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Dynamic NMR and Theoretical Study of Hindered Internal Rotation about the C-N Bond in 4-(phenyl) acetyl Morpholine

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Abstract

Variable-temperature 13C NMR spectroscopy is used to investigate barrier of C-N internal rotation in compound 4-(Phenyl) acetyl morpholine, and then with simulation of band shape broadening pattern at coalescence region, rate constants of exchange were obtained for all temperatures. For simulation of line-shape broadening Spin works software (version 3.1) was used, that with two interfaces made possible simulation with two band shape simulator programs, Dynamic Nuclear Magnetic Resonance (DNMR) and MEXICO. For obtaining the thermodynamic activation parameters Gaussian 98 program was used, resulting $\Delta G^{\#}_{298}$ value in toluene is 68.09 kJ/mol.

Keywords: Dynamic Nuclear Magnetic Resonance; Gaussian 98 Program; Rate Constant, 4-(Phenyl) Acetyl Morpholine

1. Introduction

It is thought that the NMR of molecules that are rigid can not change any of the bonds within the molecule. However, it is not true and molecules have enormous variations and changes because these movements are rapid (with frequency of 1012 to 1014 Hz), and therefore do not have direct effects on the NMR spectrum. It is considered movement so precisely that the changes leading to reversible causes and dynamic phenomena involved in this case can be investigated; in this case it is called chemical exchange. The DNMR time

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function is suitable for the study of many phenomena. Molecular mobility can be obtained from relaxation rate measurements when exchange processes exist in equilibrium systems by nuclear spins, and can be investigated by analyzing steady-state band shape. The properties of different amides have received much attention, not only they are a seminal functional group in organic chemistry [1-3]. Simple amides have been broadly used as representation compounds for experimental and theoretical studies of the protein connection. The partial double-bond nature of the C-N amide bond causes significant rotational barrier .The free energies of activation ($\Delta G^{\#}$) were started to be 79.83-88.19 kJ/mol in solution and 81.10 kJ/mol in gas- phase [4].The morpholine ring structure is an important heterocyclic present in many compounds of biological and pharmaceutical application.(S,S)-Reboxetine is free base and an example of a morpholine-containing compound that shows strong activity against many diseases counting neuropathic pain[5]. In this study both coalescence temperatures and slow exchange spectra are investigated to report the activation enthalpy ($\Delta H^{\#}$), Gibbs free energy ($\Delta G^{\#}_{298}$), and activation entropy ($\Delta S^{\#}$) differences relating the rotational barrier in this compound [6].

2. Experimental Section

2.1. Synthesis of 4-(phenyl) acetyl Morpholine

In a 50 mL flask 1/1 mmol phenyl acetyl chloride (Fluka) in 10 ml dichloromethane (DCM) was added and then it was mixed to 1 mmol morpholine (Merck). Reaction mixture stirred for 30 min and then the reaction mixture was added 20 mL of 10% NaOH solution. After stirring for 15 min, the organic phase was separated and then the solvent was removed with a vacuum pump. The resulting product was then crystallized in ethanol and the final composition of 4 - (Phenyl) acetyl morpholine (Figure 1) is achieved. This compound has 122-123 ºC boiling points and steam is used as an anti-corrosive.

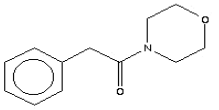

Fig. 1. 4-(phenyl) acetyl morpholine

2.2. Sample Preparation

Solution-phase NMR samples were prepared with the concentration of 0.05 M and was built in toluene solvent. Analysis of data from the ^{1}H spectrum is investigated to calculate activation thermodynamic parameters, due to the complex characteristic spectral lines, it was not practically possible. While the spectrum of acceptable range ^{13}C were available to extract thermodynamics data.

2.3. NMR measurement

NMR measurements were carried out on a Bruker AMX500. All measurements were done on spinning samples in the locked mode. For ^{13}C NMR 3000 scans were gathered at slow exchange region and coalescence temperature.

2.4. Rate analysis

Rate constants were extracted for exchange spectra by using the MEXICO program [7], which uses an iterative nonlinear least square regression analysis to obtain the best fit of the experimental spectrum. The complete band shape (CBS) scheme of analysis first requires the amount of chemical shifts and natural transverse relaxation times.

3. Methodology

3.1. Computational Methods

All computations were carried out with the Gaussian 98 abs initio program package [8] The energies and geometries of this compound were calculated with B3LYP method and 6-311++G^{**} basis set. Harmonic vibration frequencies were computed to confirm an optimized geometry corresponds to local minimum that has only real frequencies and for transition state (TS) point that has only one imaginary frequency.

