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Hydrogen as a migrating group in some pinacol rearrangements: a DFT study

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ABSTRACT: DFT calculations at the Becke3LYP/6–31G* level were employed to demonstrate that the pinacol rearrangement of ethylene glycol and the 1,1-dimethyl and 1,1,2-trimethyl analogs undergo pinacol rearrangements by a concerted hydrogen-bridged transition structure. No evidence for a bridged intermediate was found. Calculations by two methods on the ethylene glycol system were repeated with the various structures embedded in a solvent cavity with the medium dielectric constant set for water. The ratio of rates for the two methylated glycols was calculated with good agreement with the experimental value. The kinetic isotope effect for the rearrangement of 1,1,2-trimethylethylene glycol was calculated (2.8) in fair agreement with the experimental value of 1.6. Sources of error are briefly discussed. Copyright © 1999 John Wiley & Sons, Ltd.

KEYWORDS: hydrogen migration; pinacol rearrangements; kinetic isotope effects; density functional theory calculations

INTRODUCTION

By 1949 it could be seriously proposed that the pinacol rearrangement was the best studied reaction in all of organic chemistry. Wheland[1] in that year published an extensive review of the reaction applying the classical mechanistic steps previously proposed by Whitmore.[2] As applied to the long known rearrangement of ethylene glycol to acetaldehyde,[3] this mechanism may be written as shown in Scheme 1.

In the 1950s and 1960s, physical organic chemistry entered into what has been described as the 'rococo period' of carbocation mechanisms.[4] Bridged ion intermediates and neighboring group participation became pervading concepts widely applied with a lack of discrimination.

This perception began to alter with the work of Collins' group at Oak Ridge.[5] By the use of kinetic isotope effect arguments, it was established that the acid-catalyzed rearrangement of 1,1,2-triphenylethylene glycol could only be accommodated by an open classical carbocation mechanism shown above. However, when similar studies were extended to the rearrangement of 1,1-dimethylethylene glycol and 1,1,2-trimethylene glycol,[6] the kinetic isotope effects (*ca* 1.6–1.7) were interpreted as indicating hydrogen acting as a neighboring group forming a non-classical hydrogen-bridged intermediate as shown in Scheme 2.

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Recently, Nakamura and Osamura published an *ab initio* study of the pinacol rearrangement of ethylene, propylene and isobutylene glycols at the HF/6–31G level.[7] They reported that the β-hydroxycations formed by the loss of water from the first two glycols rearrange spontaneously to the appropriate protonated carbonyl products. The *tertiary* β-hydroxycation from the isobutylene glycol was stated to form a stable intermediate cation. With this exception, they discounted the importance of the classical ion mechanism, reporting that a concerted hydrogen-bridged transition structure (Scheme 2) was energetically the more favorable pathway. These early results were based on calculations with Gaussian 82 and are difficult to assess since they did not give any verification of their transition states (TSs) and zero point energy (ZPE) corrections were not included. At the time, solvent corrections to the energies or structures were not possible.

Schleyer and co-workers found the employment of *ab initio* calculations by HF or MP2 methods to be inconsistent regarding non-classical structures. They suggested that density functional theory (DFT) calculations at the Becke3LYP/6–31G* level represent a minimum satisfactory level for assessing such structures.[8,9] This paper reports the application of such calculations to the pinacol rearrangement of ethylene glycol with and without corrections for the polarity of the solvent. Prior to the arrival of computational methodology, small kinetic isotope effects were interpreted largely based on speculative reasoning. Carrying forth from the ethylene glycol results, the current study was extended to

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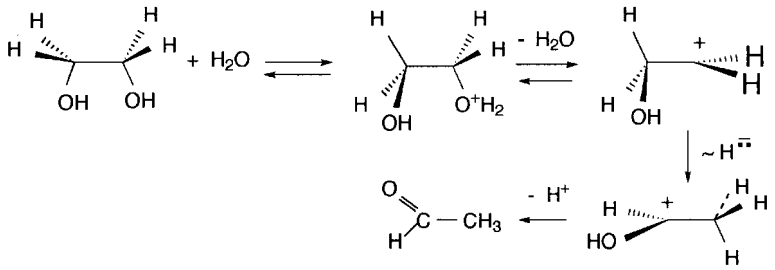


