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Thermodynamic Evaluation of Aromatic CH/ π Interactions and Rotational Entropy in a Molecular Rotor

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Supporting Information Placeholder

ABSTRACT: A molecular rotor built with a stator formed by two rigid 9 β -mestranol units having a 90° bent angle linked to a central phenylene rotator has an ideal structure to examine aromatic CH/ π interactions. Energies and populations of the multiple solution conformations from quantum mechanical calculations and molecular dynamics simulations were combined with variable temperature (VT) ¹H NMR data to establish the enthalpy of this interaction and the entropy associated with rotation about a single bond. Rotational dynamics in the solid state were determined via VT CP-MAS ¹³C NMR.

The dynamics of isolated molecular rotors depend on the nature of their potential energy, which is a function of the interactions between the rotator and the stator. While the number of orientations accessible to the rotator is related to the number of energy minima per period, the average time between sites depends on the height of the barriers that connect them and the temperature.¹ While exploring steroids as components of molecular rotors,² we recognized that the bent structure of 9 β -mestranol **5**³ with a *cis*-B/C ring junction and a nearly 90° bent angle in molecular rotor **1** (Figure 1) can be used to shield a central phenylene with a rotational potential determined by weak CH/ π interactions.⁴ An interesting feature of **1** is that the rotational dynamics of the central phenylene should be determined by a relatively shallow CH/ π minimum in an otherwise flat potential, as suggested in Figure 1. Having confirmed that the expected CH/ π interaction geometry exists in the crystalline state, and knowing that it can be easily detected in solution by the anisotropic shielding characteristic in the ¹H NMR, we set out to investigate the equilibrium of **1** in solution and its rotational dynamics in the crystalline state. One can expect that a system with a low energy minimum in an otherwise flat potential in solution should display an equilibrium

determined by an interplay between enthalpic factors favoring the CH/ π interaction (enthalpically favored region) and entropic factors related to the large number of conformations available to the CH/ π unbound rotational state (entropically favored region).

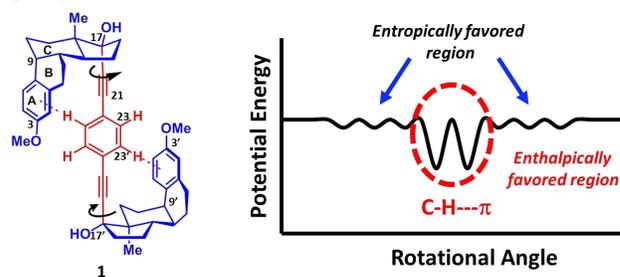
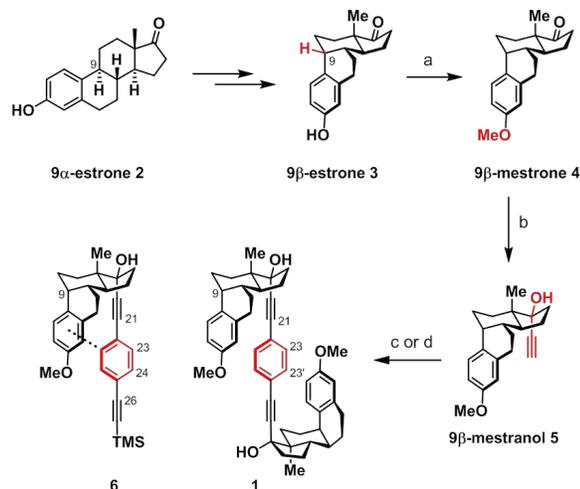


Figure 1. Structure of 1,4-bis(9 β -mestranol)phenylene rotor **1** and a schematic energy diagram showing the stabilization of CH/ π interactions and a region where the energy is approximately constant.

We prepared the double 9 β -mestranol rotor **1** and single 9 β -mestranol rotor **6** by a double Sonogashira cross coupling reaction of 9 β -mestranol **5** with 1,4-diiodobenzene as illustrated in Scheme 1. A detailed description of the synthesis, which begins with the preparation of 9 β -estrone **3** via the epimerization at C9 of 9 α -estrone **2** by a literature procedure,³ is described and analyzed in detail in the SI section. The ¹H NMR of **1** displayed signals corresponding to the steroidal moiety and a broad signal at 2.98 ppm characteristic of the 9 β -steroid series³ that is assigned to H9 (for key numbering see Figure 1). A sharp singlet at 6.53 ppm was assigned to the aromatic protons of the central phenylene (H23). Comparing the chemical shift of H23 in the bent 9 β -mestranol rotor **1** ($\delta_{\text{H23}} = 6.53$ ppm) (Figure 1) to that of a 9 α -mestranol rotor^{2b} reported previously ($\delta_{\text{H23}} = 7.39$ ppm), there is a considerable upfield shift ($\Delta\delta = 0.85$ ppm) that can be rationalized by the

