldehyde–ammonium (*anticlinal*$^+$)											
AM1	2.791	1.222	1.582	168.8	2.627	1.084	1.547	173.7	103.5	115.2	95.1
PM3	2.844	1.175	1.670	176.0	2.646	1.018	1.635	171.1	110.1	114.1	93.4
HF/3-21G	2.563	1.279	1.354	153.7	2.556	1.072	1.486	175.2	108.8	118.0	110.1
Methylamine–formaldehyde–ammonium (*anticlinal*$^-$)											
AM1	2.721	1.249	1.490	167.0	2.703	1.040	1.677	173.8	103.9	−141.0	95.3
PM3	2.742	1.342	1.404	173.6	2.688	0.993	1.704	170.2	109.1	−119.2	101.8
HF/3-21G	2.548	1.279	1.374	147.7	2.541	1.084	1.461	174.0	106.9	−163.6	108.7
Dihydropyridine–formaldehyde–ammonium											
AM1	2.776	1.195	1.659	152.8	2.633	1.081	1.555	175.0	103.6	67.1	101.7
(PM3	2.998	1.134	1.993	145.6	2.628	1.032	1.604	170.9	108.9	60.2	104.8)[b]
HF/3-21G	2.636	1.207	1.479	121.2	2.526	1.105	1.423	175.4	107.0	53.6	102.6
Dihydropyridine–formaldehyde–ammonium (*antiperiplanar* structure)											
AM1	2.728	1.436	1.292	179.5	2.625	1.522	1.119	167.4	107.0	0.0	180.0
Dihydropyridine–formaldehyde–imidazolium											
AM1	2.855	1.180	1.727	157.9	2.662	1.060	1.604	175.1	102.6	64.6	86.5
(PM3	2.776	1.258	1.524	172.1	2.672	0.998	1.675	176.6	110.3	55.3	96.7)[b]
HF/3-21G	2.596	1.265	1.383	157.3	2.470	1.170	1.302	174.9	107.4	50.1	106.0

[a] Bond lengths in Å, angles in degrees. [b] Transition structure for hydride-transfer step.

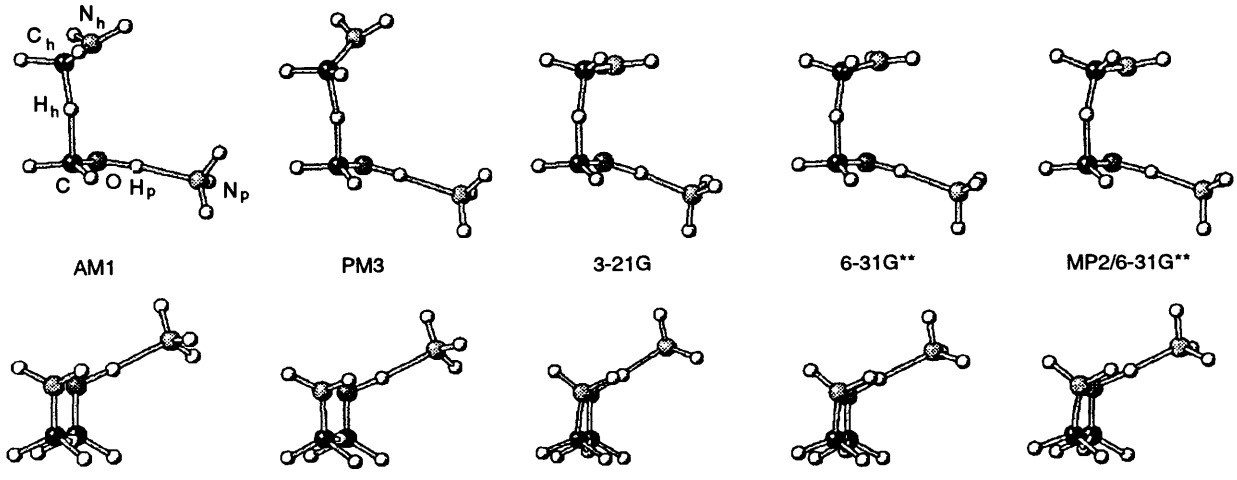

Fig. 1 Optimized transition structures for ammonium-catalysed concerted reduction of formaldehyde by methylamine proceeding through the *syn* conformation

slightly longer distances between the donor and acceptor groups for both the HT and PT components, and a slightly less bent angle C_hH_hC about the transferring hydride than do the *ab initio* methods. The donor–acceptor distances are shortest for the MP2/6-31G** method, with those for HF/3-21G being very similar. Consideration of the bond orders for H_hC and OH_p suggests that HT lags behind PT in the TS as predicted by each method. The small AM1 value for $n(H_hC)$ = 0.171 is in closest agreement with that for MP2/6-31G** (0.161). The latter method also predicts the smallest value for $n(OH_p)$. The reaction-coordinate frequency $\nu^‡$ predicted by AM1 also agrees best with the MP2/6-31G** value, being considerably less than either the PM3 or HF/3-21G predictions.

