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Transannular 1,5-hydride shift in 5-hydroxycyclooctanone: an experimental and theoretical investigation†

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Received 4th June 2007, Accepted 22nd June 2007
First published as an Advance Article on the web 12th July 2007
DOI: 10.1039/b708448j

^{1}H NMR measurements have shown that eight out of twelve methylene hydrogen atoms of 5-hydroxycyclooctanone (**1HK**) are exchanged for deuterium atoms under acidic and basic conditions. For the reaction in 7.9 M DCl/D_2O, an activation energy $E_a = 19.2 \pm 0.4$ kcal mol^{-1} is found. In order to explain these findings, a degenerate transannular 1,5-hydride shift is essential, and this reaction has been analyzed by quantum chemical calculations. Hydride transfer takes place *via* a tight transition state with a six-membered ring. The activation barrier is lowest in the presence of base. The molecular conformation of the eight-membered ring in the transition state resembles that of the starting structure. It is unlikely that solvent molecules such as water participate in the formation of the transition state.

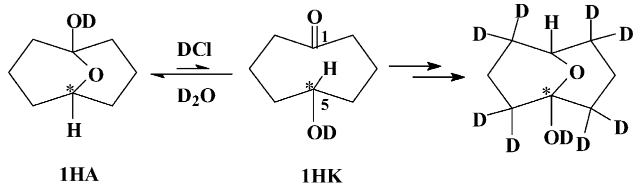
Introduction

The phenomenon of transannular hydride shifts in medium-sized cycloalkane rings (C_8 to C_{11}) involving carbocation intermediates was first observed by Prelog,[1] Cope[2] and their respective co-workers. Over the last few decades, a number of experimental and theoretical studies on such reactions have held the interest of chemists, as a means of investigating both transannular interactions and the mechanism of transannular reactions.[3–10] Several examples have been reported in the literature of degenerate and non-degenerate rearrangements of compounds containing functional groups (such as carbonyl and hydroxy) taking place in the presence of acid[11–13] or base.[5,6,9,14–17] Such hydride shifts have implications on the synthesis of natural products.[9,18] We now have investigated the transannular 1,5-hydride shift in 5-hydroxycyclooctanone (**1HK**). The degenerate 1,6-hydride shift in the homologous compound 6-hydroxycyclodecanone has previously been investigated.[19]

Results and discussion

NMR studies

We investigated the exchange of hydrogen for deuterium atoms in **1HK** in the presence of different amounts of deuteriohydrochloric acid (DCl) or sodium deuteriohydroxide (NaOD) in deuterium oxide (D_2O) (Scheme 1). Under such conditions, in addition to a transannular 1,5-hydride shift, a competing reaction is intramolecular hemiacetal formation, leading to 9-oxabicyclo[4.4.1]nonan-1-ol (**1HA**). Actually, **1HA** is thermodynamically more stable than **1HK**, and only the bicyclic isomer can be isolated.[20] However, that both forms are in equilibrium in polar solvents, in particular at elevated temperatures, has been proved by NMR spectroscopy.[21]



Scheme 1 Equilibrium between **1HA** and **1HK**, transannular 1,5-hydride shift and H/D exchange.

In the H/D exchange experiments, the degree and rate of deuteration was measured from the relative intensities of the ^{1}H NMR signals of the methylene groups, which appear as complex multiplets in the range δ 1.2–1.8 ppm. Thus, 33.3% deuteration would indicate that only the hydrogen atoms of the two methylene groups α to the carbonyl group of **1HK** were replaced by deuterium atoms, whereas 66.7% deuteration would indicate that the methylene groups α to the hydroxy group were also affected.

For the H/D exchange experiments, **1HA** was dissolved in D_2O with different concentrations of DCl or NaOD in a clean and dry NMR tube at room temperature. Initial ^{1}H and ^{13}C NMR spectra were recorded immediately after mixing the reactants. Spectra were recorded until the final state was reached (about 24 hours to several days, varying with concentration of acid or base and temperature, see the Experimental section and Electronic Supplementary Information†). Deuteration degrees of 54 to 63% were observed, which are close to $\frac{2}{3}$, the value expected for H/D exchange in all four α-methylene groups.