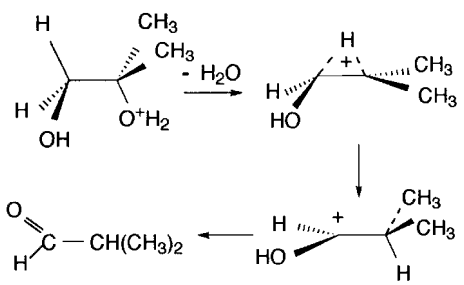
Scheme 1

establish if the observed kinetic isotope effects from our previous experiemental work were consistent with the postulation of hydrogen-bridged TSs.

COMPUTATIONAL METHODS

Preliminary calculations were carried out either with SPARTAN (Wavefunction, Irvine, CA, USA), Gaussian94[10] or Gaussian 98.[10] DFT calculations were carried out at the Becke3LYP/6–31G* level. At the request of a reviewer, certain single-point calculations were repeated on pertinent structures at the MP2/6–31 + G**//Becke-3LYP/6–31G* level. Synchronous transit-guided quasi-Newton methods were used to obtained transition structures.[11,12] In the fastest of these, QST2, a transition structure is approximated from input structures for the starting material and the product(s). This structure may then require refinement by the QST3 method in which these structures are augmented by the approximate TS leading to a new TS refined sufficiently to give a single imaginary frequency upon a frequency calculation. In some cases one may go directly to the TS by use of the starting and product structures and a guessed structure for the TS. Zero point energy corrections for all TSs were Becke3LYP/6–31G* calculations. The normal coordinate motions of the imaginary vibrational frequencies for all TSs were visualized *via* Gaussview (Gaussian, Pittsburgh, PA) to insure the correspondence with valid reaction coordinates.

The potential energy surface near the various transition



Scheme 2

structures was found to be very flat, requiring extreme strictures on the convergence criteria and frequency calculations for each cycle [opt = (TS, very tight, CalcAll)]. Solvent corrections to the ethylene glycol system were first studied utilizing the Onsager reaction field model (SCRF = dipole) with the spherical cavity approximation.[13] Based on the slight changes in starting material and TS geometries, more accurate energies were determined as single-point calculations using the polarized continuum model (PCM) method of Miertus and Tomasi.[14] Software limitations prevented optimization of the TS under the PCM method.

RESULTS AND DISSCUSSION

Initially the transition state for the pinacol rearrangement of ethylene glycol was sought by a series of bond stretching calculations in which the protonated hydroxyl group was progressively lengthened from its equilibrium value. A TS was found with the water at a considerable from a 2-hydroxy-1-ethyl cation. Nakamura and Osamura[7] reported that the 2-hydroxy-1-ethyl cation rearranged spontaneously in a zero activation energy process to the protonated acetaldehyde product. A detailed examination seemed warranted. A potential energy scan was carried out on the 2-hydroxy-1-ethyl cation while rotating about the C(1)—C(2) bond. This first found TS was established as the barrier to this rotation by an intrinsic reaction coordinate (IRC) calculation[15] and examination of the imaginary vibrational mode *via* Gaussview. The only point at which the spontaneous rearrangment occured was with the C(2)—H bond antiperiplanar to the just departing water moiety. It may be mentioned parenthetically that the spontaneous rearangement tells us nothing about the rearrangement pathway of the carbocation as the modeling program is designed to find an energy minimum but does not necessarily follow the reaction coordinate in accomplishing this.

A valid concerted TS for the rearrangement of protonated ethylene glycol was found by means of successive QST2 and QST3 calculations. The energy for this structure is given in Table 1 and the structure is

displayed in Fig. 1. Not unexpectedly, the difference in computational levels produced minor differences in bond lengths, bond angles and reaction enthalpy from the previously reported values.[7] Gaussview displayed the imaginary frequency corresponding to the expected reaction coordinate with the bridging hydrogen oscillating between carbons 1 and 2. The calculated activation enthalpy of 26.0 kcal mol^{-1} (1 kcal = 4.184 kJ) compares with the earlier published value[7] of 23.6 kcal mol^{-1}. When corrected for ZPE the value decreases to 21.4 kcal mol^{-1}. An IRC calculation clearly connected this TS with the starting glycol and the acetaldehyde product. No evidence for a stable bridged intermediate was found. Indeed, an approximation to such a structure collapsed immediately to acetaldehyde.

