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Dynamic NMR and computational study of 5,5-dimethyl-3,4-di-*p*-tolyl-2-cylopenten-1-one

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ABSTRACT

The restricted rotation of *p*-tolyl moiety in 5,5-dimethyl-3,4-di-*p*-tolyl-2-cyclopenten-1-one was studied by variable temperature NMR spectroscopy at a temperature range of 218–368 K. A free rotation, in NMR time scale, was observed at temperatures higher than 368 K; while, the rotation froze below 248 K. From dynamic NMR analysis, the Arrhenius energy of activation $\Delta G^{\ddagger}$ was calculated as 56.37 kJ mol^{-1}. The experimental results were confirmed by theoretical calculation using the density functional theory method B3LYP with basis sets, 6-31G and 6-31+G.

1. Introduction

Hindered rotation about the C–C bond is an on-going topic in conformational stereochemistry that has attracted the interest of many investigators [1–5]. It is well accepted that C–C single bond rotation is usually fast, because it does not involve any reduction in orbital overlapping. However, the rotational barrier ($\Delta G^{\ddagger}$) increases with structural factors, where bulky substituents interacted with each other [6]. It is important to fully understand how structural and environmental factors control the associated kinetics and thermodynamics. Atropisomeric compounds [2,7,8] and synthetic molecular machines [1,9] are some important results of hindered rotation phenomena. Furthermore, to understand biological mechanisms of bioactive compounds, it is necessary to investigate their minimum energy conformations and their intramolecular flexibilities [10].

Restricted rotation of sterically hindered groups in a large number of molecules has been studied by various spectroscopic, analytical, and computational studies [2,9,11,12]. Dynamic NMR studies have been extensively used to explore the kinetics and thermodynamics of the stereodynamic processes, occurring due to restricted intramolecular rotation [4]. For example, the rotational barriers are often measured by dynamic NMR methods, because at low temperatures, NMR signals for the different rotamers can be observed, and the rotational barrier ($\Delta G^{\ddagger}$) can be easily measured at signal coalescence [2–7,12,13]. In this paper, we report the dynamic ^{1}H NMR and computational study of hindered rotation of an aryl substituent in a cyclopentenone derivative.

2. Experimental

2.1. General

4-Hydroxy-5,5-dimethyl-3,4-di-*p*-tolyl-2-cyclopenten-1-one, **1**, was obtained as described earlier [14]. Other chemicals and solvents were obtained from Merck and used as received. ^{1}H NMR spectra were recorded on a Bruker Avance-300 MHz spectrometer employing tetramethylsilane as an internal reference. IR spectra were recorded with a Perkin-Elmer 843 spectrometer. Mass spectra were recorded on a Shimadzu GC/MS QP1100 EX model.

2.2. Preparation of 2,2-dimethyl-1,5-di-p-tolyl-4-cyclopenten-1,3-diol, **2**

To a solution of 4-hydroxy-5,5-dimethyl-3,4-di-*p*-tolyl-2-cyclopenten-1-one, **1** (1 g, 3.27 mmol) in methanol (30 ml) was added an excess of $NaBH_4$. The mixture was stirred at room

