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Z and E rotamers of N-formyl-1-bromo-4-hydroxy-3-methoxymorphinan-6-one and their interconversion as studied by ¹H/¹³C NMR spectroscopy and quantum chemical calculations

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Abstract

N-Formyl-1-bromo-4-hydroxy-3-methoxymorphinan-6-one (**2**), an important intermediate in the NIH Opiate Total Synthesis, presumably exists as a mixture of two rotamers (*Z* and *E*) in both CHCl₃ and DMSO at room temperature due to the hindered rotation of its N-C18 bond in the amide moiety. By comparing the experimental ¹H and ¹³C chemical shifts of a single rotamer and the mixture of **2** in CDCl₃ with the calculated chemical shifts of the geometry optimized *Z* and *E* rotamers utilizing density functional theory, the crystalline rotamer of **2** was characterized as having the *E* configuration. The energy barrier between the two rotamers was also determined with the temperature dependence of ¹H and ¹³C NMR coalescence experiments, and then compared with that from the reaction path for the interconversion of the two rotamers calculated at the level of B3LYP/6-31G*. Detailed geometry of the ground state and the transition states of both rotamers are given and discussed.

Keywords

¹H/¹³C NMR; NOE; *Z* and *E* rotamers; morphine intermediate; quantum chemistry; transition state

Introduction

N-Formyl-1-bromo-4-hydroxy-3-methoxymorphinan-6-one (**2**) is an intermediate in the NIH Opiate Total Synthesis.^[1] The NIH route is a practical process for the chemical synthesis of natural morphine and other opium-derived narcotics and antagonists essential to the effective practice of modern medicine. It is also equally applicable to the synthesis of the corresponding unnatural enantiomers^[2] that are of great practical and theoretical interest^[3]

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and which are not available from natural sources. This methodology offers independence from opium, and opium poppy eradication as a worldwide strategy to eliminate illicit heroin production. It is the only methodology for this purpose despite continuing attempts by many chemical research groups to develop such a process over the last 80 years, and major advances in organic chemical synthesis made during that time.

When **2** was synthesized from the secondary amine **1** (see Ref. [4] for the synthesis of **1**) and examined by NMR, it was initially thought that a mixture of compounds had been obtained from the reaction (Scheme 1). The *N*-formyl compound **2** was obtained by reacting **1** with ethyl formate under argon. The reaction mixture was washed with acid, base, and brine. Drying, then removal of solvent, gave what appeared to be a mixture of two products (from thin layer chromatography).

One of the “products” could be isolated as a crystalline solid in about 50% yield. However, when the crystalline solid was solubilized in CHCl₃ and examined by NMR, the same mixture was observed as was initially isolated. Presumably, **2** existed as a mixture of rotamers arising from the hindered rotation of the N-C18 bond in the amide. One rotamer could be isolated as a pure, stable solid, and that solid could equilibrate to the rotamer mixture in solution, as in the case of other amides.^[5] Since the compound was an essential intermediate in the total synthesis of morphine and morphine-like compounds, it is necessary to characterize this rotamer mixture and carefully examine its equilibration. In the present study, the experimental NMR spectra of **2** were compared with the calculated NMR spectra to fully characterize the rotamers of **2**. Chemical shift calculations by quantum chemistry are known to be useful for characterizing the isomers of comparable energetics.^[6–9] Besides the characterization of **2**, the temperature dependence of ¹H and ¹³C NMR experiments were also carried out to determine the energy barrier between the rotamers of **2** in solution, and then this experimental energy barrier was compared with the energy barrier calculated at the level of B3LYP/6-31G*.

Experimental

Thin layer chromatography (TLC) analyses were carried out on Analtech silica gel GHLF 0.25 mm plates with UV and I₂ detection. Melting points were determined on a Büchi B-545 melting-point apparatus and are uncorrected. Elemental analyses (C, H, N) were performed by Atlantic Microlabs, Norcross, GA and were within ±0.3% of the theoretical values. The Atmospheric Pressure Chemical Ionization (APCI) mass spectra were obtained on a Waters LCT Premier time-of-flight (TOF) mass spectrometer. The optical rotation was measured with a Perkin-Elmer 341 Polarimeter.

