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Spectroscopic and Computational Study of Hydrate vs. Hemiacetal Equilibria in 6,7-Epoxy-6,7-Dihydroquinoline-5,8-Dione

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Quinoline,
Quinone,
Hydration,
Hemiacetal

Abstract: The hydration of carbonyl compounds and the formation of hemiacetals have been a topic of interest in organic chemistry. Hydration plays an important role in biological processes. Quinoline derivatives are also biologically active molecules with many applications. Equilibrium between 6,7-epoxy-6,7-dihydroquinoline-5,8-dione and its hydrate or hemiacetal form was investigated in aqueous and alcoholic solutions by NMR spectroscopy. Interestingly, no equilibrium was detected for the hydrocarbon counterpart. It was presumed that the existence of this equilibrium is highly dependent on the electronic structure of the molecule. To further understand the difference in reactivity to such systems, density functional theory (DFT) calculations were performed.

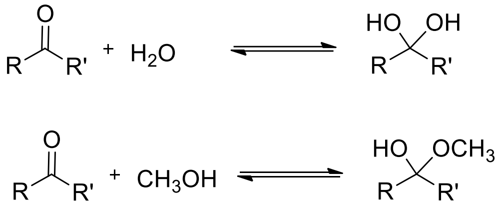
6,7-Epoksi-6,7-Dihidrokinolin-5,8-Dion'da Hidrat ve Hemiasetal Dengelerinin Spektroskopik ve Hesaplamalı Çalışması

Anahtar Kelimeler
Kinolin,
Kinon,
Hidratasyon,
Hemiasetal

Öz: Karbonil bileşiklerinin hidratasyonu ve hemiasetallerin oluşumu organik kimyada ilgi çekici bir konu olmuştur. Hidratasyon biyolojik işlemlerde özellikle de ilaç salınımında önemli bir rol oynar. Kinolin türevleri de birçok uygulama alanına sahiptir ve çok geniş spektrumda biyolojik olarak aktif moleküllerdir. Bir kinolin türevi olan 6,7-epoksi-6,7-dihidrokinolin-5,8-dion ile hidrat veya hemiasetal formu arasındaki denge, sulu ve alkollü çözeltilerde NMR spektroskopisi ile incelendi. İlginç bir şekilde, hidrokarbon analoğu için bir denge tespit edilmedi. Bu dengenin varlığının molekülün elektronik yapısına (azot atomu molekülün elektronik yapısını değiştirdiğinden) büyük ölçüde bağlı olduğu varsayıldı. Bu tür sistemlere karşı reaktiflikteki farkı daha iyi anlamak için yoğunluk fonksiyonel teorisi (DFT) hesaplamaları yapıldı.

1. Introduction

The reversible hydration and hemiacetal formation of carbonyl compounds in aqueous solutions has long been a topic of interest and investigation (Scheme 1) [1-11]. These reactions are one of the simplest addition reactions to the carbonyl group and have also been utilized to understand various organic reactions [1,4]. Moreover, it is already known that hydration plays an important role in solubility and stability of pharmaceutical solids[12].



Scheme 1 Hydration and hemiacetal formation of ketones

The mechanism proposed for the hydration of aldehydes involves attack of a water molecule to the carbonyl carbon of aldehydes and ketones and the release of the hydrogen ion of the water molecule. In the next step carbonyl oxygen attacks to the hydrogen ion to furnish hydrated forms of aldehydes and ketones [2]. The mechanism suggested for the hydrate

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formation in water is thought to be the same with the hemiacetal formation of a ketone in alcohol solutions[13].

Although, hydration and hemiacetal formation of simple aldehydes and ketones are well documented in the literature, investigation of complex systems such as heterocycle fused aldeydes and ketones are documented in a few instances [10,14-16]. Herein, we investigated the quinoline-conjugated and ketone systems.