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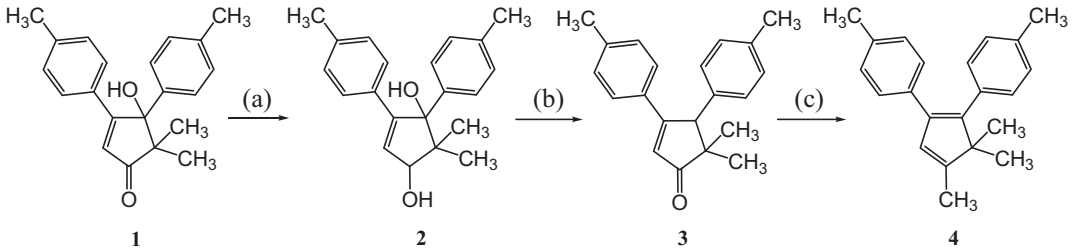
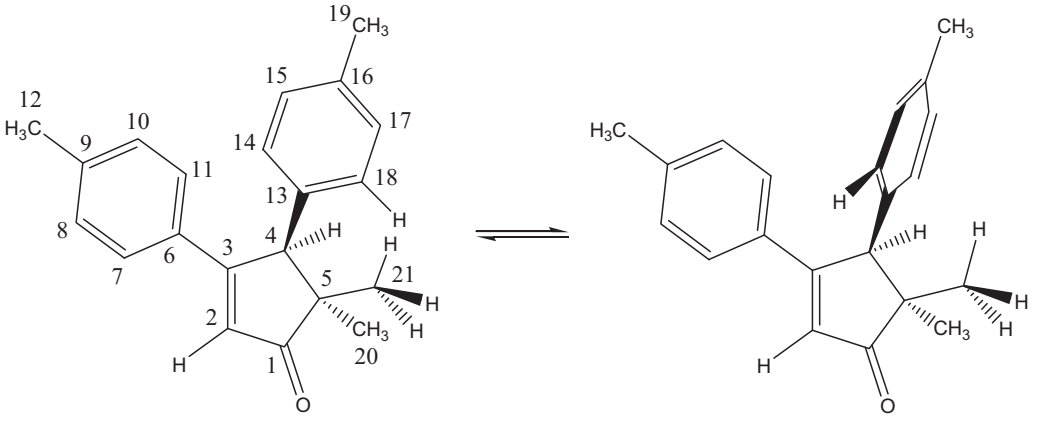


Scheme 1. The chain procedure for synthesis of 1,5,5-trimethyl-3,4-di-*p*-tolyl-1,4-cyclopentadiene **4**. Reagents and conditions: (a) $NaBH_4$/MeOH/RT/3 h; (b) conc. HCl/EtOH/80 °C/3 h; (c) CH_3I/anhydrous diethylether/RT/7 day.



Scheme 2. The chemical structure, atom numbering and conformational equilibrium of **3**.

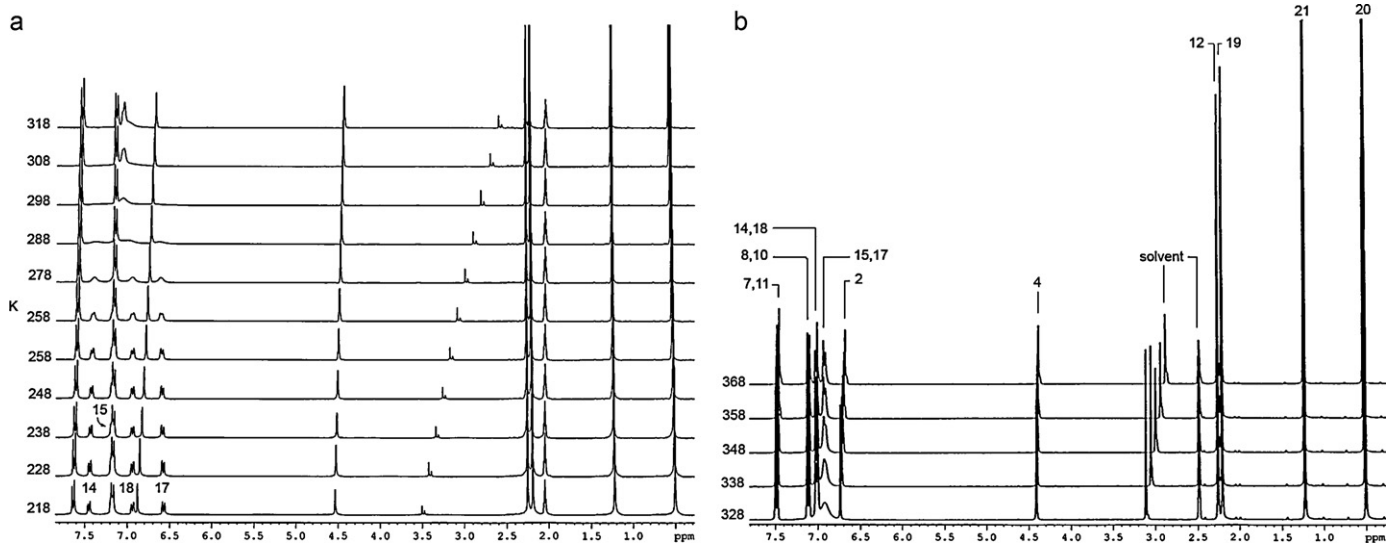


Fig. 1. The variable temperature ^{1}H NMR spectra of **3** (a) from 218 to 318 K in acetone-d_6; (b) from 328 to 368 K in DMSO-d_6.

