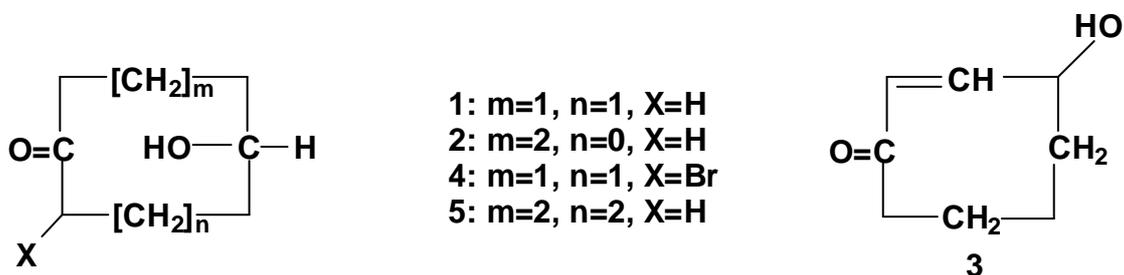


Abstract

To what extent are transannular reactions of medium-ring compounds dependent on their conformations and to what extent can reaction conditions and other factors such as ring size and substituents partially or completely control the transannular interaction? These questions have been investigated with experimental and theoretical studies in this work. A comprehensive study of hemiacetal formation and 1,x-hydride shift ($x = 4 - 6$) has been carried out for model compounds **1** – **5** in order to elucidate the influence of different factors such as ring size, presence of a C=C double bond and substituents on these transannular reactions.



The theoretical and NMR investigations on **1** – **3** indicate that the eight-membered disubstituted compounds present the optimal conditions for the ‘contact’ of substituents in the positions 1 and 5 for the transannular interactions resulting in transannular products. The X-ray crystal structures have clearly shown that compounds **1** and **3** exist as hemiacetals. The experiments clearly indicate highly dynamic behaviour of these molecules and the existence of equilibrium between tautomers especially in protic solvents, i.e., DMSO- d_6 and D₂O, which have not been reported before. The tautomeric equilibrium between **1** and its transannular product drives in the direction of hemiacetal in a range of polar and non-polar solvents. But remarkably, the combined effect of solvent polarity and temperature drives the equilibrium in the reverse direction to a significant extent. The equilibrium constant K_{eq} for forward reaction is reduced to 16.5 in DMSO- d_6 at 403 K and 31.3 in D₂O at 323 K. In the case of **2**, the transannular hemiacetal is only $\leq 1\%$ in D₂O at higher temperature. In contrast, in compound **3** the hemiacetal is favoured exclusively in benzene- d_6 at 298 and 343 K.

The experimental findings for the tautomeric equilibrium of compounds **1** – **5** are substantiated by theoretical investigations. The present results represent the first comparison of transannular hemiacetal formation as a function of conformation in eight- and ten-membered hydroxy-ketones. Since these compounds possess very

complex multidimensional potential energy hypersurfaces (PEHS), the choice of good starting geometries for these molecules was facilitated by applying molecular mechanics. The starting geometries referred as *preferred* starting conformer are selected on the basis of factors such as proximity of the reacting groups and energetics. Detailed conformational and energetic investigations carried out using DFT theory shows that the *preferred* starting conformer of **1**, **4** and **5** are 8.5, 8.6 and 8.1 kcal mol⁻¹, respectively, less stable than the corresponding hemiacetals in the gas phase. It implies thermodynamically *preferred* products in **1**, **4** and **5** are **1a**, **4a** and **5a**. In case of **2** and **3** the *preferred* starting conformers are only 3.6 and 4.6 kcal mol⁻¹ less stable than the corresponding hemiacetals. The calculated (B3LYP/6-31+G*) activation barriers for hemiacetal formation in **1**, **2**, **3**, **4** and **5** are 38.2, 35.2, 36.5, 38.2 and 36.9 kcal mol⁻¹, respectively, in the gas phase. The transannular hemiacetal formation occurs through a four-membered cyclic transition-state which is most tight in **2**. The activation barriers calculated using continuum solvation models (PCM) were not significantly different from the gas phase calculations. It is obvious that the theoretical models used are not able to handle specific solvent effects, so we consider results obtained for hemiacetal formation in water and chloroform semi-quantitatively.

The experimental data show that the transannular 1,5-hydride shift is catalysed both by base and acid. A comparative theoretical study of the transannular 1,4-, 1,5- and 1,6-hydride shifts in compounds **1**, **2**, **4** and **5** shows consensus with the experimental findings that the presence of a metal counterion or acid lowers the activation barriers. In all cases, the reaction proceeds through a hexagonal transition-state structure. The calculated (B3LYP/6-31+G*) activation barriers for 1,5-, 1,4- and 1,6-hydride shift in compounds **1**, **2**, **4** and **5** are 46.6, 52.2, 43.0 and 28.0 kcal mol⁻¹, respectively, for the uncatalysed reaction. One of the key results is that the activation barriers for 1,6-hydride shift in **5** (28.0 kcal mol⁻¹) and the corresponding intermolecular hydride shift (26.4 kcal mol⁻¹) in the methanol and formaldehyde model system are very similar in the uncatalysed reactions. Moreover, the characteristics of the six-membered cycle formed in transition-state structure of 1,6-hydride shift is similar to the six-membered cycle formed in the intermolecular hydride shift between formaldehyde and methanol.

The potential energy profiles for the degenerate 1,4-, 1,5- and 1,6-hydride shifts correspond to the two interchanging hydroxy-ketones and a high lying unsymmetrical

transition structure for interconversion of **2** and **6**, respectively and symmetrical transition structures for interconversion of **1** and **4**, respectively. In the presence of a metal counterion, the transannular 1,6-hydride shift and the intermolecular hydride shift took place *via* low energy complexes. The low energy complexes are formed by the electrostatic attraction of metal counterion with carbonyl oxygen atom. It is highly likely that similar intermediates are involved in 1,4- and 1,5-hydride shifts too, but attempts to locate similar low energy complexes in **1**, **2** and **4** all failed. The transition-state formed in the acid catalysed reaction in **5** can best be described as a localised C-H-bridged cation with a facile 1,6-hydride shift. The transition-states for the transannular hemiacetal formation and 1,x-hydride shift are likely to closely resemble the *preferred* starting conformer. Thus, it might be anticipated that knowledge of the *preferred* starting conformations would be of great predictive value in determining the type of reaction systems **1** – **5** undergo.

For the first time the synthetic potential of transannular 1,5-hydride shift in preparing keto-ethers by reaction of **1** with alcohols in presence of 0.04 M HCl is investigated. This method is attractive for the reasons that it is unexpensive and the hydroxy group can be easily deprotected. However, a major limitation of this method is that the yield of keto-ether of **1** with alcohols such as methanol and ethanol is low. On the other hand, reactions with alcohols such as 2-bromobenzyl alcohol give good yields of the keto-ether.

The transannular reactions in hydroxy-ketones reported in the present study seem to serve as good models, in terms of electronic structure and geometry, for the transition-state of transannular hemiacetal formation and hydride shift reactions in medium-ring compounds. Our results suggest that such reactions, particularly hydride shift, can be exploited *via* easy protection and deprotection of hydroxy groups in the synthesis of important target molecule. Thus, the underlying chemistry of transannular reactions in certain medium-rings reasonably offers potential as a strategic element in the synthesis of polycyclic natural products. It is anticipated that the knowledge obtained in these experiments can be fruitfully applied to the goals for the synthesis of medium rings and the chemistry related to these experiments.