The dihedral angle N_hC_hCO defines the overall conformation of the HT component of the TSs; for each structure shown in Fig. 1 this value is close to zero, indicating an approximately coplanar *syn* arrangement in this fragment of the TS. It is of interest to note that this *syn* geometry is also preferred for the TSs of the symmetrical hydride transfer reactions (4) and (5) which have been the subjects of previous theoretical studies. The donor–acceptor distance C_hC, partial bond length C_hH_h and angle C_hH_hC (Table 4) in the TSs for reaction of methylamine with methaniminium [14,15] and of methoxide with formaldehyde [14,16] vary with the theoretical method employed in the same way as for the present asymmetric hydride transfer from methylamine to (partially protonated) formaldehyde. At

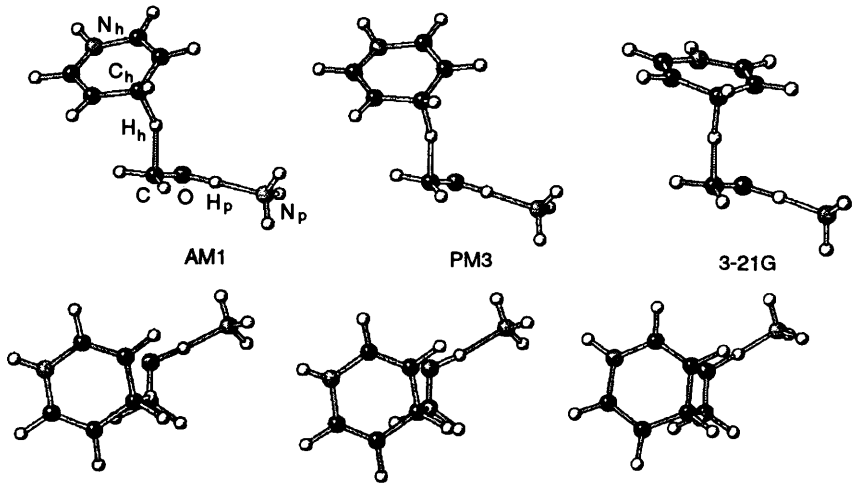

Fig. 2 Optimized transition structures for ammonium-catalysed reduction of formaldehyde by dihydropyridine. AM1 and HF/3-21G TSs are for a concerted mechanism, PM3 TS is for the hydride-transfer step of a stepwise mechanism.

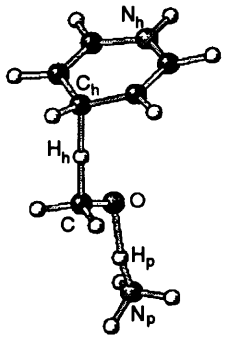

Fig. 3 AM1 optimized second-order transition structure for ammonium-catalysed reduction of formaldehyde by dihydropyridine proceeding through the *antiperiplanar* conformation

each level of theory the C_hC and C_hH_h distances for the present general-acid catalysed reaction are much closer to those in the (positively charged) methylamine–methaniminium TS than to those in the (negatively charged) methoxide–formaldehyde TS. This suggests that the hydride acceptor is essentially cationic, which is consistent with PT being significantly more advanced than HT.

As the results in Tables 2 and 3 reveal, the TS for reaction (3) may adopt two other conformations, with dihedral angle $N_hC_hCO \approx \pm 120°$; these may be denoted as *gauche*$^+$ and *gauche*$^-$, respectively. The *anticlinal*$^+$ conformer lies higher in energy than the *syn* conformer by 0.27 or 2.3 kcal mol^{-1} according to AM1 or HF/3-21G, respectively, although PM3 predicts it to be lower by 0.31 kcal mol^{-1}. The *anticlinal*$^-$ conformer is a mere 0.01 kcal mol^{-1} higher than the *syn* at the AM1 level, or 0.19 kcal mol^{-1} higher with PM3. At the HF/3-21G level no stationary point satisfying the regular criteria for convergence could be located for this conformer, despite its very low gradient, the *anticlinal*$^-$ structure reported in Tables 2 and 3 optimized spontaneously to the *anticlinal*$^+$ conformer. In all other regards the geometries of these alternative conformers are very similar to those of the *cis* conformer at the various levels of theory.