strong shielding effect of the steroid aromatic A-ring that is in close proximity to the phenylene rotator. Notably, the rotator signals in the case of **6** are split into two sets. One set is affected by the shielding of the steroid A ring and occurs at ca. 6.65 ppm and the other is outside the range for this effect and has a normal chemical shift of 7.21 ppm.

Scheme 1



Reagents and conditions: a) Me_2SO_4 , KOH, H_2O , THF, 99%; b) ethynylmagnesium bromide, THF, 0 °C – r.t., 83%; c) 1,4-diodobenzene, $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, CuI, Et_3N , THF, 65 °C, 54%; d) i. 1,4-diodobenzene, $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, CuI, Et_3N , THF, 65 °C, ii. TMS-CCH, 50% two steps.

X-Ray diffraction quality single crystals of **1** were obtained by slow evaporation of a CH_2Cl_2 -hexanes-EtOAc solution. The molecular structure of **1** (Figure 2) shows the bent steroids shielding two sides of the rotator in what can be described as an *anti*-relation with a torsional angle $\text{C}3\text{-C}17\text{-C}17'\text{-C}3' = 170^\circ$. The 1,4-bis(ethynylphenylene) moiety is almost linear with an angle $\text{C}17\text{-Ph}_{\text{centroid}}\text{-C}17' = 173^\circ$. As illustrated in Figures 1 and 2, one hydrogen atom on each side of the phenylene rotator points towards the steroid A-ring while the other points towards the MeO-group. The CH/π interactions can be described by the distances $\text{H}23\text{-Ph}(\text{A})_{\text{centroid}} = 2.86 \text{ \AA}$, $\text{H}23'\text{-Ph}(\text{A})'_{\text{centroid}} = 3.20 \text{ \AA}$, with the first very close to the theoretical 2.91 \AA ,^{4a} and by angles between C-H bond vectors and the rings centroids of $\text{C}23\text{-H}23\text{-Ph}(\text{A})_{\text{centroid}} = 153^\circ$ and of $\text{C}23'\text{-H}23'\text{-Ph}(\text{A})'_{\text{centroid}} = 148^\circ$. The angles between the planes of the central phenylene and those of the two A rings have values of 73° and 88° , with the last one being close to the ideal 90° for an aromatic edge-to-face interaction.⁴

Variable temperature ^1H NMR experiments with molecular rotor **1** in CD_2Cl_2 confirmed structural changes that affect the chemical shift of the rotator C-H group. A systematic shift of this signal is observed

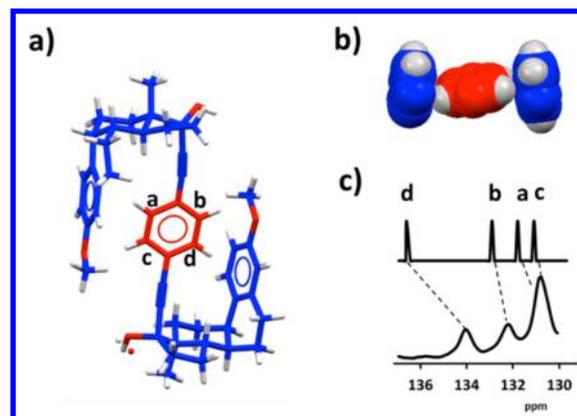


Figure 2. a) X-Ray molecular structure of rotor **1**, b) space filling model of a projection along the phenylene 1,4-axis (red), flanked by the two steroid A rings and c) calculated (top) and experimental (bottom) ^{13}C NMR chemical shifts of phenylene carbons **a-d** in the crystal of rotor **1**. For full CP-MAS ^{13}C NMR spectra, VT data, line shape analysis and Arrhenius plot see Figures S19-S21.

