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Conformational study of a strained tolanophane by dynamic ^{1}H NMR spectroscopy and computational methods

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Abstract The existence of a short C–H$\cdots\pi$ (alkyl–alkyne) interaction in the structure of a strained and relatively rigid tolanophane is expected to hinder the rotation about the C–C sp^3 single bond. Variable-temperature NMR experiments (performed in three solvents, $CDCl_3$, *THF*-d_8, and acetone-d_6) and *ab initio* density functional calculations were carried out to investigate its dynamic nature. An energy barrier of 48.6 kJ/mol is determined at coalescence (210 K) with acetone-d_6 which is in good agreement with calculation result (54 kJ/mol).

Keywords Tolanophane; Strain; Dynamic ^{1}H NMR; *Ab initio* calculations.

Introduction

Diarylacetylenes have generally a flexible nature with facile internal rotation about the alkynyl–aryl single bond because of the negligible interactions between terminal aromatic moieties [1]. The barrier to rotation about the alkynyl–aryl single bond is very low, estimated at less than 4 kJ/mol [1, 2]. The origin of the fascinating properties of diarylacetylenes, such as molecular switching [3], directly attributed to the relative orientation of the planar aromatic moieties. Therefore, the engineering control over the molecular conformation is a significant challenge. Tolanophanes **1**–**5** are excellent templates in achieving a degree of such control [4, 5], and the relative orientation of the aromatic moieties in these cyclic tolans is strongly influenced by the length of methylene chain [6, 7].

Among these cyclic alkynes, the smallest synthesized tolanophane **1** has attracted our attention because of the existence of strain in its structure.

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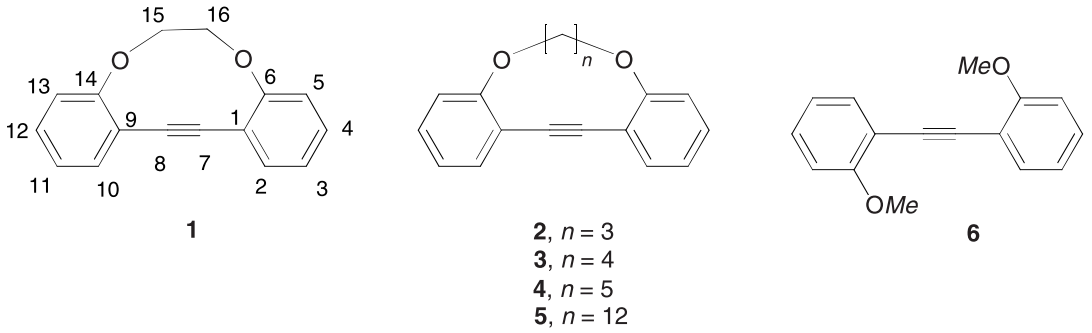
Results and discussion

The used method for the synthesis of tolanophane **1** includes a *Sonogashira* coupling of terminal alkyne, followed by intramolecular *Mitsunobu* reaction in five steps (Fig. 1, route a). From the synthesis standpoint, the use of harsh reaction conditions and a time- and cost-consuming, and tedious experimental procedure are drawbacks of the method [8].

In contrast, we applied the bromination/dehydrobromination of the corresponding stilbenophane as a practical, simple, and efficient strategy (Fig. 1, route b) [9]. The method is significantly superior to the reported method.

A comparison of the NMR spectra of **1**–**5**, as collected in Table 1, reflects the direct effects of methylene chain length on the molecular structures. The sp carbon atoms of **1** ($\delta = 95.4$ ppm) resonate highly at lower field than the ones for larger ring size **5**