Spectroscopy—The low temperature ¹H NMR spectrum in CDCl₃ was recorded on a Varian Mercury-300 spectrometer operating at 300 MHz equipped with the Temperature Controller Model L 900. The high-temperature ¹H and ¹³C NMR experiments were run in DMSO-*d*₆ on a Bruker Avance spectrometer operating at 400 MHz (¹H) and 100 MHz (¹³C), equipped with the 5 mm PAQNP probe. ¹H NMR and ¹³C NMR spectra at room temperature were recorded in CDCl₃ with a Bruker DMX500 spectrometer operating at 500 MHz (¹H) and 126 MHz (¹³C), respectively. Chemical shifts are reported in ppm using tetramethylsilane (TMS) as the internal standard, and coupling constants *J* are expressed in Hz.

Crystalline rotamer of **2**

The crystalline rotamer of **2** was obtained as white crystals through crystallization of **2** (1.0 g) from an ethyl acetate solution (430 mg), mp 117–118 °C. [α]_D²⁰ 156.83 (*c* 0.6, CHCl₃). The optical rotation was measured 2 min after the addition of the solvent to a solid sample

(time needed for dissolving the sample and filling the cell). The NMR spectra of the pure solid rotamer were recorded at -15°C .

^1H NMR of rotamer 2—The ^1H NMR spectrum was quickly obtained on rotamer 2 (30 mg/mL) in CDCl_3 at 24.7°C after sample was prepared. H-H COSY and HSQC spectra were also quickly obtained in 15 min to assist with signal assignment.

Dynamic ^1H NMR of rotamer 2—Time associated with amide bond rotation to rotamer *Z* from rotamer *E* were determined by recording ^1H NMR (CDCl_3) at different time, 1 min, 10 min, 30 min, 1 h, 2 h, 4 h, 8 h, and 16 h at 24.7°C until the ratio of formyl proton signals in rotamer *Z* and *E* reaches to 1.2.

^{13}C NMR of rotamer 2—The ^{13}C NMR spectrum was quickly obtained on rotamer 2 (30 mg/mL) in CDCl_3 in 10 min at 24.7°C after sample was prepared.

^1H NMR of mixture of rotamers of 2—The ^1H NMR spectrum was obtained at 24°C after sample rotamer 2 (30 mg/mL) in CDCl_3 was kept at 24.7°C for 32 h. H-H COSY, HSQC, and NOESY spectra were also obtained to assist with signal assignment.

^{13}C NMR of mixture of rotamers of 2—The ^{13}C NMR spectrum was obtained at 24°C after sample rotamer 2 (30 mg/mL) in CDCl_3 was kept at 24.7°C for 32 h.

Quantum chemical calculations

The chemical shifts of ^1H and ^{13}C of the *Z* and *E* rotamers were calculated to assign the experimentally observed ^1H and ^{13}C chemical shifts of the mixture at room temperature to its corresponding rotamers. For this purpose, the isotropic NMR chemical shielding tensors for the two rotamers were calculated utilizing the gauge independent atomic orbital (GIAO) method^[10,11] with B3LYP/6-311+G(2d,p) on the geometry optimized at the level of B3LYP/6-31G* utilizing the polarizable continuum (PCM) model for CHCl_3 .^[12] For comparison with the experimental chemical shifts, these calculated shielding constants were then referenced to those of TMS, which were also calculated by the same procedure. The calculated shielding constants of ^{13}C and ^1H for TMS in the solvent reaction filed of CHCl_3 are 182.7753 and 31.8168, respectively.

Results and Discussion

Characterization of the *Z* and *E* rotamers of 2 based on experimental and theoretical NMR chemical shifts

At room temperature, the doubling of several signals in the ^1H NMR spectra of **2** was observed that could be attributed to a slow rotation of the molecule about the N-CO bond. In particular, the ^1H NMR spectrum of **2** in CDCl_3 solution at room temperature revealed a doubling of the formyl proton (H-18) signal indicating the presence of two rotamers. One of the rotamers of **2**, the more polar rotamer (on thin layer chromatography), could be isolated as a crystalline solid. It was obtained as white crystals through its crystallization from an ethyl acetate solution. Prior to the full equilibration of **2** in CHCl_3 , a single peak for the formyl proton at $\delta 8.21$ at -15°C was observed (Figure S1, Supporting Information), and this peak after equilibration at room temperature split into the two sharp peaks at $\delta 8.21$ and $\delta 8.04$, with the intensity ratio of ~ 1 to 1.2. In $\text{DMSO}-d_6$, these two fully equilibrated peaks appeared at $\delta 8.15$ and $\delta 7.99$. The ^1H NMR showed full equilibration of the two rotamers in CDCl_3 after about 4 h at 25°C , and after 36 min at 35°C .