Table 3 Calculated Pauling bond orders, reaction coordinate vibrational frequencies and energies of transition structures for acid-catalysed hydride reduction

Method	$n(H_hC)$	$n(OH_p)$	$\nu^{\ddagger}$ [a]	Energy [b]
Methylamine–formaldehyde–ammonium (*syn*)				
AM1	0.172	0.703	677i	122.38
PM3	0.267	0.834	1229i	136.17
HF/3-21G	0.266	0.621	1021i	−264.144 42
HF/6-31G**	0.217	0.800	980i	−265.627 70
MP2/6-31G**	0.161	0.523	552i	−266.483 15
Methylamine–formaldehyde–ammonium (*anticlinal*$^+$)				
AM1	0.134	0.593	476i	122.65
PM3	0.100	0.758	840i	135.86
HF/3-21G	0.294	0.617	1083i	−264.140 70
Methylamine–formaldehyde–ammonium (*anticlinal*$^-$)				
AM1	0.199	0.719	648i	122.39
PM3	0.289	0.838	1297i	136.36
(HF/3-21G	0.276	0.575	1090i, 47i, 36i	−264.139 33)[c]
Dihydropyridine–formaldehyde–ammonium				
AM1	0.096	0.626	411i	149.54
(PM3	0.027	0.717	297i	156.26)[d]
HF/3-21G	0.167	0.531	984i	−415.927 09
Dihydropyridine–formaldehyde–ammonium (*antiperiplanar* structure)				
AM1	0.471	0.088	1280i & 151i	156.84
Dihydropyridine–formaldehyde–imidazolium				
AM1	0.071	0.659	287i	206.19
(PM3	0.078	0.749	812i	181.50)[d]
HF/3-21G	0.258	0.395	1477i	−583.613 68

[a] Wavenumber in cm^{-1}. [b] Heat of formation in kcal mol^{-1} for AM1 and PM3, total energy in Hartree for *ab initio* methods (1 Hartree = 627.5 kcal mol^{-1}). [c] RMS force = 5.5 × 10^{-4} au as compared with standard convergence criterion of 3.0 × 10^{-4}. [d] Transition structure for hydride transfer step.

Dihydropyridine–formaldehyde–ammonium

Replacement of methylamine by the better hydride donor, dihydropyridine, leads to TSs (Fig. 2) closely resembling those discussed above, except that now it is a carbon–carbon bond that approximately eclipses the carbonyl bond of the hydride acceptor instead of a carbon–nitrogen bond. Each theoretical method used predicts that both HT and PT are less advanced than in the TS for the methylamine–formaldehyde–ammonium system. This can be rationalized by means of a MOFJ diagram [Fig. 6(*a*)]. Substitution of the more stable pyridinium cation for methaniminium cation leads to an energetic lowering across the whole top edge. The major component of the transition vector through the TS is HT, with PT being the minor

