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BIFUNCTIONAL AND MONOFUNCTIONAL CATALYSIS IN THE CNDO/2 APPROXIMATION

FORMAMIDINE ACID-BASE AND BASE CATALYSED 1,3-PROTON TRANSFERS IN PROPENE

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Abstract—The bifunctional acid-base and monofunctional base catalysis by formamidine of 1,3-proton transfer reactions in propene has been studied with the CNDO/2 MO-method. Energy profiles for both types of catalysis were studied, and no reaction intermediate was found in either case. In agreement with orbital correlation considerations, bifunctional catalysis is preferred over monofunctional catalysis. Comparison is made with another reaction in which simultaneous transfer of two protons occurs. The mechanism of bifunctional monofunctional catalysis is discussed.

INTRODUCTION

The suprafacial sigmatropic reaction of hydrogen of order (1·3) is a forbidden process according to the Woodward-Hoffman rules.[1] Experimentally no such processes are known to this date. On the other hand, base catalyzed 1,3-proton transfers have frequently been observed and are under certain conditions intramolecular and/or stereospecific reactions.[2] Thus the basic catalyst makes accessible a low energy pathway for the 1,3-proton transfer. This pathway presumably involves a loss of orbital phase memory by the hydrogen on its travel along the reaction coordinate, a process which obviously needs high energy to occur in an uncatalyzed thermal and suprafacial manner (Fig. 1a).

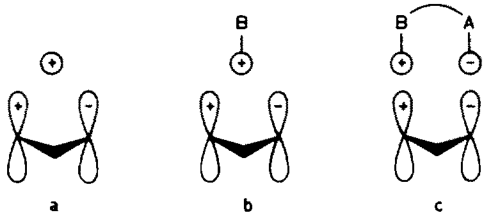

Fig. 1. Illustration of interactions in important orbitals involved in (a) uncatalyzed, (b) monofunctionally catalyzed and (c) bifunctionally catalyzed 1,3-proton transfer reactions.

A potential possibility of making 1,3-proton transfers concerted and further accelerated over monofunctional catalysis is to use bifunctional acid-base catalysts. In these molecules, the two catalytic functions can act more or less independently.

Bifunctional catalysis is a special case of multiple catalysis, which is believed to be an important mechanism in enzymatic catalysis.[3]

Bifunctional acid-base catalysis of 1,3-proton transfers has been the object of several experimental studies since Lowry first suggested the possibility of concerted catalysis.[4] Swain and Brown discovered the unusual catalytic power of 2-pyridone on the mutarotation of 2,3,4,6-tetramethyl-*D*-glucose and ascribed it to a concerted bifunctionally catalyzed 1,3-proton transfer[5] (Fig. 2a). This reaction, which involves molecules of the general type shown in Fig. 2b, has later been studied in detail by Rony and others.[6] It has also served as a model reaction for several studies in which the nature of the catalyst and of the substrate has been modified by changing the groups A, B, C, X, Y and Z.[7]

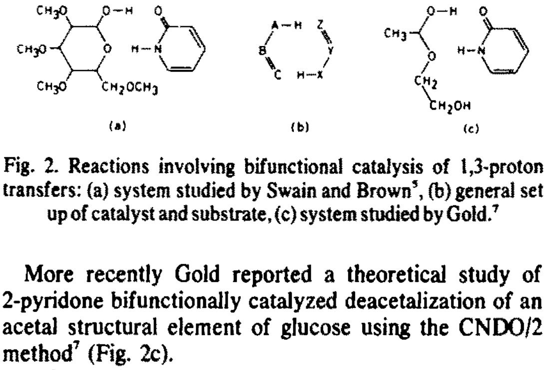

Fig. 2. Reactions involving bifunctional catalysis of 1,3-proton transfers: (a) system studied by Swain and Brown[5], (b) general set up of catalyst and substrate, (c) system studied by Gold.[7]

More recently Gold reported a theoretical study of 2-pyridone bifunctionally catalyzed deacetalization of an acetal structural element of glucose using the CNDO/2 method[7] (Fig. 2c).