In the absence of the X-ray structure of **2**, quantum chemical calculations can provide viable structural information about the rotamers of **2**. Accordingly, the rotamers of **2**, *Z* and *E*, were first constructed by modifying the geometry optimized X-ray structure of morphine. Full geometry optimization of both rotamers were then carried out at the level of B3LYP/6-31G* in the gaseous phase. The resulting geometries show that the overall topology of the *Z* and *E* rotamers (Figure 5) are essentially identical except the orientation of the formyl group as exemplified by the respective dihedral angle of O-C18-N17-C9 (ϕ), 1.6° and -179.5° (see Scheme 1 for numbering). To incorporate the solvent effect such as CHCl_3 and DMSO into the calculations, the geometry optimization was also done with the PCM model with the UAKS parameters set.^[12] Both rotamers of **2** are noted by the two fused six-membered rings, piperidine with the formyl group and another with the C6 carbonyl, each with a chair conformation. This *Z* conformation in the gaseous phase is 2.8 kcal/mol more stable than the *Z* with a boat conformation for the ring with the C6 carbonyl. The calculated energy barrier between the two conformations is 1.9 kcal/mol, making them unresolvable at room temperature. However, the C18-N bond in the amide, with the calculated bond distance of 1.37 Å, is strong enough to slow down the interconversion of the rotamers of **2** in solution as evidenced by the appearance a number of doublets of ^1H and ^{13}C NMR peaks in both CDCl_3 and DMSO-*d*6 at room temperature. In terms of the Gibbs free energy at room temperature, the *Z* rotamer is calculated to be 0.2 kcal/mol and 0.1 kcal/mol more stable than the *E* both in the gaseous phase and CHCl_3 respectively, while in DMSO they are iso-energetic. This energy difference (0.1 kcal/mol) between the rotamers in CHCl_3 is compatible with the NMR study which has shown the presence of two rotamers of **2** in CDCl_3 in the ratio of ~ 1:1.2.

The calculated small energy difference of 0.1 kcal/mol between the two rotamers in CHCl_3 , however, does not warrant the assignment of the peaks at δ 8.21 and 8.04 for the formyl proton of **2** to either the *Z* or *E* rotamer. In this instance, the ^1H chemical shifts of **2** in CDCl_3 particularly some of the singlets before and after equilibration can be valuable for the characterization when cross-referenced with the calculated chemical shifts for the geometry-optimized *Z* and *E* rotamers. For example, as seen in Figure 1, the calculated ^1H chemical shifts such as aryl H-2 (*Z*, δ 6.96; *E*, δ 7.00) and OH (*Z*, δ 6.04; *E*, δ 6.08), are in good agreement with those experimental peaks assigned to the aryl H-2 (δ 7.00) and the OH (δ 6.31) appearing as a sharp singlet in CDCl_3 at room temperature prior to equilibration; they were also observed as a singlet after equilibration (Figure 2). The isotropic shielding tensors of the aryl H-2 and OH of the *Z* rotamer are essentially identical to those of the *E* as evidenced by only 0.04 ppm difference in their calculated chemical shifts. By comparison, the calculated chemical shifts for the H-9 of *Z* (δ 5.03) is significantly different from that of *E* (δ 3.91) due to the *syn/anti* effect arising from the magnetic anisotropy of the amide group.^[15,9] As depicted in Figure 5, the H-9s of the *Z* and *E* are *syn* and *anti* to the amide oxygen, respectively; their respective distances between the H-9 and the amide oxygen are 2.29 Å and 3.71 Å. In general, protons *syn* to amide oxygen are better shielded than those *anti*. However, when a proton in the plane of the amide group such as H-9 is conformationally restricted, a reverse shielding was reported^[9,13]. This in turn supports the present calculation that the H-9 of *E anti* to oxygen is better shielded than the *syn* H-9 of *Z*. Figure 1 shows that the calculated chemical shift for the H-9 of *Z* (δ 5.03) is essentially absent in the ^1H NMR spectrum taken after 1 minute whereas a new peak appears at δ 4.90 after 32 hours (Figure 2). Based on this comparison, the experimental peaks at δ 3.97 and 4.90 can be assigned to the H-9s of the *E* and *Z*, respectively. The calculated ^1H NMR peaks also indicate that the formyl proton of *Z* (δ 8.34) is better shielded than that of *E* (δ 8.51), and this finding is consistent with the observed formyl proton of **2** in CDCl_3 at δ 8.21 before equilibration, and then by the appearance of a better shielded peak at δ 8.04 after full equilibration.

