

Article

OPENING OF THE EPOXIDE RING. X-RAY CRYSTAL STRUCTURE OF THE OPENED SPECIES AND IDENTIFICATION OF THE TRANSITION STATE BY DFT

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ABSTRACT

Ring-opening of oxiranes by nucleophiles is very important in chemical synthesis. But these reactions are limited by slow reaction rate, poor yield, use of high temperature and Lewis acid catalyst. Reaction of 5,6-dihydro-5,6-epoxy-1,10-phenanthroline (L) with 4-methylaniline produces L', a 2-amino alcohol. Good yield has been obtained in water medium at room temperature without using any Lewis acid catalyst. The product crystallizes in the space group P2₁/a as L'.H₂O with Z = 4. X-ray crystal structure shows that the water molecule acts as a donor of two H-bonds to the phenanthroline N atoms as well as an acceptor of two H-bonds from the N-H moiety of two L'. The transition state (TS) has been located at the B3LYP/6-31+G(d,p) level. The free energy of activation is estimated as 48.76 kcal mol⁻¹ in gas phase. It decreases significantly to 34.79 kcal mol⁻¹ when solvation is considered revealing the role of water in the reaction.

Keywords: epoxide, epoxide opening, X-ray crystal structure, DFT, transition state

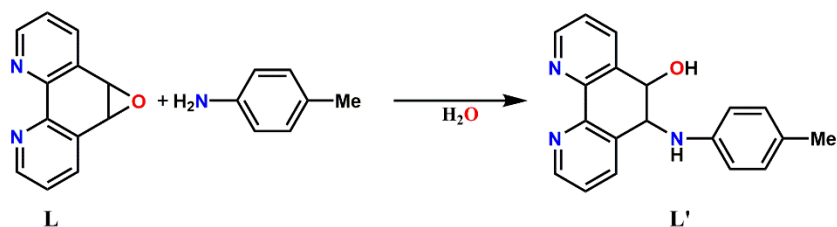
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1. INTRODUCTION

2-Amino alcohols are important versatile intermediates in the synthesis of numerous biologically active natural compounds, chiral auxiliaries, and amino acids [1-3]. These have considerable use in medicinal chemistry [4,5]. Generally, opening of the 3-membered heterocyclic strained epoxide ring by amines leads to the formation of 2-amino alcohols. However, there are some limitations of this approach such as slow reaction rate, poor yield, poor sensitivity of epoxides, need of excess of nucleophiles and often high temperature, weak nucleophilic character of amines, and regio-selective nature of the compounds [6]. In nature, phenolic proton of a tyrosine moiety catalyses the ring opening of oxiranes in water [7].

Researchers have been using a variety of Lewis acid catalysts such as alumina, metal amides, and metal triflates that can enhance the electrophilic character of epoxides [8-10]. There are some reports where use of a catalyst has not been necessary [11,12]. Hydrogen bonding interaction, hydrophobic interaction, and solvent polarity are the main factors that influence the selectivity and reactivity of the process. Recently, we

have undertaken a program to develop the transition metal chemistry of 5,6-dihydro-5,6-epoxy-1,10-phenanthroline (L). We have synthesized its tris complexes of Fe, Ni, Cu and Zn [13-16]. The epoxide ring in the metal chelates is found to be very much susceptible to nucleophilic attack. Other workers have also tried to open up the epoxide ring in L [17-19]. Previously, we have found that simple stirring of ML_3 (M: a metal) with 4-substituted anilines in equimolar proportion in water at room temperature without any Lewis acid catalyst gives high yield of chelated 2-amino alcohols [14,15]. We have determined the X-ray crystal structures of ML_3 . But could not determine the structure of the ring opened species. Here we present the X-ray crystal structure of L' where the epoxide ring in L has been opened by 4-methylaniline (Scheme I). So far X-ray crystal structure of no compounds having opened epoxide ring has been reported.



Scheme I. Opening of the epoxide ring in L by 4-methylaniline

2. RESULTS & DISCUSSIONS

Simple stirring of L with 4-methylaniline at room temperature in water in equimolar proportion affords L'.H₂O in 90% yield. We have obtained the single crystals of L'.H₂O from *n*-hexane-dichloromethane mixture. Its X-ray crystal structure is shown in Figure 1. Selected crystal data are given in Table 1.