This work presents the results of a comparative theoretical study of monofunctional formamidine base catalysis and bifunctional formamidine acid-base catalysis of 1,3-proton transfers in propene using the CNDO/2 molecular orbital method (Fig. 3).[8]

Method

The determination of energy surfaces and reaction paths by quantum chemical calculations requires approximate methods except for the simplest systems. The use of sophisticated procedures without geometry optimization may lead to unrealistic descriptions, e.g. unsymmetric double well potentials for the coupled motion of two H atoms in the dimer of formic acid.[9] The compromise between chemical relevance, numerical accuracy, and economy requires semi-empirical calculations, which are to be viewed as model systems. They provide model energy surfaces which complement the symmetry arguments of Woodward and Hoffmann, or even yield equivalent information.[1,10]

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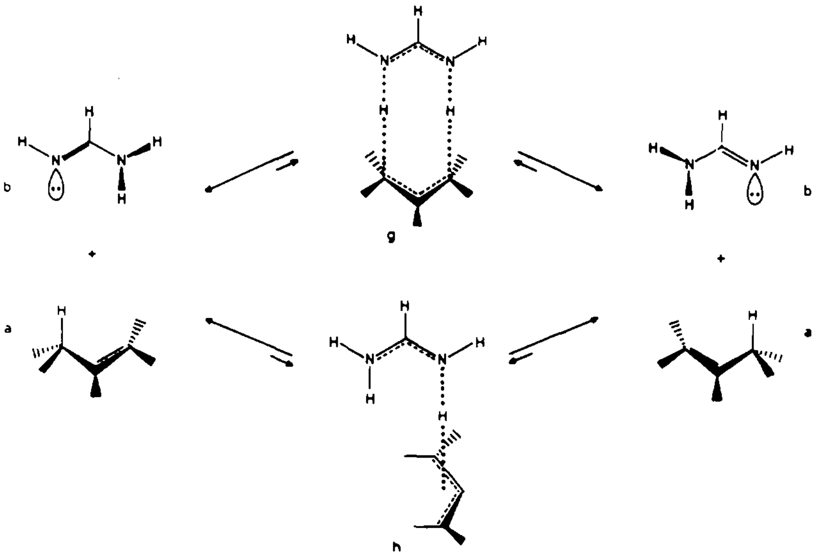

Fig. 3. Reactants, transition states and products for formamidine catalyzed 1,3-proton transfers in propene: (a) propene, (b) formamidine, (g) bifunctional transition state, (h) monofunctional transition state.

We have chosen the CNDO/2 approximation[11] since it has been intensively compared with both experiment and more elaborate calculations in a rather extensive number of situations.[12] Its limitations are well known: it gives too steep binding wells, and it is most successful when experimental geometries are used.[12] On the other hand, it has been quite successful in conformational analysis and in several reactivity problems.[13]

Of special significance is the study of the formic acid dimer by Schuster[14] using the CNDO/2 method and by Clementi *et al.*[9a] using‘ the non-empirical SCF-MO-LCAO IBMOL 5 method. These authors studied the stability of the dimer, the equilibrium distances and the energy surfaces for the concerted displacement of the two hydrogens for a given oxygen–oxygen distance. Clementi *et al.* also compared the displacement of one hydrogen keeping the other one fixed.

The coupled motion of the two hydrogens resembels at least superficially the systems studied in this article. The CNDO/2 method and the *ab initio* calculation show qualitative agreement.

Since the structures of the intermediate species are not known, optimization is required.

A second point of interest in connection with these calculations is the relatively high barrier obtained[9,14] when considering the simultaneous motion of the two protons in the formic acid dimer. This is claimed to be partially due to the lack of rehybridization of the oxygens, and partially to too large hydrogen-hydrogen repulsion in the transition state. This is of course a simplified picture.[9a]

RESULTS

The energies of the molecules and complexes studied were minimized with respect to the structural parameters believed to be the most important structural parameters. Table 1 collects the pertinent data and Fig. 4 shows the species described in more detail below.

The minimization procedure involved, for each parameter successively, the determination of the value of that parameter which gave the lowest energy. The value obtained for each parameter studied was rechecked after the other parameters had been optimized. This procedure does not guarantee full optimization but is expected to be sufficiently reliable for the present purpose.

