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Dynamic Investigation of β-Hydroxy Amide Derivatives by 400 MHz ^{1}H-NMR

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Abstract: ***In this study, T_1 and T_2 relaxation times of some β-hydroxy amide derivatives was measured at room temperature (25 ^{0}C) by 400 MHz ^{1}H-NMR spectrometer. The motion of molecules was investigated by finding τ_c correlation time from the rate of $R_1/R_2 = (1/T_1)/2(1/T_2)$. T_1 times of Ar-OH, Amide-NH and Alcohol-OH groups in β-hydroxy amide 1 appears greater than the T_1 times of Ar-OH, Amide -NH and Alcohol groups in β-hydroxy amide 2 and 3. This result shows that $\pi - \pi$ interactions as well as non-covalent intramolecular interactions in ligand 2 and 3 which carry more bulky groups. τ_c values of all molecules are found in ns range. This indicates that the motion is based on dipolar interactions.***

Keywords: β-hydroxy amide, T_1, T_2, molecular dynamic, correlation time

1. Introduction

Hydroxy amides are anti-convulsants [1], thrombin inhibitors [2], and RAR-γ-specific retinoid agonists [3]. They are also intermediates for the synthesis of oxazolidinediones [4], oxindoles [5], β-lactams [6], and antidepressant drugs, for example, (R)- fluoxetine, and building blocks for the synthesis of biologically active compounds.

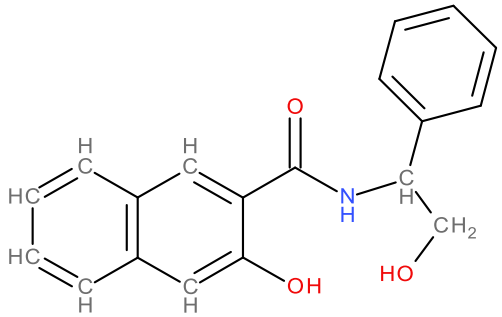
Molecular recognition determines the binding of two molecules. Thus, understanding molecular recognition is of interest in both fundamental studies and has practical applications in chemical industries and drug discovery. β-hydroxy amides have been widely studied for molecular recognition. Therefore, the relaxation studies of β-hydroxy amides give useful information about molecular dynamics in free states [7,8].

The study of viscous solutions by nuclear magnetic resonance (NMR) relaxation methods can provide useful information concerning rotational motion, transport properties, molecular structure, and molecular interactions. In fact, it is often more useful to investigate the region of reduced molecular motion (where correlation times are typically in the nanosecond to millisecond range) described by the phrase ‘‘outside of the region of extreme narrowing’’ than to investigate the region of ‘‘extreme narrowing.’’ The term ‘‘extreme narrowing’’ is used to describe rapid molecular rotation (picoseconds correlation times) which simplifies the rotational correlation equations [9-25].

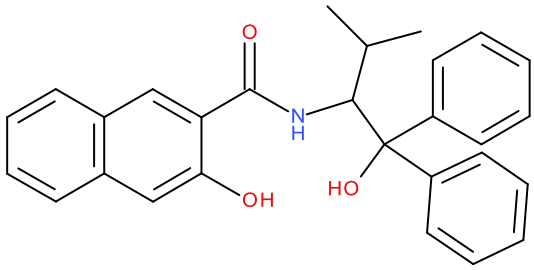
In this study, firstly, T_1 and T_2 relaxation times were measured for dynamic studies of β-hydroxy amides. Secondly, an equation was derived for τ_c from the ratio of $R = (1/T_1)/2(1/T_2)$ using the relaxation rate formulas derived for homonuclear dipolar interactions. Then the τ_c values were calculated for each peak of the β-hydroxy amide derivatives in solution. Finally, τ_c values were analyzed.

2. Material and Method

The three β-hydroxy amide derivatives used in this study are shown in Fig.1 [26-27].



β-hydroxy amide 1



β-hydroxy amide 2

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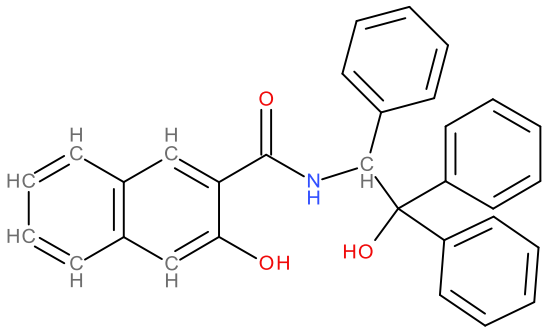

β-hydroxy amide 3

Figure 1: Schemes of β-hydroxy amide derivatives 1, 2, and 3.

3. Experimental

3.1 Preparation of Samples

10 mg of each β-hydroxy amide derivatives were taken to measure T_1 spin-lattice and T_2 spin-spin relaxation times. It was then dissolved in 5 mL of DMSO-d6 to prepare three different stock solutions of each hydroxy amide derivatives. 600 µL of each sample was transferred into 5 mm-NMR tubes and degassed three times by the freeze-thaw method and sealed for measurements.