temperature for 3 h. The solvent was then removed on a rotary evaporator. The organic layer was extracted with diethyl ether (30 ml), washed with water and dried over Na_2SO_4. The solvent evaporation in vacuo gave **2** (0.8 g, 79.5%). Mp 54–56 °C. IR (KBr) (ν max, cm^{-1}): 3462 (br, OH), 1522 (m, C=C). ^{1}H NMR (acetone-d_6): δ 0.51 (3H, s, CH_3), 1.28 (3H, s, CH_3), 2.21 (3H, s, CH_3), 2.25 (3H, s, CH_3), 3.99 (1H, d, J = 5.9 Hz, OH), 4.10 (1H, s, OH), 4.71 (1H, dd, J = 2.3, 5.9 Hz, CH), 6.28 (1H, d, J = 2.3 Hz, CH), δ 6.94 (2H, d, J = 8, C_6H_4), 6.99 (2H, d, J = 8, C_6H_4), 7.23–7.28 (4H, dd, J = 15, 8.2). MS (m/z, %): 308 (M^+, 33), 119 (100), 91 (83), 65 (41), 45 (66).

2.3. Preparation of 5,5-dimethyl-3,4-di-p-tolyl-2-cyclopenten-1-one, **3**

To a stirred solution of **2** (1 g, 3.25 mmol) in ethanol (20 ml) was added conc. HCl (5 ml). The mixture was refluxed for 3 h, then cooled and extracted with diethyl ether (30 ml). The organic layer was washed with water and dried over Na_2SO_4. Solvent evaporation in vacuo gave **3** (0.65 g, 69%). Mp 102–104 °C. IR (KBr) (ν max, cm^{-1}): 1689 (s, C=O), 1601 (m, C=C). ^{1}H NMR (acetone-d_6, 25 °C): δ 0.65 (3H, s, CH_3), 1.33 (3H, s, CH_3), 2.28 (3H, s, CH_3), 2.32 (3H, s,

Table 1
Calculated energies for ground state and transition state structures of **3**.[a,b]

Molecule	E_{elec}		ZPE[c]	E_0 [d]		ΔE_0 (calculated)[e]	$\Delta G^{\ddagger}$ (experimental)
	6-31G	6-31+G(d,p)	6-31G	6-31G	6-31+G(d,p)		
Ground state	−888.508198	−888.784979	0.375040	−888.133158	−888.409939	0.021968 h ≡ 57.68 kJ mol^{-1}	56.37 kJ mol^{-1}
Transition state	−888.485392	−888.763448	0.375477	−888.109915	−888.387971		

[a] All calculations were performed with B_3LYP method.
[b] All energies are in hartree unless otherwise mentioned.
[c] Unscaled.
[d] $E_0 = E_{elec}$ + ZPE.
[e] We used the E_0 values with larger basis set.

CH_3), 4.27 (1H, d, J = 1.1 Hz, CH), δ 6.68 (1H, d, J = 1.1 Hz, CH), 7 (2H, br), 7.11 (2H, d, J = 8.1), 7.43 (2H, d, J = 8.1). MS (m/z, %): 290 (M^+, 85), 115 (100), 91 (57), 42 (42).