Propene. The effect of the C1–C3, C3–C2, C(sp^2)–H and C(sp^3)–H bond distances was studied for the conformation of propene shown in Fig. 4. The optimal distances were found to be 1·46, 1·33, 1·115 and 1·12 Å, respec-

Table 1. Geometrical parameters[a]

	Propene			Formamidine			Allylanion		Formamidinium ion
	Calc.[b]	Values[c] from ref. 15		Calc.[b]	Values[c] from ref. 15		Calc.[b]		Calc.[b]
C2–C3	1.33	1.34	C4–N1	1.32	132	C–C	1.375	C–N	1.335
C1–C3	1.46	1.52	C4–N2	1.39	140	C–H	1.12	N–H	1.065
C1–H	1.12	1.09	N1–H	1.065	99	CCC ∢	2.36	C–H	1.12
C3–H	1.115	1.08	N2–H	1.07	101		(135°)	NCN ∢	2.16
C2–H	1.115	1.08	C4–H	1.115	108				(124°)

a) Bondlengths in Å ; bond angles in radians (degrees).

b) Values determined by this work.

c) Values recommended by Pople and Beveridge (ref. 15).

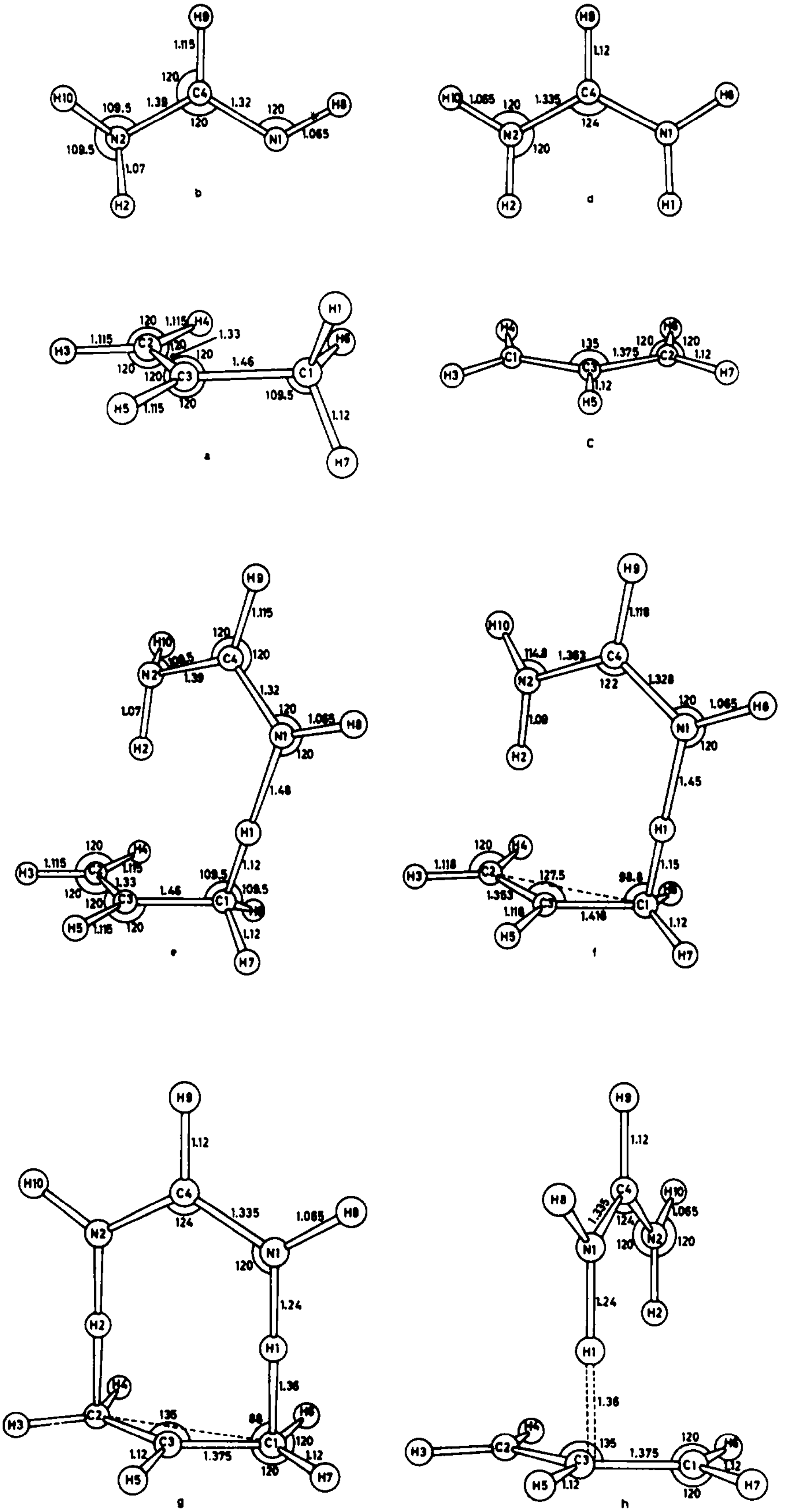

Fig. 4. Geometries of species studied: (a) propene, (b) formamidine, (c) allyl anion, (d) formamidinium cation, (e) bifunctional catalysis, 0% reaction (see text), (f) bifunctional catalysis, 50% reaction, (g) bifunctional catalysis, transition state, (h) monofunctional catalysis, transition state.

tively. The angles were taken as 1·91 rad (109·5°) around C1 and 2·09 rad (120°) around C3 and C2. The values for the parameters studied gave rise to a total energy 36·7 kJ (8·8 kcal) lower than that obtained by the use of the average parameters suggested by Pople and Beveridge.[14]

Formamidine. In this molecule the following variables were individually studied: hybridization of N2, rotation of the amino group around the C4–N2 bond, and variation of N1–C4, N2–C4, N1–H1 and N2–H2 bond distances.

The optimal hybridization of N2 was found to be sp^3, resulting in 24·7 kJ (5·9 kcal) lower energy than for sp^2 hybridization.

The favoured conformation allows for optimal conjugation between the lone pair on N2 and the π-electrons in the C4–N1 bond. This conformer was determined to be 26·2 kJ (6·3 kcal) more stable than the one having the lone pair orthogonal to the double bond and as close as possible to the lone pair on N1.

For the N1–C4, N2–C4, N1–H1 and N2–H2 bonds, the distances 1·32, 1·39, 1·065 and 1·07 Å define a structure which is 65·6 kJ (15·7 kcal) more stable than a structure with distances in accordance with Pople and Beveridge,[14] i.e. 1·32, 1·40, 0·99 and 1·01 Å.