In a control experiment, H/D exchange was studied in DCl in the presence of 1,4-dioxane as an internal standard. Equimolar amounts of 1,4-dioxane and **1HA** were used. The relative intensity of the ^{1}H NMR signal of the methine group (C^5H, δ 4.08 ppm) in **1HK** with respect to that of the hydrogen atoms of 1,4-dioxane did not change, even after 208 hours, indicating that this hydrogen atom is not exchanged for deuterium. In this experiment, a degree of deuteration of 62.6% was reached.

These results can be explained by a mechanism which includes a degenerate intramolecular (transannular) 1,5-hydride shift as

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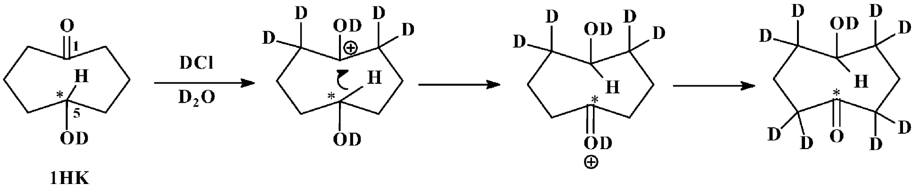
† Electronic supplementary information (ESI) available: Colour versions of Fig. 1–3; H/D-exchange data; ^{1}H-NMR spectra; deuteration profiles. See DOI: 10.1039/b708448j



1HK

Scheme 2 Proposed mechanism for H/D exchange and acid-catalyzed transannular 1,5-hydride shift in **1HK**.

the essential step by which the four α-methylene groups become equivalent and H/D exchange occurs by keto–enol tautomerism.

Under acid conditions, the following steps can be distinguished (Schemes 1 and 2):

1. Equilibrium between **1HA** and **1HK** and enolization of **1HK** are catalyzed by the acid. This leads to exchange of the four hydrogens α to the carbonyl group for deuterium.

2. By protonation of the carbonyl oxygen atom a highly electrophilic center at C^1 is generated. The methine hydrogen atom (at C^5) is shifted to the electrophilic center as a hydride ion. As a result, the former alkanol group becomes a carbonyl group and *vice versa*. Thus, the two functional groups are exchanged with each other. This step is assumed to be rate-determining.

3. The four hydrogen atoms α to the new carbonyl group are exchanged for deuterium atoms by keto–enol tautomerism.

4. Finally, the hemiacetal **1HA** with eight methylene deuterium atoms is generated since it is thermodynamically more stable than the hydroxyketone **1HK**.

Under basic conditions, the mechanism is slightly modified (Scheme 3): the hydroxy group in **1HK** is deprotonated and the nucleophilicity of the C^5-H group is considerably increased.[22] The hydride ion is shifted to the carbonyl group. Transannular 1,5-hydride shift is completed by reprotonation.

Assuming pseudo-first-order kinetics for the multi-step reaction, overall rate constants k for H/D exchange have been determined (Table ESI-1†). The results indicate that log$k$ is linearly proportional to the acid concentration (correlation coefficient $R^2 = 0.961$, 3 points), suggesting general acid catalysis. Since one experiment in 7.9 M DCl/D_2O was done at 100 °C, an Arrhenius plot is possible, from which an activation energy $E_a = 19.2 \pm 0.4$ kcal mol^{-1} and a frequency factor $A = (7.2 \pm 0.5) \times 10^8$ s^{-1} are obtained. The corresponding thermodynamic activation parameters are: $\Delta H^\# = 18.6 \pm 0.4$ kcal mol^{-1}, $\Delta S^\# = -20.0 \pm 0.1$ cal mol^{-1} K^{-1}, and $\Delta G^\# = 24.4 \pm 0.4$ kcal mol^{-1}. The last value can be compared with that found by Mills *et al.*[13] for hydride transfer in a rigid polycyclic hydroxy ketone ($\Delta G^\# = 14.7$ kcal mol^{-1}).

Theoretical mechanistic studies

We have carried out an intensive theoretical investigation on the transannular 1,5-hydride shift in **1HK** making use of the density functional theory (DFT)[23] B3LYP method.[24] The reaction pathway was studied for the uncatalyzed, acid-catalyzed (simulated with a protonated carbonyl oxygen atom) and base-catalyzed reaction (simulated by replacing OH with OLi). The importance of geometric factors such as proximity between the methine hydrogen atom and the carbonyl carbon atom were essential points in our investigation.