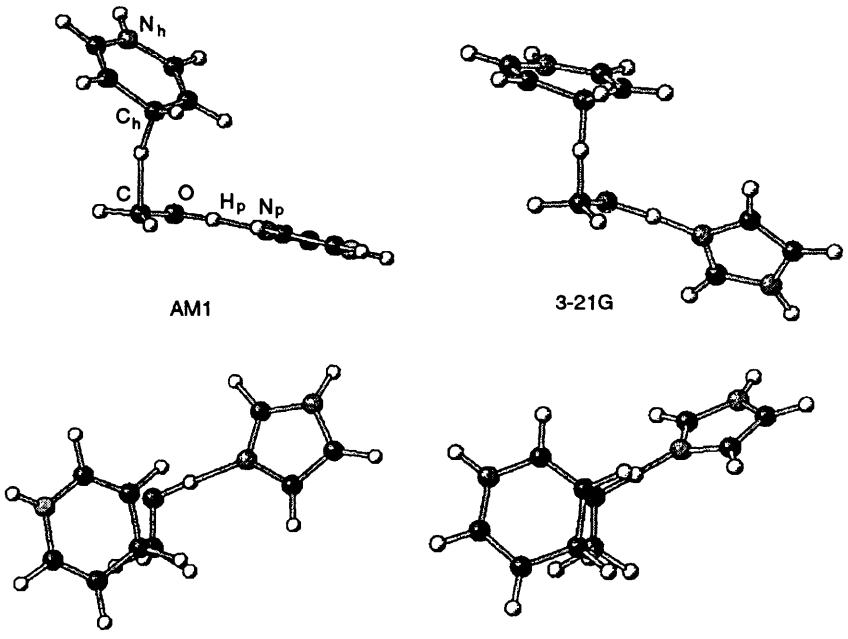

Fig. 4 AM1 and HF/3-21G optimized transition structures for imidazolium-catalysed concerted reduction of formaldehyde by dihydropyridine

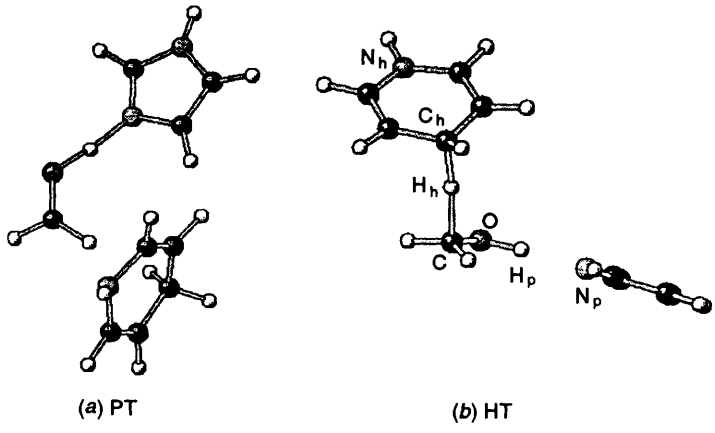

Fig. 5 PM3 optimized transition structures for imidazolium-catalysed stepwise reduction of formaldehyde by dihydropyridine: (*a*) proton-transfer step; (*b*) hydride-transfer step

Table 4 Some calculated bond lengths and angles for transition structures of symmetrical hydride-transfer reactions[a]

Method	C_hC	C_hH_h	C_hH_hC
Methylamine–methaniminium[b,c]			
HF/3-21G	2.578	1.322	154.3
HF/6-31G*	2.615	1.335	156.8
MP2/6-31G*	2.557	1.325	149.6
Methoxide–formaldehyde[b,d]			
HF/3-21G	2.662	1.420	139.2
HF/6-31G*	2.75	1.452	142
MP2/6-31+G	2.67	1.360	159

[a] Bond lengths in Å, angles in degrees. [b] Ref. 14. [c] Ref. 15. [d] Ref. 16.

component, so the resultant of the parallel effect (relatively larger shift away from the product structure, top right) and perpendicular effect (relatively smaller shift towards the HT intermediate, top left) of the substitution is a change in the TS location to smaller degrees of both HT and PT.

As the nucleophilic hydride attacks the carbon atom of formaldehyde, the electron density of the carbonyl π-bond may be expected to localize upon the oxygen atom, but on the opposite face from that of the new H_hC σ-bond. Thus naïvely it might be thought that the proton donor should be positioned in an antiperiplanar orientation with respect to the hydride donor. The C_s-symmetrical antiperiplanar TS (Fig. 3) located using the AM1 method possesses a second imaginary frequency corresponding to torsion about the axis of the carbonyl bond. Movement along this normal coordinate leads directly to the preferred TS (Fig. 2) in which the proton donor lies in a plane approximately perpendicular to the hydride donor. The antiperiplanar TS is of interest in that it shows HT to be well in advance of PT. This observation may also be understood with the aid of a MOFJ diagram [Fig. 6(*b*)]. The antiperiplanar orientation of the proton donor leads to a more favourable hydrogen-bonding interaction with the developing negative charge on oxygen, thus stabilizing the HT intermediate (top left-hand corner) with respect to the other structures. The change in TS location is predominantly the result of the perpendicular shift towards the HT

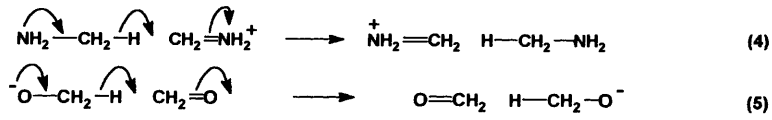

Table 5 PM3 calculated geometries, reaction-coordinate frequencies and energies of stationary structures along the reaction path for stepwise acid-catalysed hydride reduction[a]