3.2. Finding the barrier energy for C-N bond rotation

All structures were fully optimized at B3LYP/6-311++G** method with no initial symmetry restrictions. Program "Gaussian" has an ability an initial structure for optimizing of transition state which is dependent on raw materials and products, this process is done by transit-guided quasi-Newton“STQN” method. This calculation needs “QST2” version and Opt algorithm for calculation. For some cases, a hypothetical structure of the transition state structure of the input file is more appropriate. Successful completion of the transition state structure is not to ensure the accuracy of the transition state (TS) .There is a path to examine transition state, the best way is that calculation of frequency for transition state and observation of imaginary frequency for it, and ensure that the imaginary frequency of the transition state structure is expected to change the state of the raw material and product. For obtaining transition state internal rotation around C-N bond, STQN method and QST3 version were used for this purpose.

4. Results

Three main different configuration processes are possible in this study, nitrogen inversion, pseudo rotation and internal rotation around C-N bond, in this study only internal rotation is seen around C-N bond. As expected, nitrogen inversion energy barrier of the molecule is very low and is not visible with DNMR. If the acyl group (R-CO) is attached to the nitrogen, nitrogen inversion barrier greatly reduces in this purpose. Also similarly, the ring pseudo rotation takes place so fast that the temperature of the study cannot be seen by DNMR .Therefore, calculated rotation barrier only relates to internal rotation around amide bonds which is studied in different sources and is 54.40-83.70 kJ /mol. The spectra obtained and discussed the results of similar calculations for 4-(phenyl) acetyl morpholine compound.

5. Discussion

Here two facts can be verified as mentioned in combinations with aliphatic amide functional group; rotational

Barrier is higher than the compounds with aromatic amide functional group. But different morpholine compounds have lower barrier rotation rather than piperidine derivatives. In this case, these two factors are in

competition with each other. Approximate flatness of amides group is the important key in amide structure; as a result energy barrier increases around amides bond can be obtained as a baseline.

Substitute Effect, with an increase of R group in RCON (R1R2) barrier rotation decreases because of an increase in size of R group repulsion between two rotators around C-N bond increases in ground state and it causes angle of plates from zero. Therefore, mutual property of bond and stability of ground state as well as barrier rotation decreases in this case. On the other hand, if R is alkyl rotational barrier around the CN bond is higher than the case when R is aromatic. Aromatic groups have electro negativity, secondly it can contribute at resonance and mutual property of C-N bond will decrease. Additionally, in other investigation which is done between thiobenzoyl morpholine and thiobenzoyl piperidine. It was observed that the rotational barrier in thiobenzoyl morpholine combinations is lower than rotational barrier in similar thiobenzoyl piperidine. Which attribute to less ability of non-localized Nitrogen pair electron in morpholine compounds rather than piperidine compounds. Investigation of articles data in similar compound just like N-(4 chloro benzoyl) piperidine is investigated. For 4-(phenyl) acetyl morpholine $\Delta G^{\#}(kJ/mol)$ is 16/29, and for N-(4 Chloro benzoyl) piperidine is 14/30[6].

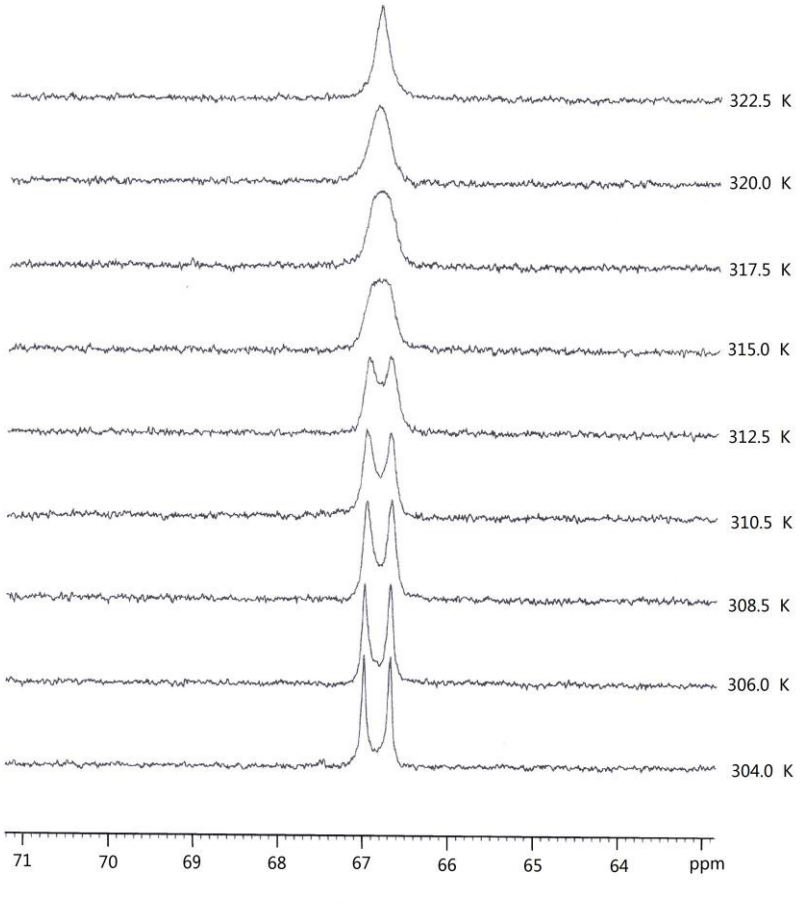

Fig 2. ^{13}CNMR spectrum of this compound , the solvent is toluene at different temperatures.