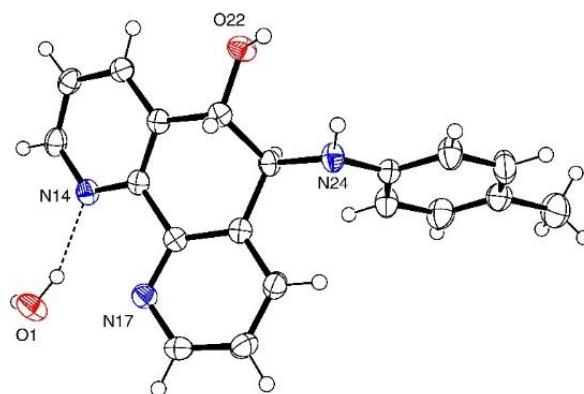


Figure 1. The X-ray crystal structure of L'.H₂O with ellipsoids at 30% probability. H-bond is shown as dotted line.

Table 1. Some crystal and structure refinement data for L'.H₂O

Empirical formula	C ₁₉ H ₁₉ N ₃ O ₂
Formula weight	321.37
Crystal system	Monoclinic
Space group	P2 ₁ /a
Cell dimensions	
<i>a</i> (Å)	17.146(9)
<i>b</i> (Å)	4.8782(10)
<i>c</i> (Å)	20.999(8)
β (deg)	110.94(5)
<i>V</i> (Å ³)	1640.4(11)
<i>Z</i>	4
<i>D</i> _{calcd} (g cm ⁻³)	1.301
μ (mm ⁻¹)	0.086
<i>F</i> (000)	680
θ _{max} (deg)	30
Unique reflections	4538
Observed reflections [<i>I</i> > 2σ(<i>I</i>)]	3007
Parameters	230
GOF on <i>F</i> ²	0.970
<i>R</i> ₁ , <i>wR</i> ₂ [<i>I</i> > 2σ(<i>I</i>)]	0.0600, 0.1331
<i>R</i> ₁ , <i>wR</i> ₂ (all data)	0.0947, 0.1532
Largest peak/hole (e Å ⁻³)	0.316/-0.216

The water molecule O(1) participates in four strong hydrogen bonds, acting twice as a donor to N(17) and N(14) and twice as an acceptor from N(24) and O(22). Thus, all four hetero-

atoms in the molecule participate in hydrogen bonding. Hydrogen bond dimensions are given in Table 2.

Table 2. Hydrogen bonds in L'.H₂O (distances, Å; angles, deg; A = acceptor, D = donor). For atom labelling, see Figure 1.

	H...A	D...A	D-H...A	symmetry operation
N(24)-H24... O(1)	2.21(2)	3.066(3)	163(2)	x-1/2, 1.5-y, z
O(1)-H(1)... N(14)	2.02(2)	2.856(3)	161(2)	
O(1)-H(2)... O(22)	1.93(2)	2.769(2)	176(2)	1/2+x, 2.5-y, z
O(22)-H(22)...O(1)	1.88(2)	2.674(2)	156(2)	x-1/2, 1.5-y, z

Opening of the epoxide ring by an amine is a typical nucleophilic reaction. We have studied the reaction by density functional theory (DFT) at the B3LYP/6-31+G(d,p) level. Here a new C-N bond is formed, and an existing C-O bond is broken as the reaction proceeds from the reactants to product. A shortening of C-N bond and lengthening of C-O bond are observed along the reaction path. The transition state (TS) is pictorially shown in Figure 2. It has a single imaginary frequency (335.52i). Some bond length and angles for the TS and the product are compared in Table 3. The free energy of activation is found to be 48.76 kcal mol⁻¹ in gas phase. However, when solvation energy in water is considered, the free energy of activation is reduced to 34.79 kcal mol⁻¹ which is comparable to the other reported values [20]. The barrier is low enough to permit a smooth reaction between L and 4-methylaniline at room temperature in aqueous medium.

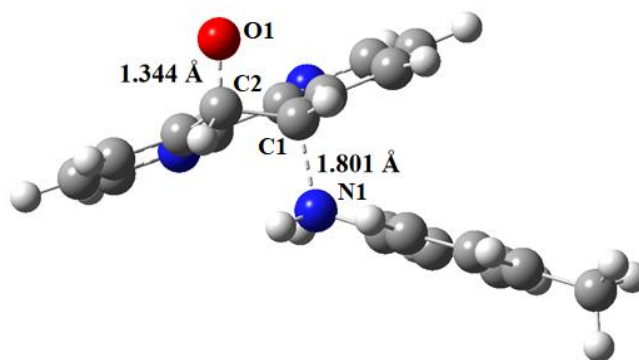


Figure 2. DFT structure of the transition state showing the C-O and C-N bond lengths. Color code: white, H; grey, C; blue, N and red, O.