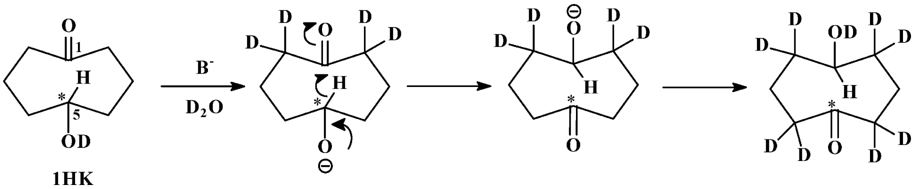
Structural features and energetics

Initially a conformational search (at MMFF level) available in SPARTAN 04 was carried out, since compound **1HK** is rather flexible. The structures of selected conformers were optimized on the B3LYP/6-31+G* level of theory. Some relevant results are summarized in Table 1. The most stable conformer is the boat-chair form (**1bc**), which is more stable by 3.38 kcal mol^{-1} than the boat-boat form (**1bb**) and by 1.66 kcal mol^{-1} than the chair-chair form (**1cc**). In **1bb** and **1bc**, the distance between the methine hydrogen and the carbonyl carbon atom is less than the van der Waals distance between carbon and hydrogen (2.95 Å); the closest proximity (2.4 Å) of the interacting groups (H and C) is found in **1bb**. The close approach of the two atoms leads to partial

Table 1 Total energies E (including zero-point energies), relative energies ΔE and important geometrical parameters in conformers **1bc**, **1bb** and **1cc**

	E/au	ΔE/kcal mol^{-1}	$d_H{}^a$/Å	$\theta_H{}^b$/°	Δ_H/Å^c
1bc	−463.525162	0.000	2.643	89.8	0.008
1bb	−463.519787	3.375	2.425	94.1	0.038
1cc	−463.522534	1.655	3.051	88.9	0.016

[a] Distance between methine hydrogen and carbonyl carbon atom. [b] Attack angle between developing C···H bond and C=O bond. [c] Distance of carbonyl carbon atom from the plane of its substituents.



1HK

Scheme 3 Proposed mechanism for H/D exchange and base-catalyzed transannular 1,5-hydride shift in **1HK**.

pyramidalization of the carbonyl carbon atom, which is expressed by its distance Δ_H from the plane of its substituents (0.038 Å in **1bb**).

The angle θ_H between the methine hydrogen atom and the carbonyl bond can be considered as the angle of attack in the nucleophilic hydride transfer. A value of 94.1° is found in **1bb**, which is closest to the optimal value (107 ± 5°) suggested by the Bürgi–Dunitz trajectory.[25] Comparison of the geometrical parameters of the three conformers clearly indicates that conformer **1bb** allows the best interaction for the nucleophilic methine hydrogen atom and the electrophilic carbonyl carbon atom.

Bonding and interactions

A natural bond order analysis (NBO)[26] can be carried out in order to understand second-order interactions and to get insight into the charge distribution on atoms in reactants. The bonding properties can be investigated with Bader's topological electron density analysis.[27–30] The one-electron density distribution $\rho(r)$ is analyzed with the aid of the Laplacian $\nabla^2\rho(r)$, which also determines the regions in space where electronic charge is concentrated or depleted. Bond-critical points are characterized by a minimum value in $\rho(r)$ along the maximum electron density path connecting two nuclei. We have performed such an analysis for the interaction between the methine hydrogen and carbonyl carbon atom in the optimized conformers **1bc**, **1bb** and **1cc** in their respective ground states. The relevant results are summarized in Table 2. The second order energy is only 0.51 kcal mol^{-1} in **1bc**. The interaction between $\sigma_{C\text{–}H}$ (donor) and $\pi^*_{C=O}$ (acceptor) is maximal in **1bb** (1.33 kcal mol^{-1}). This leads to an increase in the occupancy of $\pi^*_{C=O}$ to 0.089 e.

To simulate acidic conditions we have taken the corresponding protonated optimized conformers of **1HK**, namely **2bc**, **2bb** and **2cc**. It is well known that protonation of the oxygen atom of a carbonyl group initiates nucleophilic attack of a hydride ion from a nonactivated CH group.[31] In conformer **2cc**, interaction between donor and acceptor is found to be absent (Table 2). The second order interaction between donor and acceptor orbitals in the protonated conformer **2bb** is strongest (6.55 kcal mol^{-1}) and is about five times greater than in the neutral conformer **1bb**. The electron population in $\pi^*_{C=O}$ of **2bb** is 0.275 e, compared to the low occupancy (0.089 e) in **1bb**. Also in the protonated conformer **2bc** the second-order interaction energy is large (1.48 kcal mol^{-1}) compared to the corresponding neutral conformer **1bc** (0.51 kcal mol^{-1}).