Quinoline skeletons are available in natural compounds (e.g. Lavendamycin) [17] and these molecules show antitumor, antimalarial, antimicrobial and anti-inflammatory biologic activities [18,19]. Quinoline units are also widely used as pH-sensitive chromophore and have been suggested for several optical sensing applications [20]. Quinoline derivatives have also been widely utilized in medicinal, industrial and synthetic organic chemistry [19].

Herein, we present a computational and experimental study in an effort to gain insight on the electronic feature of quinolone derivative **1** for the hydrate and hemiacetal formation reactions.

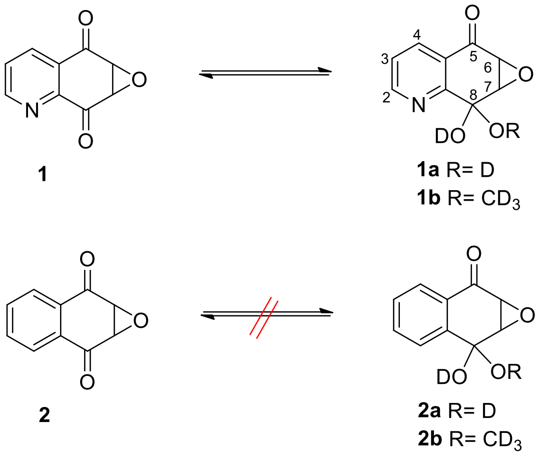
2. Material and Method

2.1 Experimental section

20 mg of samples were disolved in 0.6 ml of deuterated solvents and transferred to NMR tubes. NMR (^{1}H, ^{13}C, 2D) spectra were recorded (at 4, 23 and 40 °C) on a Bruker Instrument, Avance Series-Spectrospin DPX-400 Bruker, Ultra Shield (400 MHz). Column chromatographic separations were performed by using Fluka Silica gel 60 plates with 0.063-0.200 mm particle size. Thin layer chromatography (TLC) was applied using precoated 0,25 mm silica gel plates purchased from Fluka. Solvents were obtained from Merck and used without further purification

3. Results

6,7-epoxy-6,7-dihydoquinoline-5,8-dione (**1**) was synthesized according to the previously reported protocol (Scheme 2) [21]. Based on the ^{1}H NMR spectroscopy measured in D_2O, significant amount of compound **1** was observed in its hydrated form **1a** (Figure 1).



Scheme 2. Hydration and hemiacetal formation of compounds **1** and **2**

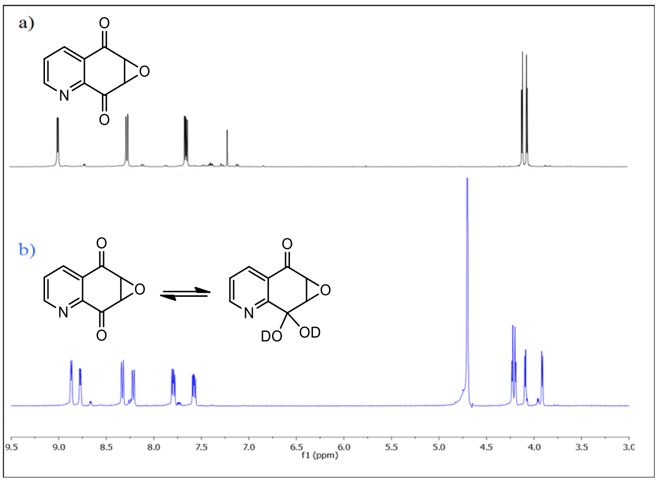


Figure 1 ^{1}H NMR spectra of **1** (a) in $CDCl_3$ (b) in D_2O

The use of CD_3OD as a solvent resulted in the formation of expected structure **1b** (Scheme 2). The reason for this observation is probably due to the electron-withdrawing nature of the nitrogen in the quinoline moiety which decreases the electron density on carbonyl carbon and facilitates the hydration reaction. To understand the influence of heteroatom on the electronic structure of the starting material, similar reaction approach was followed for compound **2**. However, neither hydrate **2a** nor hemiacetal **2b** was observed, showing that electronic effects have greater impact on the reaction (Scheme 2).