The angles around C4 and N1 were taken as 2·09 rad (120°).

Allyl anion. The parameters studied were bond distances and the C2C3C1 angle.

The C–C distance was found to be 1·37 Å. The C–H bonds were assumed to be all equal and were determined to be 1·12 Å. These values gave an energy 55·1 kJ (13·7 kcal) lower than that obtained when 1·43 and 1·085 Å were used for the C–C and C–H bonds, respectively. These later values correspond to the arithmetic average of the values given by Pople and Beveridge[14] for double and single C–C bonds and C(sp^3)–H and C(sp^2)–H bonds, respectively.

The optimal C2C3C1 angle was found to be 2·36 rad (135°), giving rise to an energy 21·0 kJ (5·0 kcal) lower than that given by an angle of 2·09 rad (120°).

Formamidinium cation. Analogous parameters as just described for allyl anion were varied in this case. The calculations yield an optimal N1C4N2 angle of 2·16 rad (124°) and C–N, C–H and N–H distances of 1·335, 1·12 and 1·065 Å, respectively. The energy obtained with these parameters is 91·8 kJ (22·0 kcal) lower than that obtained using values of 2·09 rad (120°) for the N1C4N2 angle and 1·36, 1·085 and 1·00 Å for the above mentioned distances, respectively.

Angles around N1 and N2 were taken as 2·09 rad (120°).

Transition states. Partially optimized geometries of the transition states were found to correspond, in the positions of all atoms except those of the transferring hydrogens, to allyl and formamidinium ions put together in the way shown in Fig. 4. This conclusion was based on study of the following parameters: CCC angle and C–C bond distances in the allyl moiety and NCN angle and N–C bond distances in the formamidinium moiety. Furthermore, the energies of these species were minimized with respect to the distance between the two ionic moieties (as measured from the plane of the allyl system to either N on the formamidium system) and the distance between the transferring hydrogen (s) and the nitrogen (s) bonded to it (them). These distances were found to be 2·60 and 1·24 Å, respectively, for both types of catalysis.