Species	C_hC	C_hH_h	H_hC	C_hH_hC	ON_p	OH_p	H_pN_p	OH_pN_p	$\nu^{\ddagger}$ [a]	Energy
Dihydropyridine–formaldehyde–ammonium										
TS for PT	3.688	1.111	3.225	105.9	2.524	1.110	1.425	169.5	1124i	154.55
intermediate	3.650	1.111	3.177	106.4	2.614	1.044	1.578	170.5	—	154.11
TS for HT	2.998	1.134	1.993	145.6	2.628	1.032	1.604	170.9	297i	156.26
Dihydropyridine–formaldehyde–imidazolium										
TS for PT	3.614	1.117	2.813	128.4	2.509	1.141	1.370	174.6	1522i	176.64
pre-HT intermediate	2.871	1.159	1.732	166.3	2.632	1.022	1.611	177.9	—	180.57
TS for HT	2.776	1.258	1.524	172.1	2.672	0.998	1.675	176.6	812i	181.50

[a] Bond lengths in Å, angles in degrees, wavenumber in cm^{-1}, heat of formation in kcal mol^{-1}.

intermediate, giving a greater degree of HT and a lesser degree of PT.

The PM3 method predicts a stepwise mechanism for this reaction, the details of which are discussed below. The results presented in Tables 2 and 3, and the structure shown in Fig. 2, are for the TS of the second step, in which HT is occurring.

Dihydropyridine–formaldehyde–imidazolium

Replacement of ammonium by imidazolium as the proton donor may be expected to perturb the TS as a consequence of the greater gas-phase proton affinity of (the more basic) imidazole than of ammonia. According to a MOFJ diagram [Fig. 6(*c*)] stabilization of the protonated form of the proton donor causes a lowering of the energy of the left-hand edge, and the resultant of the parallel and perpendicular components would be to shift the TS towards more HT but with little change in PT. Although this simple prediction was borne out by our earlier AM1 results with a range of modified ammonium proton donors,[2] the present results do not quite conform to expectation. Both the AM1 and HF/3-21G methods lead to TSs (Fig. 4) for concerted, general acid-catalysed hydride transfer in which, as usual, PT is more advanced than HT. However, although replacement of ammonium by imidazolium causes very little change in the degree of PT at the AM1 level, the degree of HT appears to decrease slightly rather than increase. At the HF/3-21G level, for which the transition vector is not so dominated by HT, the same replacement leads to greater HT (as expected) but also significantly less PT (unexpected!) We have shown elsewhere how simple MOFJ diagrams can be misleading:[17] the actual shifts in TS structure may arise from specific interactions within the encounter complexes not modelled by simple considerations of increased or decreased stability of individual components. In this context it may be noted that the energy of a complex in which the bond orders are finite but very small (*e.g.*, 0.01, corresponding to bond extensions of *ca.* 1.15 Å) is likely to be quite different from a system with zero bond orders (corresponding to infinite separations).[17b]

We have searched in vain for further stationary points upon the AM1 energy surface corresponding to the intermediate state, either dihydropyridinium–methoxide–imidazolium or dihydropyridine–protonated-formaldehyde–imidazole, of the alternative stepwise mechanisms, but have found only the one TS for a concerted mechanism. As shown by Fig. 4, the AM1 and HF/3-21G TSs are qualitatively similar, except that for AM1 the plane of the dihydropyridine ring is pitched more steeply with respect to the plane of the formaldehyde, and for HF/3-21G the plane of the imidazole is more twisted with respect to that of formaldehyde.

However, with PM3 the story is quite different for both the dihydropyridine–formaldehyde–ammonium and dihydropyridine–formaldehyde–imidazolium systems. These reactions are predicted by this method to follow stepwise, specific-acid-catalysed mechanisms in which HT step is rate-determining and in which the HT TSs closely resemble those for the concerted processes discussed above. The first of these is simpler in that there is just one intermediate, in which PT from ammonium to formaldehyde has occurred. Geometrical parameters of interest for the two TSs and the intermediate are given in Table 5, which also contains these data for the dihydropyridine–formaldehyde–imidazolium system. This latter reaction, however, is more complex. In the first step, PT from imidazolium to formaldehyde occurs *via* a TS with $\nu^{\ddagger} = 1522\ cm^{-1}$ leading to a shallow well for a first intermediate. The hydride donor then swings around from beside to above the carbonyl group in an extremely shallow well for a second intermediate before settling into position, poised for nucleophilic attack, in a third, pre-HT intermediate. In the final step, HT occurs *via* a TS with $\nu^{\ddagger} = 812\ cm^{-1}$ leading to methanol as the product of the reduction. The TSs for PT and HT are shown in Fig. 5. Despite the change of mechanism, it is worth emphasizing that the TSs for the rate-determining HT steps are very similar to those for the concerted processes discussed above.