The molar ratios of compounds **1** and **2** to hydrate or hemiacetal species in D_2O or CD_3OD solutions were calculated by the integration of ^{1}H NMR peaks. In order to understand the temperature effect on the equilibrium, NMR spectra were recorded at 4, 23 and 40 °C. The equilibrium constants (K_h [hydrate] / [ketone] in D_2O and K [hemiacetal] / [ketone]) CD_3OD) for hydration and hemiacetal formation of **1** and **2** are shown in Table 1. The equilibrium shifted toward products (hydrate or hemiacetal) at 4 °C while it shifted toward reactant (compound **1**) at 40 °C. These results clearly indicate that the reaction is exothermic.

Table 1. The equilibrium constants for hydration and hemiacetal formation of **1** and **2**

Compound	*T (°C)*	*Hydration,* K_h	*Hemiacetal,* K
1	4	1.19	1.14
1	23	0.85	1.32
1	40	0.63	0.37
2	23	–	–

The ^{1}H NMR spectrum in $CDCl_3$ showed that all proton signals of hydrate and hemiacetal form of **1** are shifted (0.5 ppm) to the higher field with respect to its ketone form (see Appendix A). The detail analysis revealed that the aromatic protons H-2 and H-4 resonate at 8.98 and 8.22 ppm as a doublet of doublets, respectively. The other aromatic proton H-3 appears at 7.64 ppm as a doublet of doublets as well. The aliphatic protons (H-6 and H-7) appear as an AB system at around 3.78-4.02 ppm. On the other hand, the spectrum recorded in D_2O showed three additional signals between 8.80 and 7.58 ppm in addition to the three aromatic proton signals of compound **1** and the aliphatic protons gave rise to an AB system. A part of AB system resonates at 4.25 ppm and B part at 4.01 ppm. Moreover, the resonance signal observed at 91 ppm in the ^{13}C NMR spectrum (in D_2O) indicates the hydration of **1**.

Furthermore, in ^{13}C NMR spectrum recorded in CD_3OD, the carbon signals of quinone and hemiacetal equilibrium mixture were observed as two sets of signals (see Appendix F). Additionally, a signal in the ^{13}C NMR spectrum (CD_3OD) appearing at 94 ppm supports the hemiacetal form of compound **1** [3]. For the further characterization 2D NMR spectrum (HMBC) was recorded to illustrate that the hydration occurs at C-8 carbon (see Appendix I). It was observed that C-8 no correlation with the aromatic protons. If hydration had occurred at the C-5 carbon, the correlation of this carbon signal with aromatic protons should have been observed. Therefore, we propose that the hydration and hemiacetal formation occur at the C-8 position.

The heteroatom effect on the charge distribution in compound **1** may serve for understanding the experimentally observed result. For this reason, theoretical calculations were performed. Molecular geometry of **1** was optimized in gas phase with the M06 functional [22] in conjunction with a large basis set 6-311++G(2d,2p) as implemented in the Gaussian 09 [17] program package (figure 2). Structural representation was generated using CYLview [24].

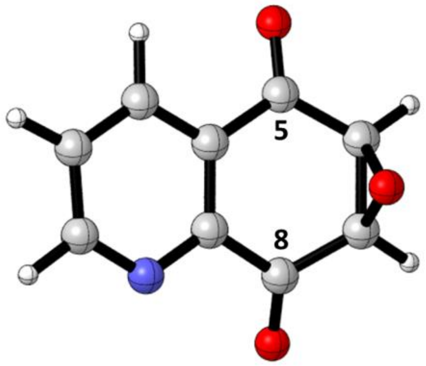


Figure 2. Optimized geometry of **1.**

The Mulliken population analysis is probably the most widely used method; however, its results may vary with the basis set employed [25]. Therefore, Mulliken charges were calculated using various basis sets and methods on atoms C-5 and C-8 (Table 2). According to the results, C-8 is found to be more electrophilic than C-5. This could be an indication for the preferred nucleophilic attack on C-8.