The above comparison of both theoretical and experimental chemical shifts of **2** suggests that the single white crystalline rotamer has the *E* configuration, and isomerizes in CDCl₃ to the more stable *Z*. The energetic calculations are also in agreement with the more intense peak appearance for the *Z* formyl proton at δ 8.04 after equilibration as seen in Figure 2. Nonetheless, a nuclear Overhauser effect (NOE) experiment^[14] was carried out to provide the unambiguous characterization of the two rotamers at room temperature. Figure 3 is the NOE spectrum of **2** in CDCl₃, and does show the enhancements of the H-9 of the *E* as well as the H-16e of the *Z*. These positive NOEs are consistent with the optimized structures (Figure 5) depicting that the formyl proton of the *E* and *Z* are 2.09 Å and 2.13 Å away from the respective H-9 and the H-16e. Based on the NOE, HSQC (Figure S2, Supporting Information) and COSY (Figure S3, Supporting Information) experiments together with the calculated ¹H chemical shifts, full proton assignments for the two rotamers of **2** have been made (Table 1). From these assignments, the reverse shielding of the H-16e as seen with the H-9 was also noticed. Namely, the *anti* H-16e (δ 3.37) of *Z* to oxygen is better shielded than the *syn* H-16e (δ 4.28) of *E*. For the axial H-16a, spanning outside the plane of the amide group, the *syn* H-16a (δ 2.41) of *E* is better shielded than the *anti* H-16a (δ 2.91) of *Z*, as expected for unrestrained methyl groups.^[13] The ¹H NMR spectrum taken after 32 hours (Figure 2) depicts the H-16e peak of *Z* at δ 3.37, which is not seen in the spectrum taken after one minute (Figure 1). The time dependent ¹H NMR spectra of **2** (Figure S4, Supporting Information) are provided to illustrate the progression of proton signals of interest. Our assignments of the germinal protons such as H-10qa/H-10qe and H-16a/H-16e agree with those of morphine^[15] in that the axial/quasi-axial protons are better shielded than the equatorial/quasi-equatorial protons. However, unlike morphine, the H-15a of **2** is better shielded than the H-15e.

Table 2 lists the calculated and experimental ¹³C chemical shifts of **2**. The calculated ¹³C chemical shifts for the OCH₃ of *Z* (δ 56.81) and *E* (δ 56.90) only differ by 0.09 ppm due to the distal formyl group; the distance between the carbons of the OCH₃ and the formyl in both rotamers is 9.15 Å. This small difference is consistent with the single experimental peak (δ 56.37) assigned to the OCH₃ of both rotamers (Figure S5, Supporting Information). By contrast, the C-9 *syn* to the amide oxygen in *Z* (δ 49.91) is calculated to be much more strongly shielded than the *anti* C-9 in *E* (δ 58.72); the experimental peaks for the C-9 of the *Z* and *E* are seen at δ 45.24 and 52.65, respectively. The calculations also indicate that the C-16 *syn* to oxygen in *E* (δ 37.59) is better shielded than the C-16 *anti* to oxygen in *Z* (δ 44.31); the respective experimental peaks for the C-16 of the *E* and *Z* are observed at δ 34.34 and 40.53. These *syn/anti* effects arise from the magnetic anisotropy of the amide group,^[9, 16, 17, 18] and are also in agreement with the previous finding that both C-9 and C-16 of *N*-formylmorphinans *syn* to oxygen are better shielded.^[19] Whereas the difference between the calculated and experimental ¹³C chemical shifts of **2** ranges from 2 to 13 ppm, the calculated value for the C-1 bonded to bromine is ~23 ppm larger than the experimental. This rather large difference might arise from the spin-orbit induced heavy atom effect of bromine on C-1, which was not included in our non-relativistic GIAO calculations and thus it would require such corrections to better approximate the shielding tensor for C-1.^[20]