2.4. Preparation of 1,5,5-trimethyl-3,4-di-p-tolyl-1,3-cyclopentadiene, **4**

To a solution of **3** (1 g, 3.47 mmol) in anhydrous diethyl ether (100 ml), was added an excess of CH_3MgI/Et_2O. The mixture was stirred at room temperature for 7 days; then poured into cold water (50 ml). The organic layer was separated, washed with water, dried on Na_2SO_4. The solvent was evaporated in vacuo. Chromatography on silica gel plate (hexane, 20 ml) gave **4** (0.85 g, 85.6%), which recrystalized from hexane. Mp 119–121 °C. IR (KBr) (ν max, cm^{-1}): 1578 (w, C=C). ^{1}H NMR (acetone-d_6): δ 1.08 (6H, s, CH_3), 1.94 (3H, d, J = 1.6 Hz, CH_3), 2.22 (3H, s, CH_3), 2.33 (3H, s, CH_3), 6.33 (1H, q, J = 1.6 Hz, CH), 6.95 (2H, d, J = 7.8, C_6H_4) 7.02 (2H, d, J = 8.2, C_6H_4), 7.09 (2H, J = 8.2, C_6H_4), 7.16 (2H, d, J = 7.8, C_6H_4). MS (m/z, %): 288 (M^+, 100), 243 (35), 165 (25), 115 (20), 91 (20).

2.5. Computational methods

The calculations were performed by the DFT method employing the Becke3-Lee-Yang-Par B_3LYP exchange correlation functional in combination with the 6-31G and 6-31+G (d,p) basis sets using the Gaussian 98 program [15]. Analytical frequencies were determined

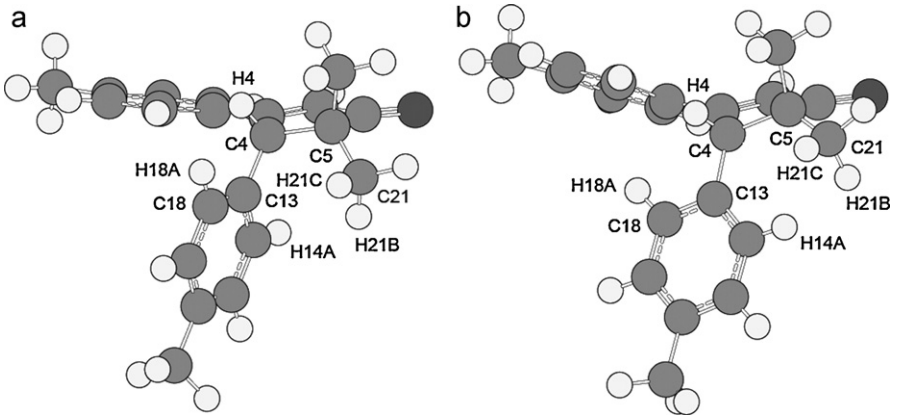


Fig. 2. B3LYP/6-31G optimized structures of **3** (a) ground state; (b) transition state.