Scheme 1

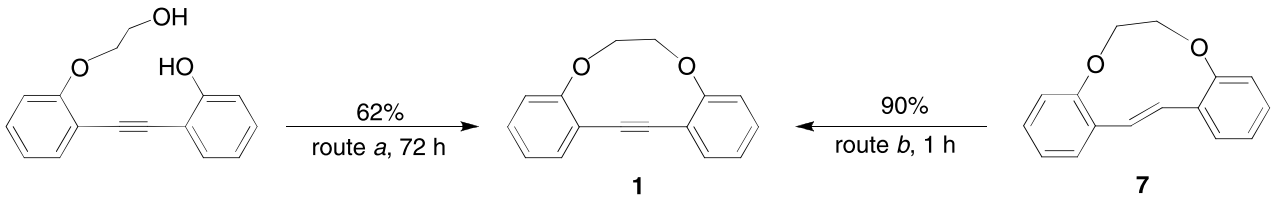


Fig. 1 Synthesis routes for the preparation of **1**

Table 1 Comparison of some selected NMR data of **1–6**

Compound	^{1}H NMR[a] ($\Delta\delta$/ppm)	^{13}C NMR (C-6) δ/ppm	^{13}C NMR (C-7) δ/ppm	Ref.
1	7.09–7.39 (0.30)	162.5	95.4	[8, 9]
2	7.10–7.52 (0.42)	161.1	92.2	[8]
3	6.93–7.43 (0.50)	161.1	91.9	[9]
4	6.93–7.52 (0.59)	160.3	90.1	[10]
5	6.87–7.54 (0.67)	159.0	89.9	[10]
6	6.88–7.59 (0.71)	159.8	89.7	[10]

[a] Aromatic hydrogens

($\delta = 89.9$ ppm) and acyclic **6** ($\delta = 89.7$ ppm), which is consistent with the increased ring strain in **1** as a consequence of its decreased ring size. The effect of ring size on the flexibility of **1–5** is revealed by the comparison of aromatic hydrogens: the ^{1}H NMR resonances for the aromatic hydrogens of **1** appeared from $\delta = 7.09$ to 7.39 ppm ($\Delta\delta = 0.30$ ppm), while it gradually becomes larger toward the biggest ring size **5** ($\Delta\delta = 0.67$ ppm) to confirm the highest rigidity in **1** due to its shorter alkyl chain.

In general, tolanophane **1** has the highest strain and rigidity compared to **2–5**. An *ab initio* calculation on **1** shows a short distance (2.5 Å) between C–H (alkyl) and π-system (alkyne) as a soft acid and a soft base. This C–H$\cdots\pi$ (alkyl–alkyne) interaction is expected to hinder the rotation about the C–C sp^3 bond and consequently give an AA′BB′ peak for diastereotopic geminal protons of methylene in ^{1}H NMR, while they otherwise resonate as a singlet.

Therefore, tolanophane **1** was examined by ^{1}H NMR spectroscopy at 500 MHz over the temperature range of 298–189 K. At ambient temperature, the

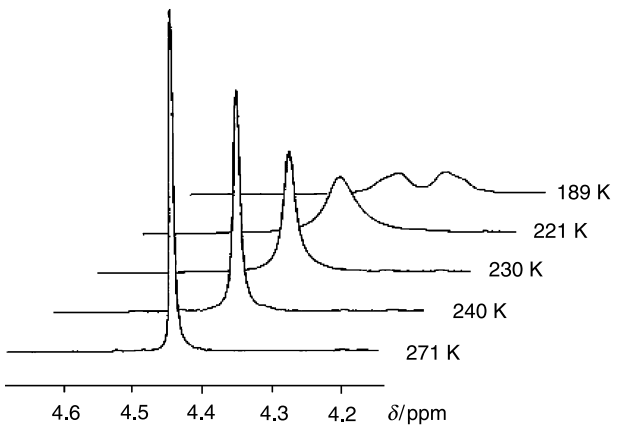


Fig. 2 ^{1}H NMR variable-temperature spectra of **1** in acetone-d$_6$ (aliphatic region: δ/ppm)

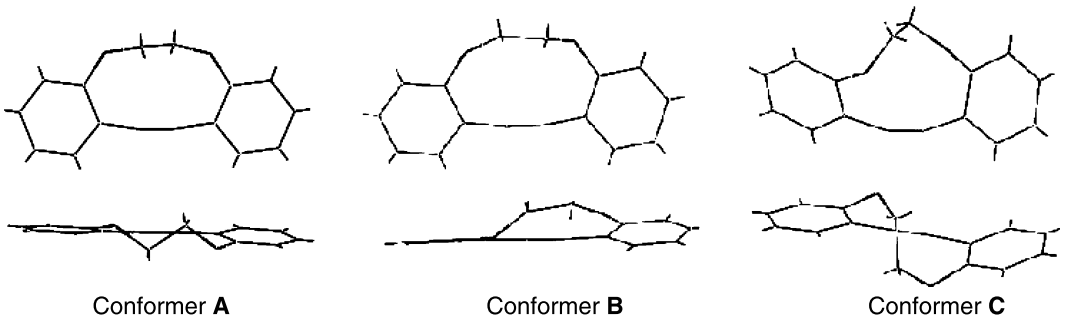


Fig. 3 Computationally obtained geometries for three possible conformations of **1**: chair conformer **A**, boat conformer **B**, and twisted conformer **C**