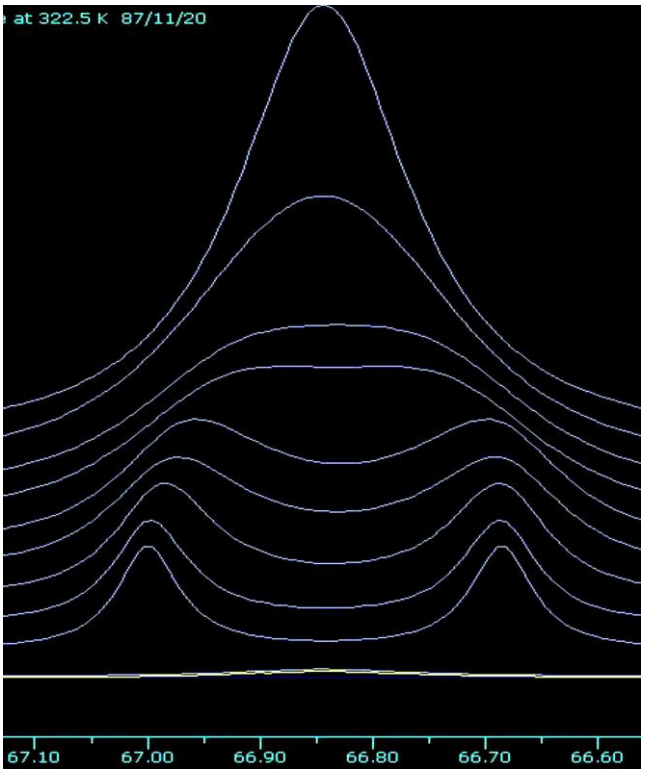

Fig 3. Simulated spectrum for 4-(phenyl) acetyl morpholine

Table 1.Activation parameters from experimental data

$\Delta H^{\#}(kJ/mol)$	$\Delta S^{\#}(J/mol)$	$\Delta G^{\#}(kJ/mol)$	$E_a(kJ/mol)$
4.43	88.32	68.09	97.4

Table 2. Activation parameters from theoretical calculation

$\Delta H^{\#}(kJ/mol)$	$\Delta S^{\#}(J/mol)$	$\Delta G^{\#}(kJ/mol)$	$E_a(kJ/mol)$
67.34	-27.21	75.4	70.2

6. Conclusion

Dynamic NMR spectroscopy was used to study the rotational barrier of morpholines. ^{13}C spectra can provide dependable activation parameters, although with more cost in acquisition time and the requirement of huge concentrations. Theoretical calculations predict B3LYP method and 6-311++G** basis-set are the best model for the calculation of computational achievements.

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References

[1] J. Zabicky, the Chemistry of Amides, Wiley-Interscience, New York, 1970.

[2] G.Solomons, C. Fryhle, Organic Chemistry, John Wiley, New York, 2000.

[3] R. Vargas, J. Garza, D. Dixon, B.P. Hay, J. Phys. Chem. 2001, A105, 774.

[4] N.G. Vassilev, V.S. Dimitrov, J. Mol. Struct. 1999, 484, 39-47.

[5] G.Assaf, G.Cansell, D.Critcher, S.Field, S.Hayes, S.Mathew, A.Pettman, Tetrahedron Letters. 2010, 51, 5048-5051.

[6] M.Tafazzoli, A.Ziyaei-Halimjani, M.Ghiasi, M.Fattahi, M. R. Saidi. J. Mol. Struct. 2008, 886, 24-31.

[7] MEXICO Program, available on Professor A.D. Bain Homepage`s at McMaster University, Hamilton, Canada.

[8] Gaussian 98 (revision A.9). M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scusevia, M.A. Robb, J.R. Cheeseman, V.G. Zakrezwski, J.A. Montgomery, R.E. Stratmann, J.C. Burant, S. Dapprich, J.M. Millam, A.D. Daniels, K.N. Kudin, M.C. Strain, O. Farkas, J.Tomasi, V.Barone, M. Cossi, R. Cammi, B.Mennucci, C.Pomelli, C. Adamo, S.Clairford, J. Ochterski, G.A. Petersson, P.Y. Ayala, Q. Cui, K. Morokuma, D.K Malich, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J.Cioslowski, J.V. Ortiz, B.B. Stefanov, G. Liu, A.Liashenko,P. Piskorz, I. Komaromi, R. Gomperts, R.L. Martin, D.J.Fax, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayahkara, C. V. Ghonzalez, M. Challacombe, P.M.W Gill, B.G. Johnson, W. Chen, M. Wang, J.L. Andres, M. Head-Gordon, E.S Replogleand, J.A.Pople, Gaussian Inc., Pittsburgh PA, 1998