For the 1,5-hydride shift reaction, we simulated basic conditions by replacing the hydrogen atom of the hydroxy group by a lithium cation (Li^+) as a metal counter-ion. We chose Li^+ instead of other alkali ions such as Na^+ or K^+ in order to save computation time. The second-order interaction energies between the donor and acceptor orbitals in conformers **3bc** and **3bb** are 0.67 and 1.68 kcal mol^{-1}, respectively (Table 2). The $\pi^*_{C=O}$ electron population is maximal in **3bb** (0.095 e). These results show that the donor–acceptor interactions are strongest when the carbonyl oxygen atom is protonated under acidic conditions. The lithium cation is a weak Lewis base. Earlier experimental and theoretical studies have clearly shown that the rate of the hydride shift depends on the metal counter-ion.[14,32] Under all conditions (neutral, acidic and basic) in the boat-chair (**bc**) and boat-boat (**bb**) conformers, considerable donor–acceptor interactions in the ground state are found. The energy difference between these conformers is low enough to allow interconversion at room temperature.

Transition state calculations

Several transition state structures for the transannular 1,5-hydride shift occurring in **1HK** are possible because of the flexibility of the carbocyclic ring, and it is very difficult to simulate the real situation. Only the optimized conformers **1bc** and **1bb** were selected for the calculation of transition states, since they already show donor–acceptor interactions between the electrophilic carbonyl and the nucleophilic methine group in their ground states. Starting with these conformers, transition states **4bc** and **4bb**, respectively, were obtained. The transition states are depicted in Fig. 1, some geometrical details are summarized in Fig. 2, and the calculated activation energies are collected in Table 3. Interesting results are the almost equal activation energies for **1bc** → **4bc** (46.58 kcal mol^{-1}) and **1bb** → **4bb** (46.57 kcal mol^{-1}).

In the transition states **4bc** and **4bb** the conformers of the starting structures, boat-chair and boat-boat, respectively, are preserved. The transfer of the methine hydrogen to the carbonyl carbon atom and of the hydroxy hydrogen to the carbonyl oxygen atom takes place *via* a symmetric six-membered ring irrespective of the conformation of the molecule. Both transition states, **4bc** and **4bb**, are characterized by a single imaginary frequency (−1401i and

Table 2 NBO analysis of different conformers (**bc**, **bb**, **cc**) of neutral (**1**), protonated (**2**) and lithiated (**3**) 5-hydroxycyclooctane. Only energies greater than the default threshold 0.5 kcal mol^{-1} are given

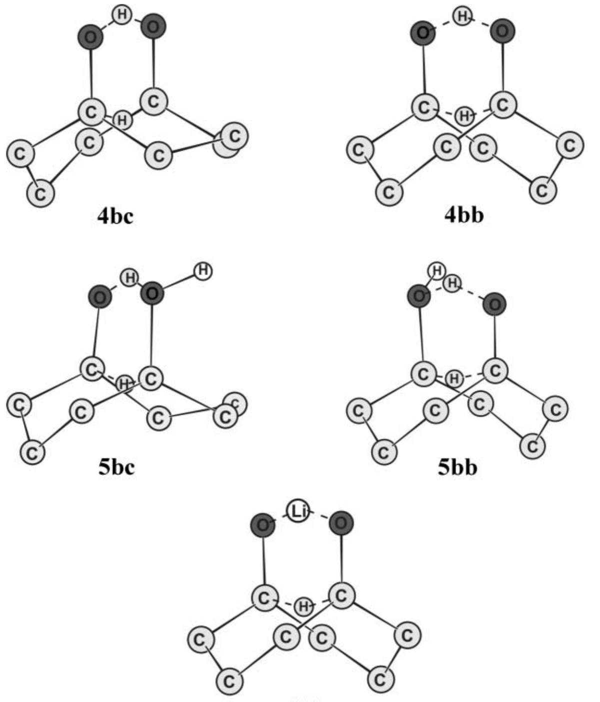
	Interaction	$E^{(2)}$ ^{a}/kcal mol^{-1}	$E_j - E_i$ /au^{b}	$F_{ij}$$^{c\ c}$/au	$\sigma_{C\text{–}H}$ ^{d}	$\pi^*_{C=O}$ ^{d}
1bc	$\sigma_{C\text{–}H} \rightarrow \pi^*_{C=O}$	0.51	0.52	0.015	1.980	0.085
1bb	$\sigma_{C\text{–}H} \rightarrow \pi^*_{C=O}$	1.33	0.52	0.024	1.974	0.089
1cc	$\sigma_{C\text{–}H} \rightarrow \pi^*_{C=O}$	—	—	—	1.972	0.084
2bc	$\sigma_{C\text{–}H} \rightarrow \pi^*_{C=O}$	1.48	0.38	0.022	1.971	0.237
2bb	$\sigma_{C\text{–}H} \rightarrow \pi^*_{C=O}$	6.55	0.40	0.048	1.923	0.275
2cc	$\sigma_{C\text{–}H} \rightarrow \pi^*_{C=O}$	—	—	—	1.983	0.081
3bc	$\sigma_{C\text{–}H} \rightarrow \pi^*_{C=O}$	0.67	0.49	0.016	1.975	0.089
3bb	$\sigma_{C\text{–}H} \rightarrow \pi^*_{C=O}$	1.68	0.49	0.026	1.966	0.095
3cc	$\sigma_{C\text{–}H} \rightarrow \pi^*_{C=O}$	—	—	—	1.979	0.082