Table 2. Selected Mulliken charges of compound **1** in different methods.

	Mulliken Charges	
Method	**C-5**	**C-8**
B3LYP [26-28] /6-31G(d)	0.429	0.454
B3LYP/6-31G(d,p)	0.421	0.444
M06/6-31G(d)	0.462	0.486
M06/6-31+G(d,p)	0.120	0.150
B3PW91[26-29] /6-31G(d)	0.451	0.469
ωB97XD [30] ^{30}/6-31G(d)	0.451	0.465
ωB97XD/6-31G(d,p)	0.443	0.455

4. Discussion and Conclusion

Herein, we present a combined experimental and computational study aimed at understanding the equilibrium between 6,7-epoxy-6,7-dihydroquinoline-5,8-dione and its hydrate or hemiacetal form in alcoholic and aqueous solutions.
In the reaction of compound **1**, nucleophilic attack on C-8 took place leading to its hydrate or hemiacetal form. However, in the case of its hydrocarbon counterpart, the reaction was failed. Our calculations indicate that charge distribution is responsible from this outcome.

In most cases for the hydration and hemiacetal formation reactions, the equilibrium does not favor the generation of hydrate and hemiacetal forms. However, in our case, 6,7-Epoxy-6,7-

dihydroquinoline-5,8-dione has been found reactive enough to furnish its hydrate and hemiacetal forms. With this work, it is also shown that the hydration and hemiacetal formation of **1** can occur intrinsically without any catalysts such as acid, base and/or metal.

Declaration of Ethical Code

In this study, we undertake that all the rules required to be followed within the scope of the "Higher Education Institutions Scientific Research and Publication Ethics Directive" are complied with, and that none of the actions stated under the heading "Actions Against Scientific Research and Publication Ethics" are not carried out.

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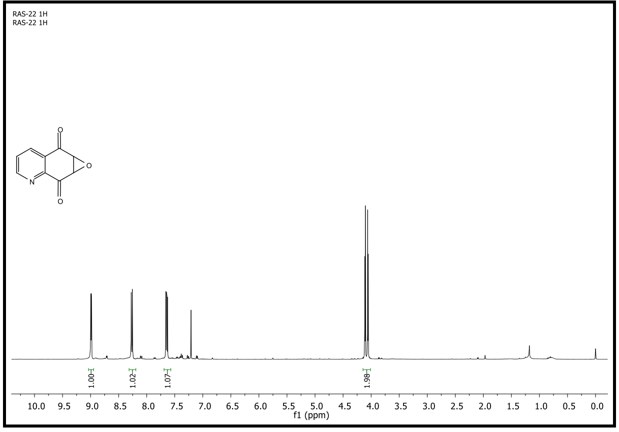
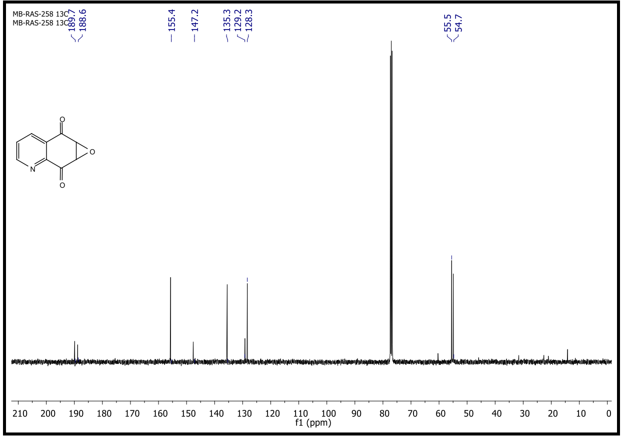
Appendices