3.2. Measurements of T_1 Spin-Lattice and T_2 Spin-Spin Relaxation Times

T_1 was measured using the Inversion Recovery technique $(\pi-\tau-\pi/2)$ at room temperature by AVANCE BRUKER 400 MHz ^{1}H-NMR spectrometer. τ delay times were taken 0.2 s, 0.4 s, 0.8 s, 1.2 s, 1.5 s, 2 s, 3 s, 4 s and 5 s. Pulse repetition time was taken 10 s. Single magnetization decay was found to be exponential for each peak. T_2 measurements were performed using CPMG (Carr-Purcell-Meibomm-Gill) pulse technique. τ delay times were taken 2 ms, 4 ms, 8 ms, 16 ms, 32 ms, 64 ms, 128 ms, 256 ms, 512 ms, 1024 ms and 2048 ms. Pulse repetition time was taken 10 s. Single magnetization decay was found to be exponential for each peak.

3.3. Arrangement of R Ratio for Calculation of τ Correlation Time

Equation 1 was obtained for a homonuclear spin system from the ratio of $1/T_1$ and $1/T_2$ equations.

$$\frac{R_1}{R_2}=\frac{[3\gamma^4\hbar^2/10r^6].[\tau_c/(1+\omega^2\tau_c^2)+4\tau_c/(1+4\omega^2\tau_c^2)]}{[3\gamma^4\hbar^2/20r^6].[3\tau_c+5\tau_c/(1+\omega^2\tau_c^2)+2\tau_c/(1+4\omega^2\tau_c^2)]}$$

$$12R(\omega\tau_c)^4+(37R-8)(\omega\tau_c)^2+(10R-5)=0 \quad (1)$$

where, $R=(1/T_1)/2(1/T_2)$ ratio and can be found experimentally. τ_c values were calculated from Equ. 1.

4. Results and Discussion

The proton spectrums of the β-hydroxy amide derivatives (1, 2 and 3) are given in Figures 2, 3 and 4.

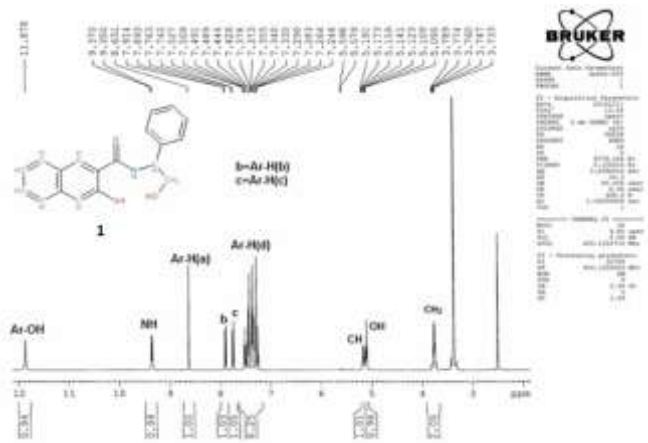

Figure 2: 400 MHz ^{1}H-NMR spectrum of β-hydroxy amide derivative **1** at room temperature. Chemical shift values of ^{1}H NMR (DMSO-*d*6): δ (ppm) 3.76-3.79 (m, 2H), 5.1 (t, 1H, *J*= 5.2 Hz), 5.17 (q, 1H, *J*=6.8 Hz), 7.25- 7.53(m, 8H), 7.75 (d, 1H, *J*= 8.3 Hz), 7.90 (d, 1H, *J*= 9.5 Hz), 8.64 (s, 1H), 9.35 (d, 1H, J=7.8 Hz), 11.87 (s, 1H).

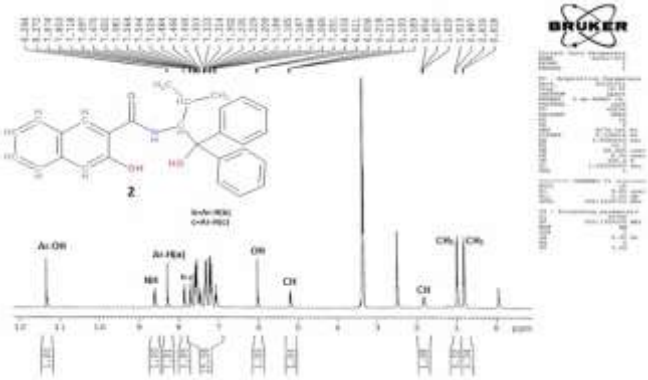

Figure 3: 400 MHz ^{1}H-NMR spectrum of β-hydroxy amide derivative **2** at room temperature. Chemical shift values of ^{1}H NMR (DMSO-*d*6): δ (ppm) 0.84 (d, 3H, *J*=6.8 Hz), 1.02 (d, 3H, *J*= 6.8 Hz) , 1.83-1.89 (m, 1H), 5.22(dd, 1H, *J*= 1.8 ve 10.0 Hz), 6.04 (s, 1H), 7.05-7.62(m, 13H), 7.71(d, 1H, *J*= 8.2 Hz), 7.86 (d, 1H, *J*=8.2 Hz), 8.31(s, 1H), 8.62(d, 1H, *J*=10.0 Hz), 11.37(s, 1H).