Energy profile for bifunctional catalysis. A reaction coordinate describing the catalysis with a bifunctional mechanism has been considered in which all the bond distances and angles, with the exception of the bond distances involving the transferring hydrogens, have been lumped together and assumed to change synchronously. These changes have been expressed in units of per cent reaction defined as follows. 0 per cent reaction corresponds to formamidine approaching propene with C1, H1 and N1 on the same line, and C1, C2 and the formamidinium moiety in the same plane (Fig. 4). 100% reaction corresponds to the transition state described above. All intermediate values of per cent reaction can be obtained by linear interpolation between these two extremes using the formula 1:

$$\text{per cent reaction} = \frac{X - X_0}{X_{100} - X_0} \times 100 \qquad (1)$$

where X is any reaction variable (bond distance or angle) and the subscripts 0 and 100 refer to the values these quantities have at 0 and 100% reaction, respectively. Two examples will clarify this concept: the C1–C3 distance varies from 1·46 Å at 0% reaction to 1·37 Å at 100% reaction. At 50% reaction this distance is taken as 1·415 Å. Similarly, the angle H6C1H7 varies from 1·91 to 2·09 rad. At 50% reaction the value adopted is 2·00 rad.

The energy profile for the catalysis with a bifunctional mechanism was constructed on the basis of points for 0, 25, 50, 75, 90, 95 and 100% reaction. A C1–N1 distance of 2·60 Å has been used in all cases, and the energy of the complex has been minimized with respect to the position of the two migrating hydrogens (Fig. 5).

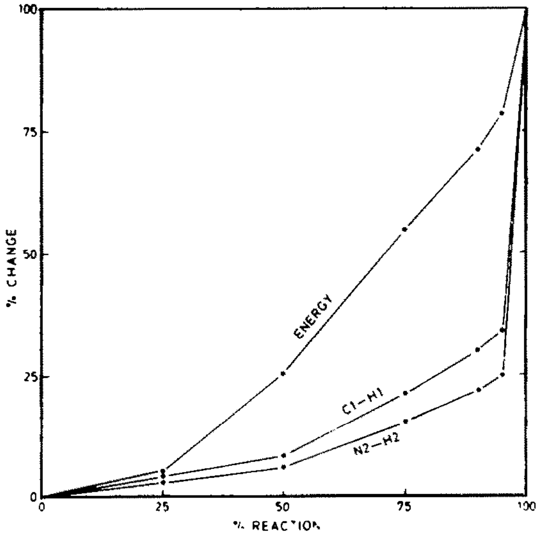

Fig. 5. Changes in energy, C1–H1 distance and N2–H2 distance along the reaction coordinate for bifunctional catalysis. For definition of per cent reaction and per cent change, (see eqn 1).

Energy profile for monofunctional catalysis. In monofunctional catalysis the reaction involves complex changes since the formamidinium moiety has to slide across from C1 to C2 to deliver the abstracted proton. The timing of these events is difficult to anticipate. Nevertheless, three regions of the energy profile were studied.

In the first region, the two ions were placed with C1, H1 and N1 on a straight line, C1, C2 and the formamidinium moiety in the same plane, and N2 as distant as possible from C2, in order to avoid any contribution of bifunctionality. The hybridization around C1 was then varied simultaneously with the C1–H1 distance. The energy was found to increase monotonically as the hybridization around C1 got closer to sp^2 and as H1 was further transferred from C1 to N1.

The second region studied was near the transition state. The plane of the formamidinium ion was kept perpendicular to the plane of the allyl system, and it was at all times oriented radially towards C3. The distance between C3 and the intersection of the line containing N1 and H1 and the plane of the allyl system to which the line is perpendicular was then varied. The energy surface in this region was found to be flat with a minimum corresponding to the transition state as shown in Fig. 4. In this species the distances between C3 and the intersection of the line containing N1 and H1 and the plane of the allyl system was found to be 0·35 Å. Not surprisingly, attempts to protonate at C3 along the line connecting C3 and N1 in the activated complex of Fig. 4h, led only to increased total energy.

Finally, in the third region studied, the formamidinium ion was moved from the place it occupied in the transition state towards C1 until it sat over the C1 atom as described for the first region studied. The distance between N1 and the plane of the allyl system was kept at 2·6 Å, and the distance between H1 and the plane of the allyl system was kept at 1·36 Å. The energy was found to decrease monotonically as the formamidinium moiety moves towards C1.