Concerted *vs.* stepwise mechanisms: comparison with related studies

The criteria for concerted general-acid catalysis of complex reactions in aqueous solution as summarised by Jencks[18] may be restated for gas-phase reactions as follows: the site of protonation must undergo a large change in basicity during the reaction to convert an unfavourable proton transfer from the catalyst into a favourable one. As the data presented in Table 6 show, proton transfer from either ammonium or imidazolium is unfavourable to formaldehyde but is strongly favourable to methoxide according to both the AM1 and PM3 methods. Correspondingly, it may be noted that protonation on oxygen converts a very unfavourable hydride transfer to the carbonyl group into a favourable one. It is no surprise, therefore, that concerted general acid-catalysed hydride transfer is predicted for most of the reactions studied here. What is surprising is that

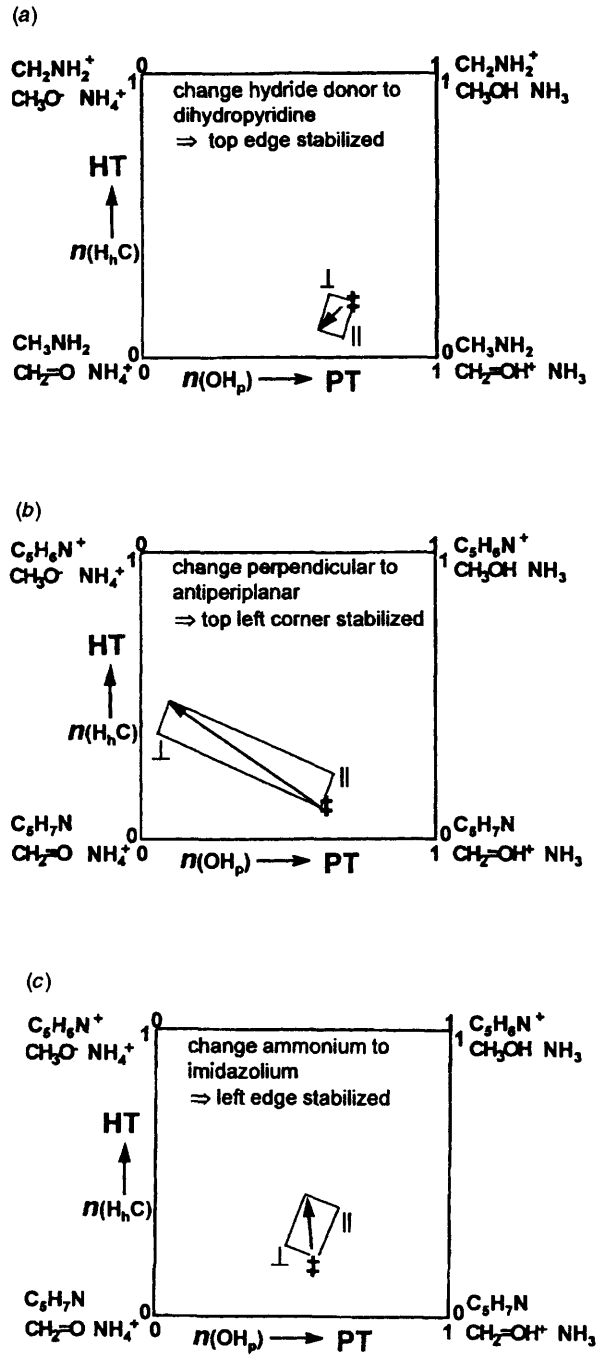

Fig. 6 More O'Ferrall–Jencks diagrams to illustrate changes in TS structure arising from: (*a*) substitution of dihydropyridine as hydride donor in methylamine–formaldehyde–ammonium system; (*b*) change from perpendicular to antiperiplanar conformation of dihydropyridine–formaldehye–ammonium system; (*c*) substitution of imidazolium as proton donor in the dihydropyridine–formaldehyde–ammonium system

the PM3 method actually predicts stepwise mechanisms for the reactions involving dihydropyridine as the hydride donor.