[a] Second order perturbation energy between Φ_i and Φ_j. [b] Energy difference between NBOs Φ_i and Φ_j. [c] Fock matrix element. [d] Occupancy (ρ).

Table 3 Total energies including zero-point energies E and activation energies E_a for the 1,5-hydride shift in **1HK**

Transition state	E^a/au	E_a/kcal mol^{-1}
4bc^b	−463.450931	46.58
5bc^c	−463.775939	40.73
4bb^b	−463.445576	46.57
5bb^c	−463.770597	41.90
6bb^d	−467.479572^e	18.80

^{a} B3LYP/6-31+G* results. ^{b} Uncatalyzed. ^{c} Acid-catalyzed. ^{d} Base-catalyzed. ^{e} HF/6-31G**.


4bc **4bb**

5bc **5bb**

6bb

Fig. 1 Transition states for the 1,5-hydride shift reaction.

−1432i, respectively) corresponding to the motion of the hydrogen atoms.

The migrating methine hydrogen atom has the same distance from the donating and the accepting carbon atoms (C^5 and C^1, respectively) of 1.21 in **4bc** and 1.20 Å in **4bb**. According to Bürgi *et al.*,[33] the minimum-energy position for a hydride ion in a nucleophilic attack is at a distance of 1.9 Å (as the hydride ion is approaching or leaving) in the plane perpendicular to the carbonyl group running through the carbonyl carbon atom. The deviations of this parameter in **4bc** and **4bb** are certainly caused by the constraints of the medium-sized ring which connects the participating groups.

The tight geometry of the transition states **4bc** and **4bb** leads to non-bonded repulsions, and these result in high activation barriers. Evidence for this was obtained by strain energy calculations at the MMFF level. The strain energies for **4bc** and **4bb** are 763.5 and 791.1 kcal mol^{-1}, respectively. When a methylene group of the ring flips, converting **4bb** to **4bc**, about 27.6 kcal mol^{-1} of strain energy is thus released.

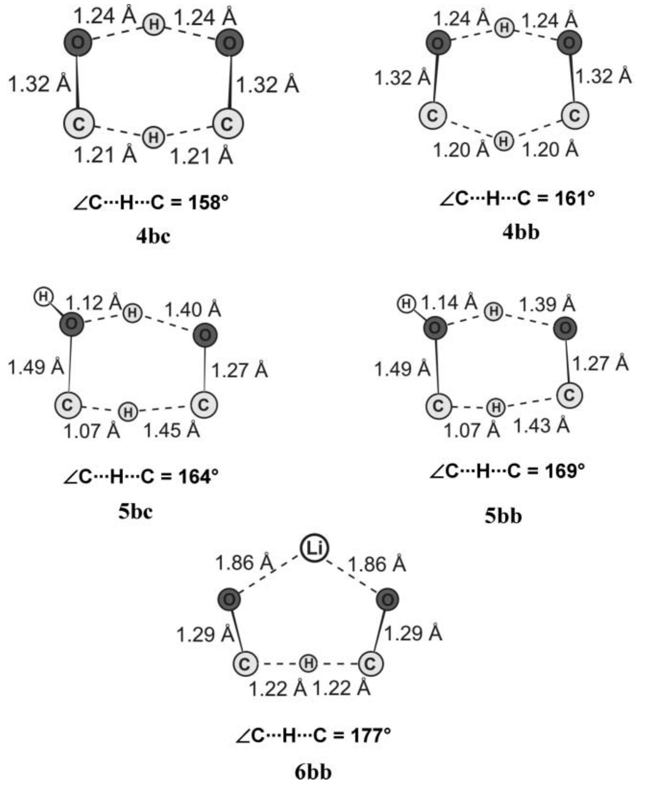


Fig. 2 Six-membered cyclic transition states in the hydride shift reaction.