Currently available software does not permit a detailed examination of specific solvent interaction with charged substrates. The self-consistent reaction field method employing the spherical cavity model[13] produced only a slight lengthening of the bond to the departing water in the TS (Fig. 1). As stated previously, computational limitations dictated the use of single-point energies to evaluate the effects of employing the more sophisticated PCM[14] model. As seen in Table 2, dielectric constant effects are minimal with the simpler spherical cavity model and considerably more realistic with the PCM model. However as reflected in Table 3, the effect of increasing the dielectric constant is to increase the activation enthalpy to 34.1 kcal mol^{-1}. This result is due to the enhanced interaction of the medium with the

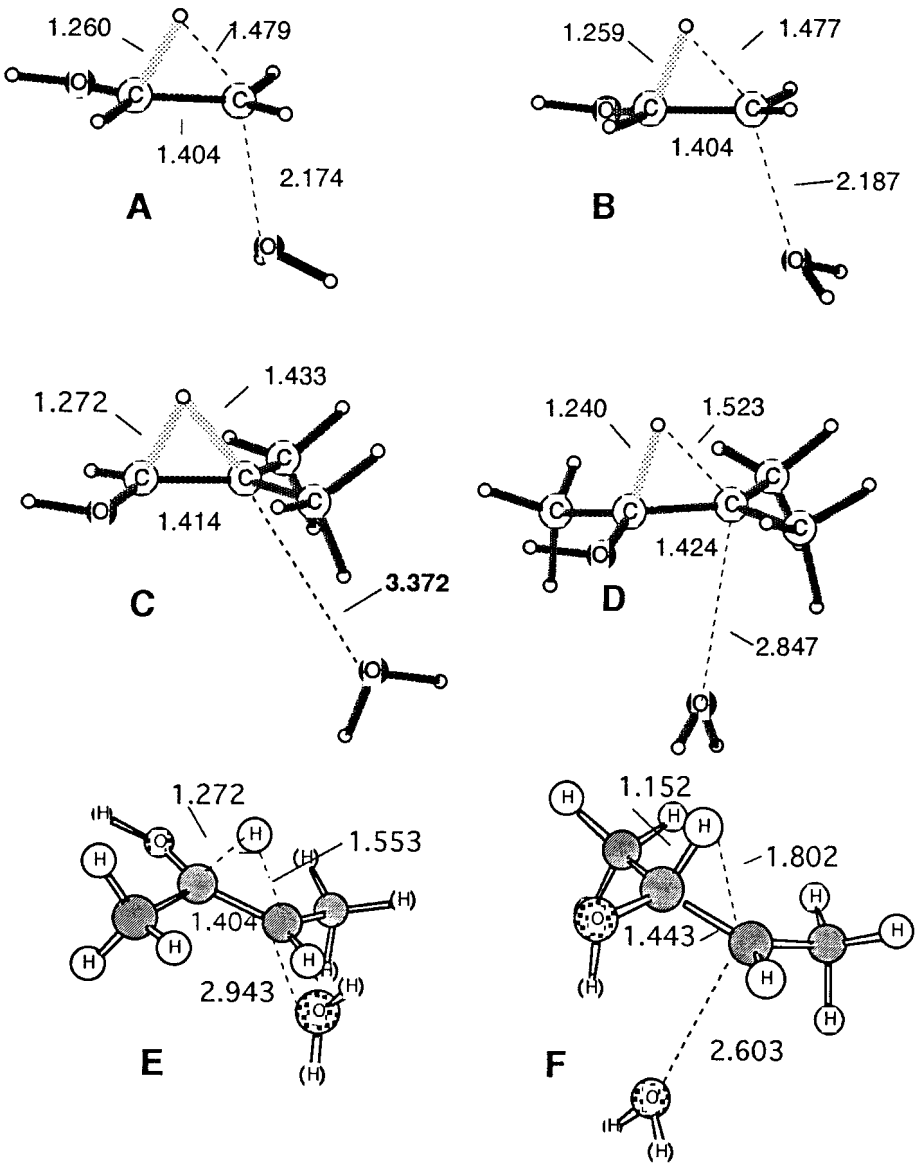


Figure 1. Becke3LYP/6–31G* TS structures for (A) ethylene glycol, (B) ethylene glycol in the simple dipole model water cavity, (C) 1,1-dimethylethylene glycol, (D) 1,1,2-trimethylethylene glycol, (E) *threo*-butane-2,3-diol and (F) *erythro*-butane-2,3-diol

Table 1. Becke3LYP/6–31* and MP2/6–31 + G** energies (hartree) including Becke3LYP/6–31* ZPEs

Species	Energy[a]	ZPE[a]	MP2[b]
$CH_2(OH)CH_2(O^+H_2)$	−230.560710	0.098126	−229.933466
TS	−230.519260	0.090856	−229.892096
$CH_3CH(=O^+H)$	−154.136705	0.068648	
H_2O	−76.408953	0.021159	
H_3O^+	−76.685908	0.032479	
$(CH_3)_2C(O^+H_2)CH_2(OH)$	−309.213303	0.153790	−308.327345
TS	−309.179983	0.145576	−308.292655
$(CH_3)_2$ $CHCH(=O^+H)$	−232.774397	0.126325	
$(CH_3)_2$ $C(O^+H_2)CH(OH)CH_3$	−348.533442	0.181868	−347.518761
TS	−348.504739	0.1735583	−347.485092
$(CH_3)_2CHC(=O^+H)CH_3$	−271.113693	0.154277	
threo-Butane-2,3-diol	−390.212960		
TS	−309.175870		
erythro-Butane-2,3-diol	−390.210921		
TS	−390.171567		

[a] Energies in hartrees.
[b] MP2/6–31G*//Becke3LYP/6–31G*.

compact charge of the protonated glycol as opposed to the more diffuse charge of the TS.