spectrum of **1** itself in various solvents (a 5% solution) shows similar NMR pattern with no unusual features. ^{1}H NMR spectra of **1** in $CDCl_3$ and *THF*-d_8 shows a sharp singlet for the protons of methylenes which remains as a broad peak when the samples are cooled to 220 and 175 K. In contrast, the ^{1}H NMR spectra of **1** in acetone-d_6 show a significant change, as shown in Fig. 2. Gradual cooling of the solution of **1** in acetone-d_6 broadens the ^{1}H NMR signal of the hydrogens of the CH_2 group ($\delta = 4.47$ ppm) and a coalescence peak was observed at 210 K, which then splitted to a symmetrical doublet at 200 K and remained unchanged till 189 K. Since the aromatic peaks remain sharp in all solvents, the broadening and splitting of the methylene signal cannot be attributed to an increase in viscosity at low temperatures. The coalescence temperature of **1** is 210 K with $\Delta G^{\#} = 48.6$ kJ/mol, $\Delta H^{\#} = 49$ kJ/mol, and $\Delta S^{\#} = -0.5$ eu, using the *Eyring* equation [11]. The observed coupling constants are found to be $^3J = 7.51$ Hz and $^2J = -10.51$ Hz. The value of $\Delta S^{\#}$ indicates that the rotation proceeds fast because the transition state is highly disordered compared to the ground state.

In order to gain a prediction on conformational behavior of **1**, its possible conformers were fully optimized at *B3LYP*/6-311g(d) level with no initial symmetry restrictions by considering the acetone as the solvent at room temperature. A search was directed for transition state while conformer **A** was converted to conformer **B** using the QST2 procedure by considering acetone as solvent. Conformer **C** with half chair configuration and one imaginary vibrational frequency was found as a transition state.

As shown in Table 2, the chair conformation **A** is 21.8 kJ/mol more stable than the boat conformation **B**. This calculation showed that the energy barrier to convert the stable symmetry planar **A** through orthogonal geometry **C** to planar **B** is 54 kJ/mol. The twist angle between the two arene rings is decreased from conformer **C** (~44°) to the conformers **B** and **A** (~16°). Furthermore, the torsinal angle between two oxygenes through the O–C(sp^3)–C(sp^3)–O is increased from conformer **A** (~22°) to conformer **B** (~52°) and then to conformer **C** (~78°) and so, this regularity may also be invoked to justify the observed computational stability trend. On the other hand, the less stablility of **B** compared to **A** may be due to the high deformation of its O–C(sp^3)–C(sp^3) bond angle (150°).

Table 2 Selected data from conformers **A**, **B**, and **C**

Entry	Conformer **A**	Conformer **B**	Conformer **C**
C15C16O/deg	110	150	120
C1C7C8/deg	172	172	160
OC15C16O/deg	22	52	78
OC14C9C8/deg	0.3	0.3	17
C1C7C8C9/deg	15	16	11
C1C6C14C9/deg	16	16	44
(sp^3) C–H···C (sp)/Å	2.48, 3.98	2.45, 3.85	3.60, 4.39
H–C–C–H/deg	33	25	39
Barrier energy/ kJ · mol^{-1}	0.0	21.8	54

Calculated chemical shifts of conformer **A**, employing the GIAO method [12], in the coalescence and lower temperature indicate the doublet peak at 4.81 and 4.62, which should be compared with the experimental results of $\delta = 4.39$ and 4.34 ppm.

The energy barrier of **1** (48.6 kJ/mol) derived from the dynamic NMR method is in good agreement with the calculated value (54 kJ/mol) to prove that interconverting of **A** and **B** conformations, *via* conformer **C**, is possible. However, no trace of conformer **B** was captured from both ^{1}H and ^{13}C NMR spectra even at the lowest temperature. Therefore,

the changing in the appearance of the spectrum is due to the rotation about single bonds between sp^3 carbons of methylene, leading to detection of geminal protons of methylene at $\delta = 4.34$ and 4.39 ppm.