Interconversion energy barriers of the *Z* and *E* rotamers in DMSO probed with dynamic ¹H and ¹³C NMR spectroscopy

The ¹H and ¹³C NMR experiments at high-temperature with the 400 MHz instrument were recorded for **2** in DMSO-*d*₆ solution. NMR line broadenings and coalescence of the two rotamers were observed at higher temperatures. In the ¹H NMR spectrum of **2** the phenolic hydroxyl proton signal appears downfield as a doublet at δ 8.99 due to a strong interaction with the polar solvent, DMSO-*d*₆. As the temperature increased, the two signals from the formyl proton of **2** at δ 7.99 and 8.15 broadened, and coalesced at ~428 K. The ¹H NMR

spectrum at 433 K showed a partial decomposition of the compound under these conditions. Accordingly, for the formyl proton, the rate constants, k_1 (for rotation from *E* to *Z*) and k_{-1} (for *Z* to *E*), were calculated at the coalescence temperature ($T_C = 428$ K) using equations^[21] in Table 3. From these rate constants, free energies of activation for the isomerization^[22,23], ΔG_E (for rotation from *E*) and ΔG_Z (from *Z*), were also calculated. In the ^{13}C NMR spectrum of **2**, two sets of several signals were observed at room temperature. Table 3 lists ΔG_E and ΔG_Z for the carbonyl and formyl carbons as well as for the aromatic and quaternary carbons; these values range from 20 to 21.5 kcal/mol at the coalescence temperature.

Reaction path from quantum chemical study

To calculate the energy barrier between the two rotamers, a reaction path was constructed by varying ϕ of the *Z* rotamer from 1.6° in increments of -10° while relaxing the rest of the structure. Figure 4 depicts a potential energy surface (PES) for the interconversion of the *Z* and *E* rotamers in the gaseous phase. As ϕ of the *Z* changes from 1.6° to -118.5° , the potential energy increases to 23.8 kcal/mol due to the weakening of the amide bond. Further change in ϕ leads to the formation of the *E* (0.26 kcal/mol less stable than the *Z* rotamer) at -178.5° , and then to another energy barrier of 22.4 kcal/mol at 71.5° . A sharp drop in the energetics in the PES after passing the approximate first and second transition state (TS_1 and TS_2) is a consequence of the constraint imposed on the reaction coordinate ϕ . This kind of hysteresis can be avoided with the Replica Path method^[24] that allows the movement of all atoms of a molecule undergoing isomerization or conformational change. Figure 5 shows the structures of both *Z* and *E* rotamers that were further optimized without any constraint as well as the exact TS_1 and TS_2 obtained with the TS search algorithm with the keywords, opt=(ts, calcfc noeigentest). In *vacuo* and in CHCl_3 , the *Z* rotamer is more stable than the *E* by 0.2 kcal/mol and 0.1 kcal/mol at 298.15 K, respectively, while in DMSO both rotamers are iso-energetic. The extra stability of the *Z* rotamer in both *vacuo* and CHCl_3 likely arises from a lesser steric repulsion between the formyl oxygen and the single H of C-9 in the *Z* as compared to between the formyl oxygen and the two Hs of C-16 in the *E* (Figure 5). Moreover, the calculated difference in Gibbs free energy (0.1 kcal/mol) between the two rotamers in CHCl_3 at 298.15 K gives the ratio of *E/Z* to 0.9 that is in full agreement with the experimentally determined ratio of ~ 0.8 at room temperature.

In the gaseous phase, both the TS_1 and TS_2 lie 23.3 and 22.4 kcal/mol, respectively, above the ground state *Z*, and these energy barriers primarily arise from the weakening of the amide bond of the *Z* rotamer as evidenced by the increase in the calculated bond distance from 1.37 Å to 1.44 Å. It was noted that the planar arrangement of atoms N, C-16, C-9, and C-18, existing in the *Z* and *E* rotamers, is not preserved in the TS s (i.e., whereas the deviation from coplanarity is calculated to be 1.1° for the *Z*, it is -29.3° in the TS_1). Each of the two TS s in Figure 5 is also characterized by a single imaginary frequency (-228.8 cm^{-1} for TS_1 and -300.2 cm^{-1} for TS_2) associated with the torsional vibrational motion of the formyl hydrogen and oxygen connecting the two rotamers. In all three cases (Table 4), the TS_2 is more stable than the TS_1 , and this can be attributed to the lone pair of electrons on the nitrogen of the TS_2 positioned *anti* to the formyl oxygen as compared to that of the TS_1 positioned *syn* to the formyl oxygen (Figure 5). As compared to the experimental energy barrier ($\Delta G^\ddagger$) of ~ 21 kcal/mol listed in Table 3, the calculated energy barrier for the conversion of the *Z* to the *E* rotamer via the TS_2 in the gaseous phase and DMSO is about 1 kcal/mol and 2 kcal/mol higher, respectively. Another coalescence temperature experiment for the H-18 on the 500 MHz instrument with calibration of the sample temperature to ± 1 K has given a $\Delta G^\ddagger$ of 22.0 ± 0.2 kcal/mol that is very close to those in Table 3. This points that the discrepancy of ~ 2 kcal/mol between the theory and experiment may arise from the lack