We have also investigated the transition states **5bc** and **5bb** corresponding to the protonated conformers **2bc** and **2bb** as starting structures (Table 3, Fig. 1 and 2). **5bc** and **5bb** are unsymmetrical, as is indicated by the different distances and angles of the atoms involved in the six-membered cycle. The migrating hydrogen is localized on the carbinol carbon atom rather than forming a symmetrical three-center two-electron bond as reported by Sorensen and McMurry.[34,35] The C · · · H · · · C angle in **5bc** and **5bb** is 163.7° and 168.6°, respectively. This implies that the transfer of hydride is nearly linear, and this is consistent with the predicted preference.[36–40] Slightly different activation energies were found, namely 40.73 and 41.90 kcal mol^{-1}, respectively. These values are more than twice as large as the experimental result (see above), indicating that the actual conditions in strong acid are insufficiently simulated by the mono-protonated systems. However, comparing the calculated data with the experimental, one has to take into account that the latter value has been determined for the multi-step H/D exchange reaction in concentrated deuteriohydrochloric acid, and not simply for the hydride transfer.

For the protonated molecules the calculated activation energy is clearly lower than for the neutral molecules: For **2bc** → **5bc** the difference relative to **1bc** → **4bc** is 5.85 kcal mol^{-1}, and for **2bb** → **5bb** the difference relative to **1bb** → **4bb** is 4.7 kcal mol^{-1}. The $\Delta G^{\#}$ value found experimentally for the 1,5-hydride shift in the 2,4,4,6-tetramethylheptyl cation is 5.20 ± 0.15 kcal mol^{-1} at −122 °C and 5.0 ± 0.5 kcal mol^{-1} in the 2,6-dimethyl-2-heptyl cation.[41,42] These low barriers were considered either to be due to a linear or a less strained six-membered transition state.

Attempts were made to calculate transition states starting with the lithiated conformers **3bb** and **3cc** at the B3LYP/6-31+G* level of theory. However, frequency calculations indicated an absence of imaginary frequencies, thus characterizing these structures as minima. Despite much effort, no transition state structure could be located at this level. On the other hand, Hartree–Fock (HF/6-31G**) calculations were successful in finding transition state **6bb** (Fig. 1). **6bb** was obtained starting from both **3bb** and **3cc** (also optimized at HF/6-31G**). It is highly likely that the reaction takes place with the initial formation of a low-energy complex in which the lithium cation is coordinated with both oxygen atoms of the carbinol and the carbonyl group, but we were not able to localize such a low-energy complex. The activation barrier is 18.8 kcal mol^{-1} for **3cc** → **6bb**. The activation energy calculated by B3LYP/6-31+G*//HF/6-31G** is only 4.3 kcal mol^{-1}, but the atoms $C \cdots H \cdots C$ are almost linear in **6bb** (Fig. 2).

The natural charge calculated for the migrating hydrogen atom in the transition states under neutral, acidic and basic conditions was found to be positive (Fig. 3).