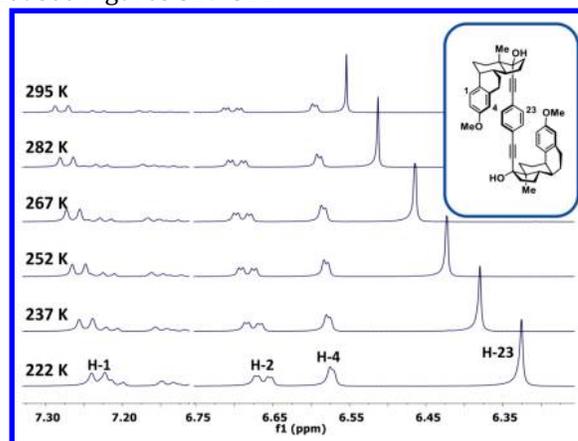


Figure 3. VT- ^1H NMR of double 9β -mestranol rotor **1** in CD_2Cl_2 at 500 MHz showing the temperature dependence of the H23 signal.

from 6.55 ppm at 295 K to 6.32 at 222 K (where the full spectrum broadened), while the rest of the spectra remained basically unchanged (Figure 3). A singlet that integrates for all four aromatic hydrogens is indicative of a temperature-dependent process that occurs in the fast exchange regime, as expected for structures with and without the CH/π interactions. Analogous measurements with the single 9β -mestranol **6** between 296-207 K in CD_2Cl_2 also resulted in the gradual upfield shift of the H23 aromatic signal, while no changes were observed in the signal at 7.21 ppm, which is outside of the shielding effects of the steroid A ring (Figure S18). Considering that the observed chemical shift of H23 is a weighted average of all conformers at equilibrium, we developed a simplified model to calculate the energetics of the CH/π interaction that assumes a fast equilibration

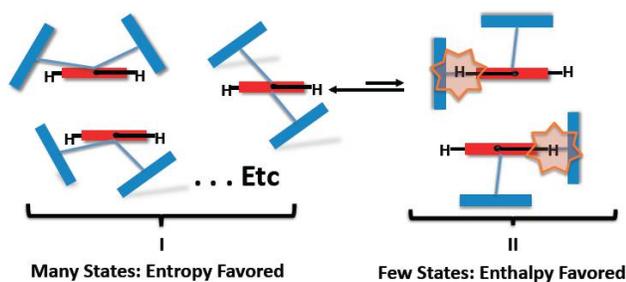


Figure 4. Schematic representation of the conformational equilibrium of rotor **1** viewed down the long molecular axis. The flanking blue bars represent a cross section of the steroids A-rings and the red bars the central phenylene rotator. The CH/ π interaction is highlighted on the enthalpically favored states.

between two sets of states. States I represent conformations where the CH/ π interaction is absent and states II depicts conformations where the interaction is present (Figure 4). The observed chemical shifts (δ_{obs}) are given by the weighted average of the chemical shift of the main conformers as follows,

$$\delta_{\text{obs}} = \chi_I \delta_I + \chi_{II} \delta_{II}$$

where the χ_i are the populations of conformers I and II, which can be used to determine the equilibrium constant ($K_{\text{eq}} = \chi_{II}/\chi_I$), free energy ($\Delta G = -RT \ln K_{\text{eq}}$), enthalpy (ΔH), and entropy (ΔS) by analysis of a Van't Hoff plot.

MD simulations in explicit solvent revealed multiple stacked and non-stacked conformations coexisting at 298 K; non-symmetric conformations different to that observed in the solid state appeared to be dominant (see Supplementary Information). In order to estimate the relative populations of conformers I and II, one needs to know their corresponding chemical shifts. The value for H23 in the CH/ π unbound states I in rotor **1** was considered (and subsequently computationally supported) to be equal to that of the non-interacting hydrogens in **6** ($\delta_{\text{H24}} = 7.21$ ppm). With regard to the chemical shift of the same proton in the CH/ π bound state II, we undertook a complete conformational analysis of **1**. Calculations at the SCS-MP2/6-311+G(2d,p) level of theory (see SI for benchmarking results of up to 29 methods) with a polarizable continuum solvent model indicate that rotor **1** preferentially exists in two lowest-free-energy conformations with edge-to-face interactions, **1- β -IV** and **1- β -IV'**, (Figures 5 and S24) that lack the apparent symmetry observed in the crystal. The two steroids have a tendency to approach each other so that only one C-H group can experience the CH/ π interaction in solution at any given time. Calibrated chemical shifts were obtained for the major conformers using the GIAO⁵ method (Table S6) and the calculated chemical shifts for H23 were used to de-

termine the weighted average value representative of conformer II, $\delta_{\text{H23}} = 6.1$ ppm. Conformational analysis on the single 9 β -mestranol rotor **6** at the same level of theory revealed one major conformer, which provided the same calculated chemical shift for H23 as that in compound **1**, and an excellent agreement for the proton without the CH/ π interaction ($\delta_{\text{H24}} = 7.24$ ppm). We were able to validate the computational result by comparing the calculated and experimental ¹³C chemical shifts of the central rotor using the crystal structure as the input for the calculation and comparing those with the CP-MAS ¹³C NMR spectrum of a micro crystalline sample (Figure 2c). Variable temperature CP-MAS ¹³C NMR confirmed the relative chemical shifts by the site exchange line shape changes that occur when the phenylene starts to rotate (Figure 2c) with a barrier of 14.1 kcal/mol (Figures S20 and S21), which was