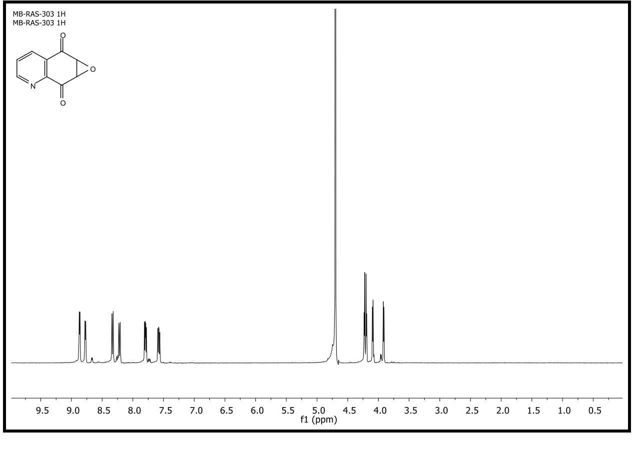
Appendix A: ^{1}H spectrum of 6,7-epoxy-6,7-dihydroquinoline-5,8-dione (**1**) in $CDCl_3$ at 23 °C (400 MHz)



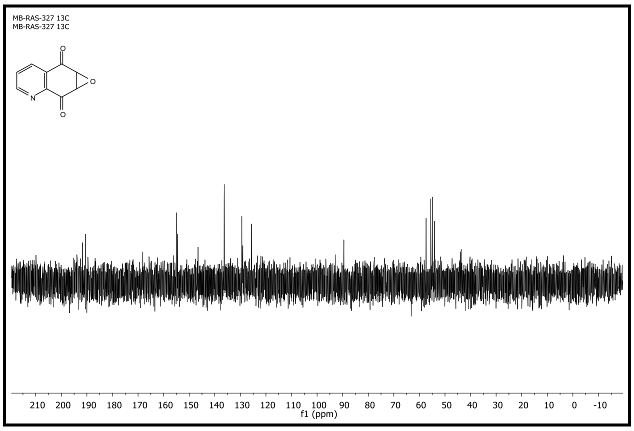
Appendix B: ^{13}C NMR spectrum of 6,7-epoxy-6,7-dihydroquinoline-5,8-dione (**1**) in $CDCl_3$ at 23 °C (400 MHz)



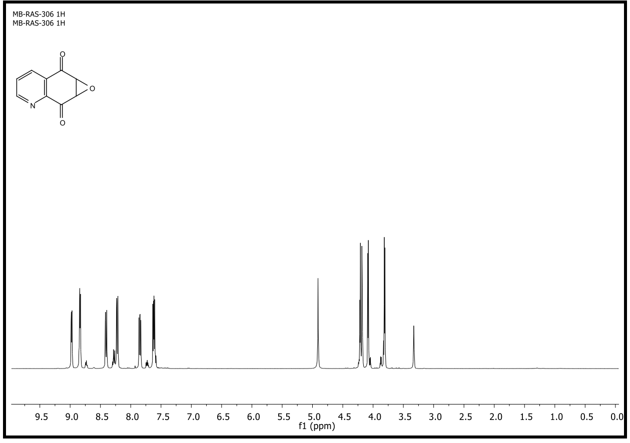
Appendix C: ^{1}H NMR spectrum of 6,7-epoxy-6,7-dihydroquinoline-5,8-dione (**1**) in D_2O at 23 °C (400 MHz)



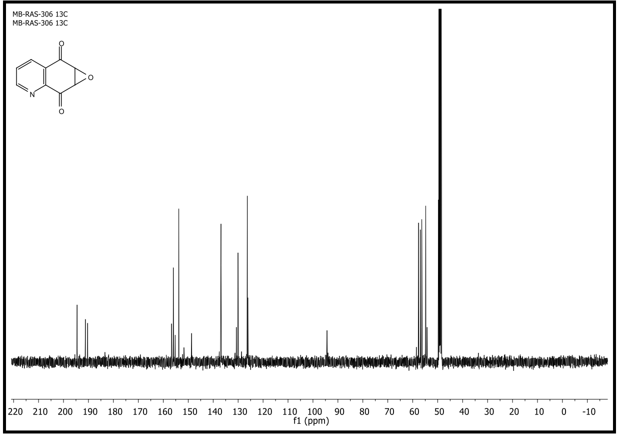
Appendix D: ^{13}C NMR spectrum of 6,7-epoxy-6,7-dihydroquinoline-5,8-dione (**1**) in D_2O at 23 °C (400 MHz)