of explicit solvation of **2** by DMSO in the present calculations since the structure of solvation shells is known to affect the solute energetics.^[25]

Conclusions

By comparing the experimental and calculated chemical shifts of ^1H and ^{13}C of the rotamers of **2**, the crystalline rotamer has been identified as having the *E* configuration. In solution, this *E* rotamer undergoes amide bond isomerization to a more stable *Z* isomer. The temperature dependence of ^1H and ^{13}C NMR coalescence experiments has determined the energy barrier of ~21 kcal/mol between the two rotamers. This rather high energy barrier is consistent with the doubling of signals observed in the ^1H and ^{13}C NMR spectra for **2** at room temperature. The present study of both structures and energetics of the rotamers of **2** will provide insight into the control of the thermo-chemical stability of rotamers, as exemplified in the NIH Opiate Total Synthesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
 ^1H NMR spectrum of **2** in CDCl_3 at 24°C after 1 min.

Figure 2.

^1H NMR of mixture of rotamers of **2** in CDCl_3 at 24 °C after 32 h.

Figure 3. NOESY spectrum of **2** in CDCl₃ at 24 °C. Arrows indicate the NOEs between the two protons in the *Z* and *E* isomers.

Figure 4. Plot of the potential energy vs. the dihedral angle O-C18-N17-C9 (ϕ) in **2**. Labels indicate ground and transition states before full geometry optimization.

Figure 5. Geometry optimized *Z* and *E* rotamers and the two transition states (TS_1 and TS_2) in the gaseous phase. The values of the dihedral angle of O-C18-N17-C9 (ϕ) (see Scheme 1 for numbering) and the amide bond distances are given for each state. Broken lines indicate the distances between H-18 and H-16e in the *Z* as well as between H-18 and H-9 in the *E*. Atoms represented by colors as follows: white, hydrogen; green, carbon; blue, nitrogen; red, oxygen; violet, bromine.

Scheme 1.

Preparation of *N*-formyl-1-bromo-4-hydroxy-3-methoxymorphinan-6-one (**2**).

Table 1

Assignment of ^1H NMR chemical shifts for the *Z* and *E* rotamers of 2 from theory [(B3LYP/6-311+G(2d,p)//B3LYP/6-31G*)] in the reaction field of CHCl_3 and experiment (CDCl₃).

Proton	Chemical shift (δ) and coupling constant <i>J</i> (Hz)			
	<i>Z</i>		<i>E</i>	
	Theory	Experimental [<i>J</i> (Hz)]	Theory	Experimental [<i>J</i> (Hz)]
H-2	6.96	7.00 (s)	7.00	7.00 (s)
H-5a	2.23	2.26 (<i>d</i> , 13.5)	2.26	2.26 (<i>d</i> , 14.0)
H-5e	4.45	4.26 (<i>dd</i> , 13.5, 1.5)	4.43	4.27 (<i>dd</i> , 14.0, 4.0)
H-7a	2.50	2.46 (<i>m</i>)	2.47	2.44 (<i>m</i>)
H-7e	2.16	2.31 (<i>m</i>)	2.21	2.30 (<i>m</i>)
H-8a	1.51	1.60 (<i>m</i>)	1.54	1.63 (<i>m</i>)
H-8e	1.94	1.97 (<i>m</i>)	1.90	1.96 (<i>m</i>)
H-9	5.03	4.90 (<i>m</i>)	3.91	3.97 (<i>m</i>)
H-10qa	2.50	2.64 (<i>d</i> , 18.5)	2.66	2.69 (<i>d</i> , 18.5)
H-10qe	3.06	3.03 (<i>dd</i> , 18.5, 6.5)	3.10	3.07 (<i>dd</i> , 18.5, 6.5)
H-14	2.03	2.07 (<i>m</i>)	2.13	2.12 (<i>m</i>)
H-15a	1.72	1.63 (<i>m</i>)	1.69	1.60 (<i>m</i>)
H-15e	2.16	2.05 (<i>m</i>)	2.07	2.05 (<i>m</i>)
H-16a	2.91	2.91 (<i>td</i> , 13.5, 3.5)	2.29	2.41 (<i>m</i>)
H-16e	3.33	3.37 (<i>dd</i> , 13.5, 4.5)	4.41	4.28 (<i>dd</i> , 13.5, 2.0)
H-18	8.34	8.04 (s)	8.51	8.21 (s)
O-H	6.04	6.31 (s)	6.08	6.31 (s)
OCH ₃	3.86 ^a	3.84 (s)	3.87 ^a	3.85 (s)