The TSs for the rearrangements of 1,1-dimethylethylene glycol and 1,1,2-trimethylethylene glycol were determined in the same fashion. The ZPE-corrected energies for the starting protonated glycols, TSs and products are given in Table 1. The structures and energies relative to each protonated glycol are given in Fig. 1. The ZPE-corrected enthalpies of activation (0 K) for the three glycols in this study fall in the sequence 21.5, 15.8 and 12.8 kcal mol^{-1}, reflecting the stabilizing influence of increasing methyl substitution.

In ethylene glycol, the C—H bond length to the carbon with the protonated OH group was 1.089 Å, in contrast to the more normal C—H distance of 1.095 Å. The bond lengths to the bridging hydrogen are of interest in reflecting the state of development of each TS. In the TS for ethylene glycol the lengths to the migrating H moiety are 1.260 Å to the migration origin and 1.479 Å to the migration terminus. Clearly the TS is not symmetrically bridged. For the 1,1-dimethyl case, the corresponding values are 1.272 and 1.433 Å, respectively, indicating this TS to be slightly further along the reaction coordinate than the less substituted case. However, for the 1,1,2-trimethyl case, TS development is clearly at an earlier point reflecting the inductive help of the methyl group at C(2).

At 73 °C in 1.2 M perchloric acid, the ratio of the first-order rate constant for 1,1-dimethylethylene glycol to that for 1,1,2-trimethyl compound is 1.1 ± 0.3.[6b] If one accepts that the pre-expontential factor in the Arrhenius equation must be similar for both processes,[16] the rate ratio may be written as

$$k_1/k_2 = \exp[(\Delta G_2^* - \Delta G_1^*)/RT] \qquad (1)$$

where the ΔG^* s are the differences in the temperature-corrected and scaled[17] sum of electronic and thermal free energies for the transition structures and reactants. The calculated value for this system is 1.0, which must be considered as very good agreement as free energies are calculated *via* statistical thermodynamics from the calculated vibrational frequencies which are subject, in