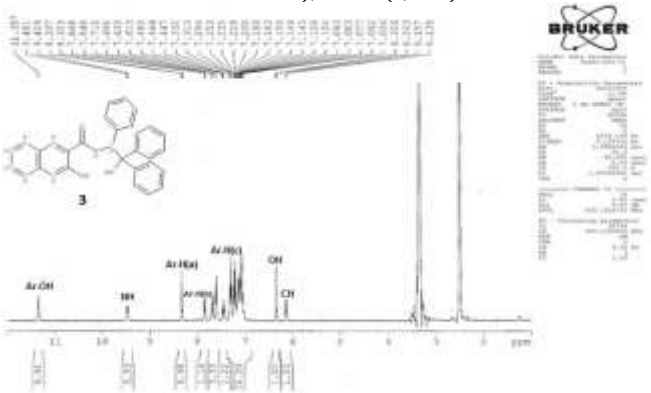

Figure 4: 400 MHz ^{1}H-NMR spectrum of β-hydroxy amide derivative **3** at room temperature. Chemical shift values of ^{1}H NMR (DMSO-*d*6): δ (ppm) 6.15 (d, 1H, *J*=9.2 Hz), 6.34(s, 1H), 7.05-7.86 (m, 20H), 8.34(s, 1H,), 9.45 (d, 1H, *J*=9.2 Hz), 11.34(s, 1H).

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T_1, T_2 and τ_c values for each peak of spectrums shown in figs. **2-4** are given in Table 1, 2, and 3.

Table 1: T_1, T_2 and τ_c values of β-hydroxy amide derivatives **1**

	1		
	T_1 (s)	T_2 (s)	τ_c (ns)
Ar-OH	1.374	0.11	1.50
NH	0.456	0.073	0.97
Ar-H(a)	0.912	0.192	0.80
Ar-H(b)	1.232	0.237	0.86
Ar-H(c)	1.327	0.305	0.75
Ar-H(d)	1.375	0.299	0.78
CH	1.060	0.292	0.64
OH	1.290	0.074	0.19
CH_2	0.353	0.071	0.44

Table 2. T_1, T_2 and τ_c values of β-hydroxy amide derivatives **2**

	2		
	T_1 (s)	T_2 (s)	τ_c (ns)
Ar-OH	1.259	0.100	1.51
NH	0.372	0.044	1.19
Ar-H(a)	1.138	0.204	0.90
Ar-H(b)	1.255	0.172	1.08
Ar-H(c)	1.247	0.194	0.93
OH	0.673	0.096	1.05
CH	0.811	0.084	0.84
CH	0.430	0.132	0.96
CH_3	0.478	0.087	0.89
CH_3	0.402	0.078	0.85

Table 3: T_1, T_2 and τ_c values of β-hydroxy amide derivatives **3**

	T_1 (s)	T_2 (s)	τ_c (ns)
Ar-OH	1.277	0.105	1.47
NH	0.388	0.056	1.04
Ar-H(a)	1.290	0.225	0.92
Ar-H(b)	1.310	0.210	0.97
Ar-H(c)	1.356	0.196	1.04
OH	0.890	0.130	1.04
CH	0.977	0.115	1.19

T_1 times of protons of Ar-OH, Amide-NH, Alcoholic-OH and -CH-groups at the stereo center were compared. The following results were obtained. T_1 values of Ar-OH, Amide –NH ve Alcoholic–OH groups in β-hydroxy amide 1 are bigger than the groups in β-hydroxy amide 2 (containing two phenyl and isopropyl groups) and β-hydroxy amide 3 (containing three phenyl groups).

This result indicates that $\pi - \pi$ interactions are effective as well as intramolecular non-covalent interactions of β-hydroxy amide 2 and 3.

The τ_c correlation times of all molecules belonging to β-hydroxy amide derivatives are shown in Table 1. These τ_c values were calculated from the equation 1 which obtained from the ratio of R_1 / R_2. All τ_c values are in the order of ns.

5. Conclusion

Although the origins of spin-lattice and spin-spin relaxation mechanisms are very different, T_1 and T_2 relaxation times are equivalent in fast molecular motions $(\omega^2\tau_c^2 \ll 1)$. At the same time, there is an inequality between T_1 and T_2 in the slow molecular motions $(\omega^2\tau_c^2 \gg 1)$. $R_1 = 1/T_1$ and $R_2 = 1/T_2$ relaxation rates measured under these conditions can be used to find the all unknown parameters. In our study, τ_c correlation times were found in the extreme narrowing condition $(\omega^2\tau_c^2 \ll 1)$ from Equation 1. The best line range of correlation time in the dipolar mechanism is 10^{-7}-10^{-9} seconds. We found τ_c correlation time values in order of ns for all peaks. This indicates that the τ_c correlation time, which modulates the motion, is based on dipolar interaction. Therefore, we can say that the dominant mechanism is molecular tumbling for all groups [16].

6. Acknowledgements

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