The primary driving force for a concerted mechanism is the avoidance of extremely unstable species as intermediates in either of the alternative stepwise mechanisms (top left- and bottom right-hand corners of the MOFJ diagrams, Fig. 5).[18] From the opposite viewpoint, it may be that concerted catalysis occurs only when intermediates are too unstable to exist for a finite time.[18,19] The intermediates on the PM3 energy surfaces for dihydropyridine–formaldehyde–ammonium and dihydropyridine–formaldehyde–imidazolium occur in very shallow wells (< 1 kcal mol^{-1}, Table 5) and are located at (0.68, 0.00) and (0.75, 0.08), respectively, in bond-order coordinates (PT, HT). Although the degree of HT is small or negligible, the hydride donor is nonetheless present in each case and exerts an influence upon the energy profile for proton transfer along the bottom edge of the MOFJ diagram, and is thus more than a mere spectator. Since this study has not included any evaluation of entropies or of solvation effects, it is not meaningful to consider whether these would be intermediates in stepwise pre-association mechanisms.

The change in mechanism which results from perturbation of the energy surface either due to variation of the hydride donor (replacement of methylamine by dihydropyridine) while keeping the method (PM3) unchanged, or else due to switching the method (from AM1 to PM3) while keeping the hydride donor unchanged, occurs in a structurally continuous fashion:[17] the intermediate created by means of a fold catastrophe in the energy surface has essentially the same geometry as the TS on the unperturbed surface for the concerted mechanism. In the present examples the perturbations are indeed small and the resulting fold is merely a ripple on each surface.

Andres *et al.*[20] recently published a PM3 theoretical supermolecule study of pyruvate reduction with *N*-methyl-1,4-dihydronicotinamide as the hydride donor, 4-methylimidazolium as the proton donor, and 1-methylguanidinium to bind the substrate carboxylate group. Apparently, the computed energy surface suggests a stepwise mechanism in this model for catalysis by LDH, and the TS for the rate-determining second step of HT was reported to be very similar to ours;[2] bond orders of $n(H_hC) = 0.27$ and $n(OH_p) = 0.84$ may be computed from their data, showing PT well in advance of HT. Ranganathan and Gready[21] have very recently reported the results of an AM1 study, analogous to that of Andres *et al.*, but in which the carboxamide side-chain of the model cofactor adopted a different orientation. This work also found a stepwise mechanism, although no TS for PT could be located. Their TS for the HT step has bond orders of $n(H_hC) = 0.27$ and $n(OH_p) = 0.91$. In each of these TSs the dihydronicotinamide ring is oriented such that one of its carbon–carbon bonds is approximately eclipsed with the ketone carbonyl bond of the pyruvate moiety, just as a carbon–carbon bond of the dihydropyridine ring is approximately eclipsed with the carbonyl bond of formaldehyde in the present work (Figs. 2, 4 and 5).

Independently of our work, Andres and co-workers have performed a comparative study of TSs for the model LDH mechanism, as described above, using the AM1 and PM3 methods, the results of which are reported in the preceding paper in this issue.[22] They find a single TS for the *N*-methyl-1,4-dihydronicotinamide–pyruvate(methylguanidinium)–4-methylimidazolium system with each method: these structures show PT to be much more advanced than HT, *i.e.*, bond orders of $n(H_hC) = 0.31$ and $n(OH_p) = 0.93$ for AM1 and $n(H_hC) = 0.27$ and $n(OH_p) = 0.84$ for PM3. Furthermore, they report that the intrinsic reaction coordinate path leads backwards to a reactant complex containing pyruvate and forwards to a product complex containing lactate: there is no evidence for any protonated pyruvate intermediate. Consequently it appears that each method predicts a concerted acid-catalysed mechanism for pyruvate reduction in this system, in agreement with our AM1 and HF/3-21G results for the simpler process of formaldehyde reduction, but in apparent contrast with the findings of Ranganathan and Gready. By all accounts, however, it seems that the factors responsible for determining the stepwise or concerted nature of these mechanisms are extremely subtle.