Table 2. Effects of a solvent correction to $\varepsilon = 78.38$ D for species of interest in the ethylene glycol series[a]

Molecule	Onsager (h)	$\Delta\Delta H^b$ (kcal mol^{-1})	PCM (h)	$\Delta\Delta H^b$ (kcal mol^{-1})
$CH_2(OH)CH_2(O^+H_2)$	−230.563440	1.7	−230.677382	73.2
TS	−230.520391	0.7	−230.623089	65.2
$CH_3CH(=O^+H)$	−154.139363	1.7	−154.245681	68.4
H_2O	−76.410251	0.8	−76.418088	5.7
H_3O^+	−76.690145	2.7	−76.858425	108.3

[a] Becke3LYP/6–31 G* energies.
[b] $\Delta\Delta H$ = the change in enthalpy due to the solvent effect.

Table 3. Activation enthalpies (kcal mol^{-1}) for the various glycols in this study

Compound	Becke3LYP[a]	Becke3LYP + *ZPE*	MP2
$CH_2(OH)CH_2(OH)$	26.0	21.4	25.7
$(CH_3)_2C(OH)CH_2(OH)$	20.9	15.8	19.3
$(CH_3)_2C(OH)CH(OH)CH_3$	18.0	12.8	21.1
$CH_3C(OH)CH(OH)CH_3$[b]	23.3		
$CH_3C(OH)CH(OH)CH_3$[c]	24.7		

[a] The solvent-corrected value (PCM) was 34.1 kcal mol^{-1}.
[b] *threo*-Diol.
[c] *erythro*-Diol.

turn, to the assumption of simple harmonic vibrations and good structures including electron correlation.

Equation (1) can also be applied to the kinetic isotope effects by replacing the subscripts 1 and 2 with H and D, respectively. On this basis, the calculated kinetic isotope effect for 1,1,2-trimethylethylene glycol was found to be 2.8, which can be compared with the experimental value of 1.6. In considering the divergence here, one must consider that there is some experimental error in the rate measurements and in the required four sums of electronic and thermal free energies with errors as described above. Rauk has extended Eqn. (1) by incorporating the effects of internal rotors in the molecule.[18,19] He recalculated these data with his version of the equation, arriving at the same value for k_H/k_D.

In the interest of completeness, a reviewer suggested that the rearrangement of butane-2,3-diol be included in this study. The energies for the protonated *threo* and *erythro* glycols and the correponding transition structures are given in Table 1 with the activation energies in Table 3. As can be seen in Fig. 1, the C—H bond length to the carbon at the rearranement origin for the *threo* glycol **E** corresponds to that of the 1,1-dimethylethylene gylcol **C;** the distance to the migration terminus indicates the TS to be later than for **C**. The activation enthalpy is iintermediate between those for ethylene glycol and 1,1-dimethylethylene glycol. With the eclipsing interaction of the two methyls in the *erythro* glycol **D** the TS is considerably earlier than for the *threo* case. This interaction is reflected in the higher activation enthalpy (24.7 vs 23.3 kcal mol^{-1}) for **F** over **E** and in the slightly longer (0.04 Å) C–C bond length.

In summary, it has been demonstrated that for the glycols considered here the concerted mechanism involving a hydrogen-bridged TS offers the lowest energy pathway to products. No evidence for the existence of a bridged hydrogen intermediate was found. The activation enthalpies calculated at the Becke3LYP/6–31G* level are consistent with the number and location of methyl groups. Reaction rate differences between the 1,1-dimethyl and 1,1,2-trimethylethylene glycols are modeled fairly well. Within the limits of error expected for such calculations, replacement of the migrating hydrogen by deuterium for the 1,1,2-trimethyl case gives a computed kinetic isotope effect consistent with the formation of a hydrogen-bridged TS. As shown in Fig. 1, the C(1)—C(2) bond lengths (1.40–1.42 Å) are significantly more sp^2–sp^2-like than the average length of 1.53 Å found in the protonated glycols.

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