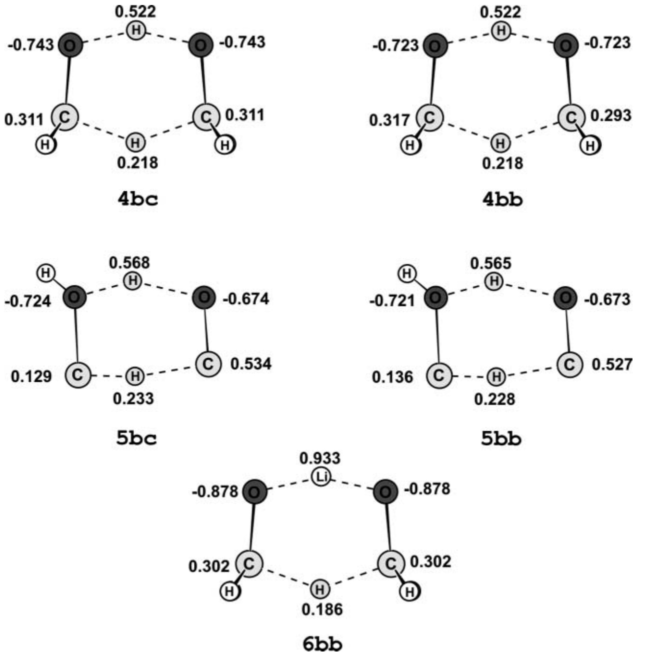


Fig. 3 Natural charges on atoms in the six-membered cyclic transition states in the hydride shift reaction.

The role of a catalytic amount of water in dihydrogen transfer between formaldehyde and methanol has been reported,[43] and the calculated enthalpic barriers for the uncatalyzed and catalyzed processes were found to be similar. This implies that the reaction is not catalyzed by the presence of water, but whether this also holds for our case remains to be investigated.

Conclusion

The transannular 1,5-hydride shift in 5-hydroxycyclooctanone (**1HK**) occurs both in the presence of acid and base. The rate of the reaction is dependent on the concentration of the acid or base and the temperature. In the uncatalyzed reaction, the potential energy profile has global minima that correspond to the two interchanging hydroxy-ketones and a high-lying symmetrical six-membered cyclic transition state. The calculated activation barriers for two conformers, **1bc** → **4bc** and **1bb** → **4bb**, are nearly the same (Table 3).

The acid-catalyzed 1,5-hydride shift occurs through an unsymmetrical six-membered cyclic transition state, and the activation energy is about 5.0 kcal mol^{-1} lower than for the uncatalyzed reaction. The base-catalyzed rearrangement has a much lower activation barrier, and proceeds *via* a symmetrical six-membered cyclic transition state.

In addition, the natural charge on the migrating hydrogen atom remains positive, the structures of the transition states resemble those of the starting conformers, and the tight transition states indicate that participation of solvent molecules such as water is unlikely.

Experimental

Methods

NMR spectra were recorded using a Bruker Avance 500 (DRX) spectrometer. The following frequencies were used: 499.7 MHz (^{1}H), 125.7 MHz (^{13}C). Chemical shifts are reported in units of parts per million (δ) relative to tetramethylsilane as internal standard.

Compound **1HA** (about 60.0 mg, 0.42 mmol) was weighed into a clean and dry 5 mm NMR tube. A solution (about 0.7 ml) of known concentration of DCl or NaOD in D_2O was added at room temperature. **1HA** dissolves readily in acidic or basic solution. ^{1}H NMR spectra were recorded at intervals until equilibrium was reached. For details see the Electronic Supplementary Information†.

Calculations were performed using SPARTAN 04,[44] GAUSSIAN 98[45] and GAUSSIAN 03.[46] Molecular orbitals and modes of nuclear motion corresponding to imaginary frequencies were viewed using MOLDEN,[47] PCMODEL[48] and PERGRA.[49] If not stated otherwise, structures and transition states were investigated at the B3LYP/6-31+G* level of theory, which has generally been found to give a good representation of reaction energies.[50] Diffuse functions were included in order to correctly represent the lone pair electrons on oxygen. Frequency calculations were done for all stationary points to characterize them as minima (NIMAG = 0). Each transition state structure was characterized as possessing one imaginary frequency (NIMAG = 1), corresponding to the motion which carries the system over the energy barrier. Zero-point energies are unscaled. To represent a hydride ion properly, p-polarization for the H atom is needed, so single-point calculations were carried out at the B3LYP/6-31+G**//B3LYP/6-31+G* level of theory.

Materials

The hemiacetal 9-oxabicyclo[4.4.1]nonan-1-ol (**1HA**) of 5-hydroxycyclooctanone (**1HK**) was synthesized as described by Meier and Peterson.[51]

Acknowledgements

We acknowledge support in planning and performing the research project by Prof. Dr H. Singh (Center for Computational Natural Sciences and Bioinformatics, International Institute of Information Technology, Gachibowli, Hyderabad, India), and by

Prof. Dr T. Singh (Punjab University, Chandigarh, India). Assistance by Prof. Dr G. Jansen (Universität Duisburg–Essen, Essen, Germany) with quantum chemical computations is gratefully acknowledged.

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