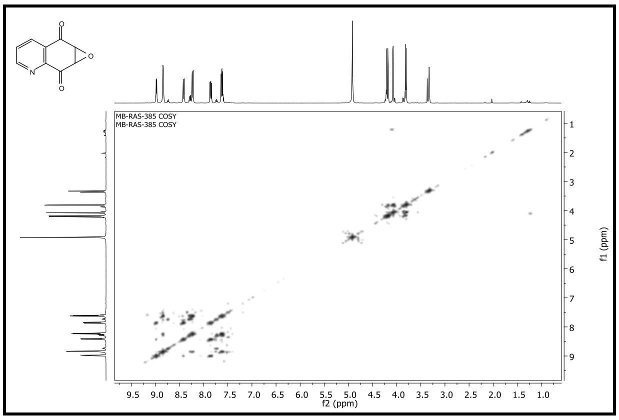
Appendix E: ^{1}H NMR spectrum of 6,7-epoxy-6,7-dihydroquinoline-5,8-dione (**1**) in CD3OD (400 MHz)



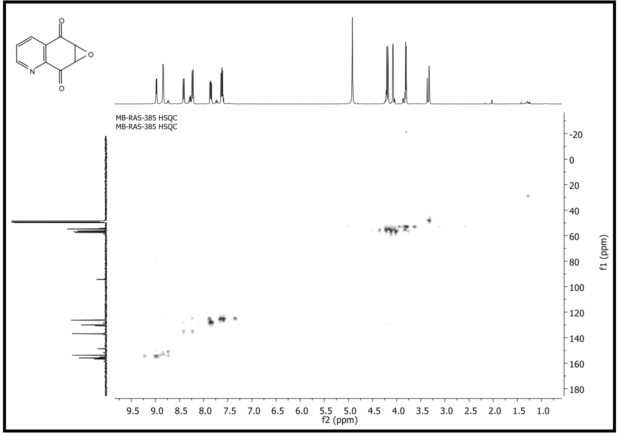
Appendix F: ^{13}C NMR spectrum of 6,7-epoxy-6,7-dihydroquinoline-5,8-dione (**1**) in CD_3OD (400 MHz)



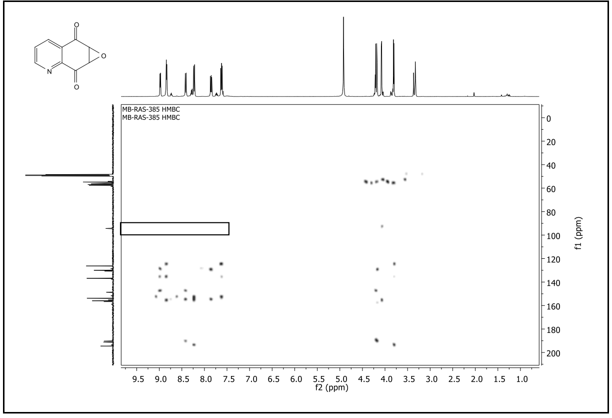
Appendix G: COSY spectrum of 6,7-epoxy-6,7-dihydroquinoline-5,8-dione (**1**) in CD_3OD (400 MHz)



Appendix H: HSQC spectrum of 6,7-epoxy-6,7-dihydroquinoline-5,8-dione (**1**) in CD_3OD (400 MHz)



Appendix I: HMBC spectrum of 6,7-epoxy-6,7-dihydroquinoline-5,8-dione (**1**) in CD_3OD (400 MHz)



Appendix J: ^{1}H NMR spectrum of naphtho[2,3-b]oxirene-2,7(1aH,7aH)-dione (**2**) in CD_3OD (400 MHz)