Numbering of protons is shown in Scheme 1. [a = axial, e = equatorial, qa = quasi-axial, and qe = quasi-equatorial].

^a Average value of three protons.

Table 2

Assignment of ^{13}C NMR chemical shifts for the *Z* and *E* rotamers of **2** from theory [(B3LYP/6-311+G(2d,p)//B3LYP/6-31G*) in the reaction field of CHCl_3] and experiment (CDCl_3).

Carbon	Chemical shift (δ)			
	<i>Z</i>		<i>E</i>	
	Theory	Experimental	Theory	Experimental
C-1	136.09	113.72	136.30	113.56
C-2	115.83	113.85	116.15	113.85
C-3	152.59	144.50	152.71	144.52
C-4	153.09	146.01	152.95	146.11
C-5	53.44	49.88	53.07	49.85
C-6	222.26	209.68	222.09	209.44
C-7	45.85	40.78	46.22	40.68
C-8	32.04	26.55	32.44	26.90
C-9	49.91	45.24	58.72	52.65
C-10	37.18	33.35	38.73	34.71
C-11	136.66	123.38	135.90	123.40
C-12	131.13	127.68	130.98	127.06
C-13	52.04	43.21	52.04	43.33
C-14	49.16	43.40	50.56	44.58
C-15	43.09	38.38	41.87	37.19
C-16	44.31	40.53	37.59	34.34
C-18	165.74	160.96	165.90	160.90
OCH3	56.81	56.37	56.90	56.37

Numbering of carbons is shown in Scheme 1.

Table 3
Experimental free energy of activation ($\Delta G^\ddagger$) for the isomerization of compound **2** in DMSO-*d*₆

	Δ (ppm)		$ \Delta \nu $ (Hz)	T_c (K)	k_1	k_{-1}	$\Delta G^\ddagger_E$	$\Delta G^\ddagger_Z$
	Z	E						
H-18	7.99	8.15	48.78	428	108	90	21.4	21.5
C-6	209.27	209.22	15.27	398	34	28	20.7	20.9
C-18	160.68	160.66	5.76	393	13	11	21.2	21.4
C-3	145.21	145.23	4.95	368	11	9	20.0	20.1
C-13	42.71	42.78	21.84	403	49	40	20.7	20.9

$\Delta \nu$ = frequency difference between Z and E rotamers at room temperature; T_c = coalescence temperature; $k_1 = (\pi/2) |\Delta \nu|$; $k_{-1} = (\pi/K_{eq} 2) |\Delta \nu|$; $K_{eq} = 1.2$; $\Delta G^\ddagger = 4.57 TC[(10.32 + \log(TC/k_{ex}))]$; $k_{ex} = k_1$ or k_{-1} ; k_1/k_{-1} in s^{-1} ; $\Delta G^\ddagger$ in kcal/mol.

Table 4

Relative Gibbs free energy (kcal/mol) of *Z* and *E* rotamers of **2** calculated at the B3LYP/6-31G* level in both the gaseous phase and the reaction field of CHCl₃ and DMSO at 298.15 K

	Gaseous phase	CHCl ₃	DMSO
<i>Z</i>	0	0	0
TS ₁	23.3	23.7	23.8
TS ₂	22.4	23.2	23.5
<i>E</i>	0.2	0.1	0