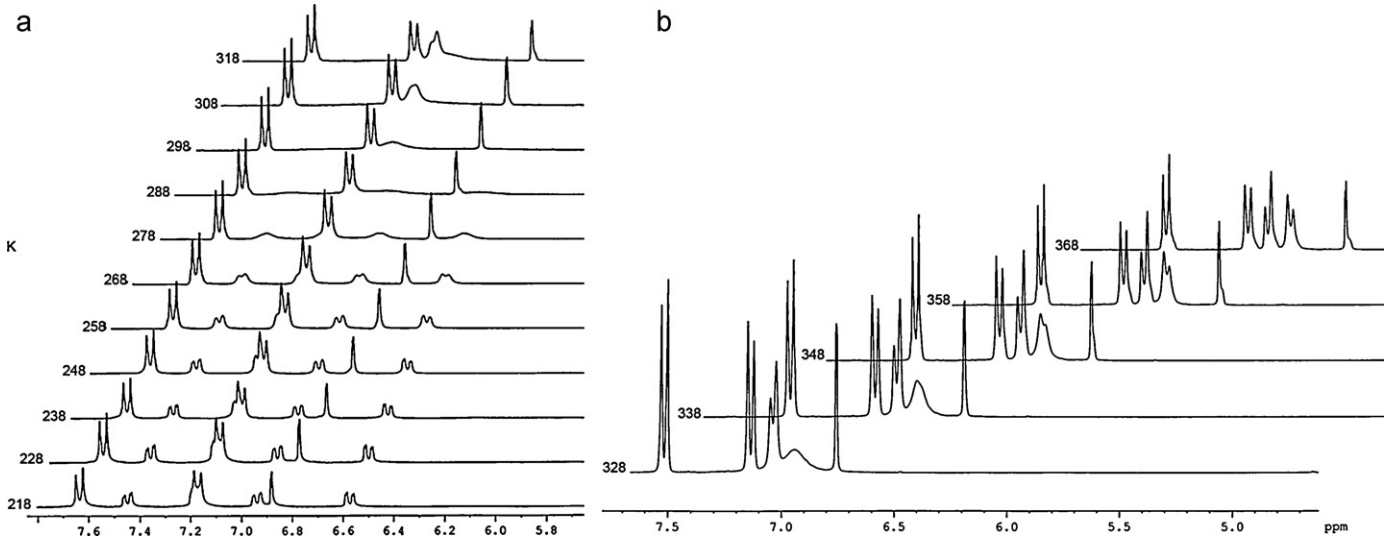


Fig. 3. The aromatic region of ^{1}H NMR spectra of **3** (a) from 218 to 318 K in acetone-d_6; (b) from 328 to 368 K in DMSO-d_6.

at the B_3LYP/6-31G level of theory to confirm the nature of each stationary point and to provide zero-point energies (ZPEs).

3. Results and discussion

Diphenylcyclopentenones were often prepared *via* aldol condensation of benzil with acetone derivatives in alkaline media. This procedure was first introduced by Japp [16–18], and was used for preparation of cyclopentenones [14,19–24]. We have recently extended Japp's procedure to the preparation of diarylcyclopentenones [25], and utilized them as starting materials for the preparation of other synthetic targets. Scheme 1 shows our procedure for the synthesis of 5,5-dimethyl-3,4-di-*p*-tolyl-2-cyclopenten-1-one, **3**, and its conversion to 1,5,5-trimethyl-3,4-di-*p*-tolyl-1,3-cyclopentadiene, **4**. The starting compound, **1**, was prepared by Japp's procedure [26].

During the work, we encountered an unusual feature in the ^{1}H NMR spectrum of **3**. A peak for two aromatic protons was absent in the room temperature spectrum of **3**. There was no doubt in the structure of product, since it was confirmed by a single crystal X-ray diffraction analysis, apart from other spectral and analytical evidences [27]. Furthermore, two related compounds, **2** and **4**, presented normal ^{1}H NMR spectra as expected from proposed structures. Therefore, we performed a dynamic NMR study, followed by a theoretical calculation, to achieve a reasonable understanding of the ^{1}H NMR spectra of **3**.

3.1. Dynamic NMR experiments

Fig. 1 shows the variable temperature ^{1}H NMR spectra of **3**. Due to the limitations imposed by physical properties of solvents (boiling and melting points), the NMR experiments were performed in two different solvents, from 218 to 318 in acetone-d_6 and from 328 to 368 in DMSO-d_6.

The signal assignments are depicted in the spectra, with numbering of protons as indicated in the Scheme 2. The first two signals at high field, 0.5 and 1.22 ppm, are assigned to the geminal methyl groups, 20 and 21. The next two signals, 2.19 and 2.25 ppm, correspond to the methyl substituents of *p*-tolyl moieties, 12 and 19. The signal at 2.05 ppm and the temperature dependent signal at around 3 ppm correspond to acetone-d_5 and HOD impurities, respectively. Two protons of five-membered ring, 4 and 2, present signals at 4.54 and 6.68 ppm. Four aromatic protons of conjugated *p*-tolyl, 7, 8, 10 and 11, present two doublets centered at 7.58 and 7.15 ppm, each integrated for two protons. The aromatic protons of other *p*-tolyl moiety, 14, 15, 17 and 18, exhibit temperature dependent signals; four doublets at 218 K, which are joined to form two doublets at 368 K. There is also a signal overlap below 278 K, between the doublet assigned to protons 8, 10 and that of proton 18.

The dynamic NMR behavior of **3**, arises from the restricted rotation of substituted phenyl ring around C(4)–C(13) bond. The restriction may be best explained by two structures depicted in Fig. 2. The structure a shows an almost planar cyclopentenone ring, which imposed an eclipsed conformation for substituents of C(4) and C(5). This conformation puts a methyl group, C(21), very close to the phenyl ring, C(13)–C(18). The distance between H(18A) of the phenyl ring, and H(21C) of the methyl group, is only 2.98 Å. On the other side of phenyl ring, H(14A) is 2.99 Å apart from H(21B) [27].