DISCUSSION

It is of utmost importance on studying cyclic reactions to investigate how the orbitals in the initial state correlate with those of the products. In this way an erroneous prediction of a low energy barrier for a "symmetry" forbidden process may be avoided.[16]

Prior to reaching the transition state only some atomic orbital coefficients with small absolute values changed sign. Therefore, we conclude that for the bifunctional catalysis all the bonding orbitals in the initial state correlated with the bonding orbitals of the products as well as with those of the transition state.

The energy of the molecular complex on bifunctional catalysis (expressed as per cent change according to Eqn1) is plotted in Fig. 5 against the per cent reaction defined in the preceeding section. The monotonic increase of the energy in going from the initial state to the determined transition state points to the absence of an intermediate and thus to a concerted reaction. The degree of migration of the transferring hydrogens along the reaction co-ordinate has also been studied. The appropriate values collected in Table 2 are also plotted in Fig. 5.

The following facts can be deduced from this figure:

(i) The movement of the protons is almost synchronous.

(ii) The movement of the protons lags behind all other structural changes involved in the definition of per cent reaction, and

(iii) The changes in energy are more closely related to the structural changes than to the transferring of the protons.

The following simplified mechanistic picture arises from these observations: once the reactants are at an interaction distance, structural changes occur rather independently of the bonds that involve the hydrogens to be transferred. These changes involve a gradual change in hybridization of C1 and N2 from sp^3 to sp^2 that allows the electron pair of the C1H1 bond in one case and the lone pair in the other to delocalize into their adjacent π systems. Thus a partial negative charge on C2 and a partial positive charge on N2 are developed. Most of the energy of activation of the reaction is spent in these structural changes. The system then reaches a configuration suitable for fast concerted proton transfers to occur.

This overall picture agrees very well with experimental findings related to the verification of Marcus' theory of proton transfer reactions.[17] Thus, Kreevoy and Oh have found that in the reaction of proton transfer from acid catalysts to different basic substrates, a major contribution to the barrier to proton transfer arises from reorganizations occurring before the rate determining proton transfer.[18]

In the monofunctional case, the limited studies carried out along the reaction coordinate did not show the presence of an intermediate. However earlier Extented Hückel calculations of ammonia catalyzed 1,3-proton transfer in the indene system suggested the existence of an intermediate in this specific case.[2c]

The symmetrical transition states for bifunctional and monofunctional catalysis were found to be less stable than the initial state by 121 and 453 kJ/mole (29 and 108 kcal/mole) respectively, strongly suggesting that bifunctional catalysis of the present type could be the favoured type of catalysis in laboratory experiments. The calculated dipole moments of the transition states are 4·0 and 9·8 D for the bi- and monofunctional cases, respectively. This suggests that non-specific solvent interactions

Table 2. Bifunctional catalysis energy profile

% Reaction[a]	C1-H1 Å	(% change[b])	N2-H2 Å	(% change[b])	Energy kJ	(% change[b])
0	1.13	(0)	1.08	(0)	0	(0)
25	1.14	(4.3)	1.09	(3.1)	5.2	(4.3)
50	1.15	(10.6)	1.09	(6.3)	31.4	(25.6)
75	1.18	(21.3)	1.10	(15.6)	64.5	(52.7)
90	1.19	(29.8)	1.11	(21.9)	87.0	(71.0)
95	1.21	(34.0)	1.12	(25.0)	95.9	(78.3)
100	1.36	(100)	1.24	(100)	122.5	(100)

a) See text for definition

b) Calculated by equation 1

stabilize the monofunctional transition state more than the bifunctional one.[19] However in this particular case this is not expected to be sufficient to alter our previous conclusions.

Parallel to this theoretical study we have undertaken a reaction mechanistic investigation of some amidine catalyzed 1,3-proton transfer reactions.[20] Amidines have been chosen as catalysts partly because some of them possess basicities that make them potential catalysts in the laboratory for transfer of protons from carbon. The use of a substrate with C atoms as proton donors as well as proton acceptors makes it possible, at least in principle, to use hydrogen isotopic labelling as well as stereochemical mechanistic probes. Such probes are present in our experimental model systems, and in principle a distinction can be made between monofunctional and bifunctional pathways. These mechanistic probes have not been present in earlier investigations on bifunctional catalysis.

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