Table 6 AM1 and PM3 calculated proton and hydride affinities[a]

Reaction	AM1	PM3
Proton transfer		
$CH_2O + NH_4^+ \longrightarrow CH_2OH^+ + NH_3$	30.58	43.90
$CH_3O^- + NH_4^+ \longrightarrow CH_3OH + NH_3$	−175.47	−170.41
$CH_2O + C_3H_5N_2^+ \longrightarrow CH_2OH^+ + C_3H_4N_2$	34.85	52.99
$CH_3O^- + C_3H_5N_2^+ \longrightarrow CH_3OH + C_3H_4N_2$	−171.21	−161.32
Hydride transfer		
$CH_3NH_2 + CH_2O \longrightarrow CH_2NH_2^+ + CH_3O^-$	176.78	186.66
$CH_3NH_2 + CH_2OH^+ \longrightarrow CH_2NH_2^+ + CH_3OH$	−29.28	−27.65
$C_5H_7N + CH_2O \longrightarrow C_5H_6N^+ + CH_3O^-$	156.09	157.69
$C_5H_7N + CH_2OH^+ \longrightarrow C_5H_6N^+ + CH_3OH$	−49.97	−56.62

[a] Energy in kcal mol^{-1}.

Optimal donor–acceptor distance for hydride transfer

It is of interest to establish what is the intrinsically preferred geometry for hydride transfer in the absence of external perturbations. In an earlier study we have examined this question in some detail for simple, symmetrical hydride transfers in isoelectronic systems and concluded that the preferred angle about the transferring hydride depended on the subtle interplay of several factors, namely steric effects, electrostatic interactions, and the possibility of 2e or 6e transition-state aromaticity.[14] It seems probable to us that whatever structural features of an enzyme active site serve to stabilize the TS might also perturb the balance of forces responsible for the angular aspect of the HT geometry. Thus there might not be a strongly preferred angle of attack which an enzyme must maintain. On the other hand, the distance between the donor and acceptor groups is of considerable significance. Kraut and co-workers have observed[23] in dihydrofolate reductase (DHFR) that the binding sites for the dihydropteridine ring of the substrate dihydrofolate and for the dihydronicotinamide ring of the NADPH cofactor overlap by about 1 Å. The predicted van der Waals contact distance[24] between sp^3 and sp^2 carbon atoms (including attached hydrogens) is about 3.6 Å, as compared to a calculated donor–acceptor distance C_hC of about 2.6 Å in the TS for HT from methylamine to methaniminium.[14,15] This distance is about 3.1–3.3 Å between the substrate and cofactor in ternary complexes of DHFR.[23] Short donor–acceptor distances for HT have also been reported for glutathione reductase.[25] This observed crowding between substrates and cofactors may serve to stabilize the TS for an enzyme-catalysed reaction.[26]

Inspection of the data in Table 2 provides average values for the C_hC distance of about 2.77 Å (AM1), 2.82 Å (PM3) and 2.58 Å (HF/3-21G). The results obtained for the preferred conformer of the TS for the methylamine–formaldehyde–ammonium system with higher levels of *ab initio* theory (HF/6-31G** and MP2/6-31G**) confirm the HF/3-21G geometry and suggest that the semiempirical methods overestimate the C_hC distance in the TSs by about 0.2 Å. The data in Table 4 suggest that in TSs bearing an overall negative charge in the HT moiety this distance may be about 0.1 Å longer than in those bearing an overall positive charge.

Conclusions

There is a striking similarity between the TS geometries calculated for general-acid-catalysed hydride reduction of carbonyl groups using both semiempirical and *ab initio* MO methods and with different hydride donors and proton donors. Although there are differences of detail in regard to the relative degrees of HT and PT in these TSs, which are often (but not always) amenable to rationalization using very simple MOFJ diagrams, the overall structures do not differ greatly between TSs for concerted or stepwise mechanisms. The AM1 method may tend to overestimate the distance between the donor and acceptor groups for HT, but is not obviously inferior to any other theoretical method in regard to prediction of the TS bond orders for the making H_hC and OH_p bonds. All the TSs show PT to be very considerably in advance of HT. The use of simple models for the hydride donor (methylamine or dihydropyridine instead of *N*-methyldihydronicotinamide), substrate (formaldehyde instead of a pyruvate–methylguaninidinium complex) and proton donor (ammonium or imidazolium instead of 4-methylimidazolium) affects the energetics of the reduction, and thereby the relative degrees of HT and PT in the TS, but does not materially alter the nature of the TS, which seems to be a rather structurally robust entity.

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