In solution, the rotation of phenyl ring around C(4)–C(13) bond, should impose a closer contact and lead to more repulsion between protons. So, the rotation of phenyl ring is restricted by steric influence of its vicinal methyl substituent.

Fig. 3 shows the aromatic region of variable temperature ^{1}H NMR spectra of **3**. At temperatures lower than 248 K, the phenyl ring (C13–C18) is frozen with respect to the NMR time scale; so its protons become non-equivalent because of their different environments. Therefore, the ^{1}H NMR spectrum at 218 K exhibits four distinct doublets centered at 7.45, 7.18, 6.94 and 6.57 ppm. At higher temperatures, these signals become broadened until their splitting become disappeared at 278 K. Under fast exchange, the protons can no longer be distinguished by NMR spectroscopy. So at 288 K, the four signals coalescence to a broad signal. This signal is sharpened at higher temperatures until splits at 368 K to form two distinct doublets, centered at 7.04 and 6.94 ppm. The dynamic NMR behavior of **3** indicates that the phenyl ring gradually overcomes the barrier of rotation at 298 K and higher temperatures. A free rotation, respect to NMR time scale, is achieved at 368 K. The rate constant (k_r), and the free energy of activation ($\Delta G^{\ddagger}$) for rotation of phenyl ring are calculated from the variable temperature ^{1}H NMR data by following literature equations [28]; $k_r = 2.22\Delta\upsilon$, $\Delta G^{\ddagger} = 19.1T_c\,[10.32 + \log(T_c/k_r)] \times 10^{-3}$ kJ mol^{-1}. From the $\Delta\upsilon$ of 153 Hz and the coalescence temperature T_c of 288 K, k_r and, $\Delta G^{\ddagger}$, were calculated to be 339.66 s^{-1} and 56.37 kJ mol^{-1}, respectively.

3.2. Theoretical calculations

In order to verify the interpretation of experimental results, the rotational barrier about C4–C13 single bond was calculated using a computational approach. First, the ground state of **3** was optimized at B_3LYP/6-31G level of theory (**F**ig. 2a). According to frequency calculation it has no imaginary frequency, thus, it is a minimum on the PES.

The H4–C4–C13–C18 dihedral angle value (for simplification we call it "*D*" in the following discussion) is −22.80°. The distances between atoms H18A and H21C and also between H14A and H21B are 3.22 Å and 2.88 Å, respectively (Fig. 2a). Increasing the *D* value leads to the corresponding transition state structure (Fig. 2b) which was then optimized at the same level of theory as the ground state structure. It has one imaginary frequency, thus it is transition structure on the PES. The *D* value for this structure is 70.59°. IRC calculation demonstrated that these two structures are related to each other by rotation about C4–C13 single bond. The distances between atoms H18A and H21C and also between H14A and H21B are 5.36 Å and 1.91 Å, respectively (Fig. 2b).

It should be mentioned that, because of resource limitation, performing frequency calculation at B_3LYP/6-31+G(d,p) level is impossible. This limitation is the reason of applying ZPE values at B_3LYP/6-31G level in our calculations.

Table 1 contains some results of optimizations, frequency and single point energy computations. From this data, the rotational barrier about C4–C13 single bond, ΔE_0, is obtained equal to 57.68 kJ mol^{-1}, which is in good agreement with the $\Delta G^{\ddagger}$ calculated from dynamic NMR data (56.37 kJ mol^{-1}). The supplementary information contains the Cartesian coordinates of optimized geometries of ground state and transition state structures of **3**.

4. Conclusion

The dynamic NMR behavior of **3** results from the eclipsed conformation of C4–C5, which is imposed by the planar structure of the cyclopentenone ring. This conformation restricts the rotation of a *p*-tolyl moiety at room temperature. The energy associated with the barrier of rotation was calculated as 56.37 kJ mol^{-1}, from dynamic NMR data, and 57.68 kJ mol^{-1}, from theoretical calculation. Such a dynamic NMR behavior was not seen in the ^{1}H NMR spectra of **2** or **4**; because, the *p*-tolyl groups in both later compounds are not in eclipsed conformations.

Acknowledgments

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