Table 3. Data of some bond lengths (Å), bond angles (°) and a torsion angle (°) in the transition state and the final product at the B3LYP/6-31+G(d,p) level. For atom labelling, see Figure 2.

metric parameter	transition state	product
N1-C1	1.801	1.456
C1-C2	1.516	1.546
C1-O1	2.197	2.463
C2-O1	1.344	1.420
N1-C1-C2	108.29	112.13
O1-C2-C1	106.32	112.18
N1-C1-C2-O1	169.26	60.83

3. COMPUTATIONAL

All electronic structure calculations have been carried out using the Gaussian 09 program package [21]. The hybrid nonlocal density functional B3LYP and 6-31+G(d,p) basis set are employed for the calculation. The transition state is optimized using Berny algorithm as implemented in Gaussian 09. Conductor like polarization continuum model (CPCM) [22] has been used to calculate the solvation energy in water ($\epsilon = 78.54$). Single point energies of the optimized geometries (gas phase) in aqueous medium are calculated to consider the solvation effect.

4. EXPERIMENTAL

4.1. Materials and physical measurements

L, 4-methylaniline were purchased from Aldrich. Micro-analyses were performed by a Perkin-Elmer 2400II elemental analyser. FTIR spectra (KBr) were recorded on a Shimadzu FTIR-8400S spectrometer, 300 MHz NMR spectra on a Bruker DPX300 spectrometer, and ESI mass spectra on a Waters Qtof Micro YA263 spectrometer.

4.2. Synthesis of *L'*·H₂O

Method A. L (0.039 g, 0.2 mmol) and 4-methylaniline (0.021 g, 0.2 mmol) were taken in water (50 ml) and stirred for 72 h. The white compound precipitated was collected by filtration, washed with water (2 ml) and dried in vacuo over fused CaCl₂. Yield: 0.055 g (90%).
Method B. The reactants were refluxed for 14 h. Then the clear orangish solution was evaporated to 10 ml and cooled to room temperature. A yellowish compound so obtained was filtered off and dried in vacuo over fused CaCl₂. Yield: 0.037 g (60%). m. p. 239 °C. *Anal.* Calc. for C₁₉H₁₉N₃O₂: C, 70.99; H, 5.96; N, 13.07. Found: C, 70.81; H, 5.82; N, 13.10%. FTIR: ν/cm^{-1} : 3371 vs (NH). ESI-MS (CH₃CN): m/z : 342.2 [(L' + K)⁺, 100%]. ¹H NMR (DMSO-d₆): δ /ppm: 2.15 (s, 3H, methyl), 4.62 (t, 6 Hz, 1H, CHN), 4.84 (t, 6 Hz, 1H, CHO), 5.69 (d, 6 Hz, 1H, NH), 5.78 (d, 6 Hz, 1H, OH), 6.61 (d, 9 Hz, 2H, phenyl), 6.90 (d, 9 Hz, 2H phenyl), 7.40 (m, 2H, phen), 7.74 (d, 6 Hz, 1H, phen), 7.89 (d, 6 Hz, 1H, phen), 8.65 (t, 6 Hz, 2H, phen).

4.3. X-ray crystallography

4538 independent reflection data were collected with MoK α at 150K using the Oxford Diffraction X-Calibur CCD System. The crystals were positioned at 50 mm from the CCD and 321 frames were measured. Data analyses were carried out with the CrysAlis program [23]. The structure was solved using direct methods with the Shelxs97 program [24]. The non-hydrogen atoms were refined with anisotropic thermal parameters. The hydrogen atoms bonded to carbon were included in geometric positions and given thermal parameters equivalent to 1.2 times those of the atom to which they were attached. Hydrogen atoms bonded to nitrogen or oxygen were located in a difference Fourier map and refined with distance constraints. The structure was refined on F^2 using Shelxl97 [24].

5. CONCLUSIONS

It is concluded that L can undergo opening of the epoxide ring by 4-methyl aniline in water at room temperature in the absence of any Lewis acid catalyst to form L'.H₂O. The crystal structure of L'.H₂O shows presence of N-H...O and O-H...N type of hydrogen bonding. DFT calculations show breaking of a C-O bond formation of a C-N bond in the TS. The free energy of activation decreases significantly when solvation in water is considered proving the role of water in easing the reaction.

SUPPLEMENTARY MATERIALS AVAILABLE

CCDC-1936996 contains the supplementary crystal data for L'.H₂O. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via w.w.w.ccdc.cam.ac.uk/data_request/cif.

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