Conclusion

The C–H$\cdots\pi$ (alkyl–alkyne) interaction in strained and rigid tolanophane **1** hinders the rotation about single bonds between sp^3 carbons of the methylene groups. Therefore, variable-temperature NMR experiments were performed in three solvents, $CDCl_3$, *THF*-d_8 and acetone-d_6. For acetone as the solvent, which exerts a better splitting of the methylene protons, a free energy of 49 kJ/mol at coalesence temperature (210 K) was found. In parallel, theoretical study shows that the chair conformer **A** is energetically preferred to the boat conformer **B** by about 21.8 kJ/mol. Considering the solvent effect using the PCM method ($\varepsilon = 20.7$), the energy barrier is 54 kJ/mol which is in good agreement with the experimental result (48.6 kJ/mol). As no trace of other conformers was captured by either ^{1}H or ^{13}C NMR spectra, the splitting of methylene protons at lower temperatures is due to the slow rotation about the C–C sp^3 single bond. In other words, ring inversion interconverts the two enantiomeric forms, and at the same time exchanges the diastereotopic protons mutually.

Experimental

13,14-Didehydro-6,7-dihydrodibenzo[e,l][1,4]dioxecine (***1***)
A solution of 270 mg Br_2 (1.50 mmol) in 5 cm^3 CCl_4 was added dropwise to 119 mg stilbenophane **7** (0.50 mmol) [13] in 15 cm^3 CCl_4. The red color of the solution fades gradually to a pale yellow during about 30 min. More bromine was added until a permanent red color indicates a slight excess of bromine in the flask. The reaction mixture was quenched by a dilute solution of sodium thiosulfate and then washed with water. The organic layer was dried (Na_2SO_4), and evaporated to afford the dibromide quantitatively ($m/z = 396$).

To a cooled mixture of crude dibromide in 15 cm^3 *THF* were added, in portions, 130 mg *tBu*OK (1.2 mmol). After being stirred for 30 min, the mixture was quenched with distilled water. The organic layer was separated, dried (Na_2SO_4), and evaporated. A flash column chromatography on silica gel (ethyl acetate:hexane = 2:8) afforded 105 mg pure **1** (90%). Colorless solid; mp 77°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.45$ (s, 4H), 7.09 (d, $J = 7.6$ Hz, 2H), 7.13 (t, $J = 7.9$ Hz, 2H), 7.28 (dd, $J = 1.5$, 7.9 Hz, 2H), 7.39 (dd, $J = 1.5$, 7.6 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 73.7$ (t), 95.4 (s), 117.0 (d), 122.2 (s), 123.8 (d), 129.8 (d), 129.9 (d), 162.5 (s) ppm; MS: m/z (%) = 236 (M^+, 80).

NMR rate analysis
Rate constants were calculated for exchange spectra by using an iterative nonlinear least squares regression analysis to obtain the best fit of the experimental spectrum. Rate constants were extracted from the ^{1}H NMR exchanging spectra. The complete band shape (CBS) method of analysis first requires the measurement of chemical shifts and natural transverse relaxation times (T_{2nat}) in the absence of exchange to separate spectral changes due to natural temperature dependence from those due to exchange. A linear relationship was assumed and adjusted parameters were estimated for exchanging temperatures. In the calculation of the kinetic activation parameters, the *Eyring* equation was used to obtain $\Delta H^{\#}$ and $\Delta S^{\#}$. The *Gibbs* free energy of activation, $\Delta G_{298}{}^{\#}$, was obtained from $\Delta G^{\#} = \Delta H^{\#} - (298\ \mathrm{K})\ \Delta S^{\#}$ assuming $\Delta H^{\#}$ and $\Delta S^{\#}$ to be independent of temperature.

Computational methods
Ab initio calculations were carried out with the Gaussian program series 1998 [14]. The optimization of the geometry was performed employing a hybrid *Hartree-Fock* density functional scheme, the adiabatic connection method – *Becke* three-parameter with *Lee-Yang-Parr* (*B3LYP*) functional [15] of density functional theory (DFT) [16] with the standard 6-311++G** basis set. Full optimizations were performed without any symmetry constrains. We computed the harmonic vibrational frequencies to confirm that an optimized geometry correctly corresponds to a local minimum that has only real frequencies. The solvent effects on the conformational equilibrium have been investigated with a PCM method at the *B3LYP*/6-311++G** level. Solvation calculations were carried out for acetone ($\varepsilon = 20.7$) with the geometries optimization for this solvent. QST2 were used to search for transtion state. The TS geometry was double checked by using IRC method and FREQ calculations. In this case, one imaginary frequency confirmed the TS observed, after carrying out proper geometry optimizations.

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