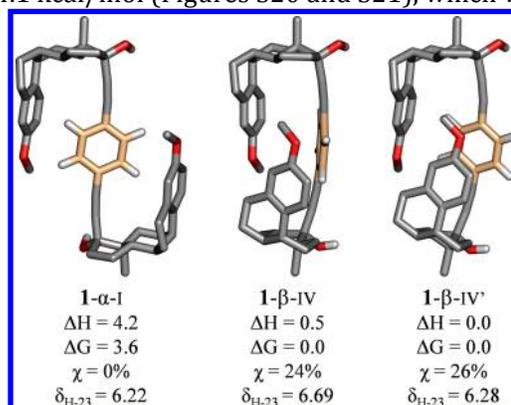


Figure 5. Selected QM calculated conformations **1- α -1** (analogous to the crystal structure), **1- β -IV** and **1- β -IV'** for **1**. Relative enthalpies (ΔH) and free energies (ΔG) in kcal/mol are at the SCS-MP2/6-311+G(2d,p)// ω -B97X-D/6-31G(d) level. Conformer Boltzmann populations (χ) were obtained at 298 K. The calculated chemical shifts for H-23 (average of four protons) are given in ppm.

further supported by QM calculations (Figure S25). The excellent agreement between experimental and calculated ¹³C signals provides strong support of the predicted ¹H shielding. Furthermore, using the Johnson-Bovey⁶ ring current model that takes into account the geometry of the interaction, we arrive at the same result. Thus, with the δ_I and δ_{II} values at hand we calculated the relative populations χ_I and χ_{II} and the corresponding equilibrium constants at each of the temperatures explored for compounds **1** and **6**. Van't Hoff plots ($\ln K$ vs $1000/T$, Figures S22 and S23) of the corresponding equilibrium constants provided us with the values of ΔH , ΔS and ΔG for the corresponding conformational equilibria. From the data shown in Table 1 we note that the free energy (ΔG) at 298 K slightly favors the CH/ π bound state II. As expected from statistical entropy considerations,

the entropy term for the double 9 β -mestranol rotor **1** is larger than that for the single steroid structure in **6**, since the number of conformational states that arise by rotation of the phenylene ring and the steroids in **1** is greater than that in **6**. The fact that the entropy factor for both compounds is within 3-5 cal mol⁻¹ K⁻¹ is indicative of the entropy cost associated with freezing rotations about a single bond, as suggested by Jencks.⁷ It is reassuring that the enthalpy term favors state II (**1**- β -IV' in Figure 5 being a representative structure) at the lowest temperatures when the TAS term is minimal, in agreement with the attractive nature of the edge-to-face-interaction. Correspondingly, the rotationally CH/ π unbound state I, although higher in enthalpy, is favored at higher temperatures because it can occupy more rotational states. A comparison of thermodynamic parameters of compounds **1** and **6** shows that the energetics of the edge-to-face interaction are not a factor of two, in agreement with the fact that having the two simultaneous interactions is unlikely.

Table 1. Enthalpy and entropy values for the conformational equilibrium of compounds **1 and **6** derived from variable temperature ¹H NMR.**

Rotor	ΔH^a	ΔS^b	$\Delta G^{a,c}$
1	-1.74	-5.12	-0.21
6	-1.01	-3.29	-0.03

Units: ^akcal mol⁻¹; ^bcal mol⁻¹ K⁻¹, ^cCalculated at 298 K.

The free energy values for the edge-to-face interaction reported here and in the literature by Wilcox ($\Delta G = -0.24$ kcal mol⁻¹),⁸ Jennings ($\Delta G = -0.05$ to -0.67 kcal mol⁻¹)⁹ and Hunter¹⁰ ($\Delta G = -0.33$ kcal mol⁻¹), are small and slightly different. It is noteworthy that there are remarkable similarities between our measured enthalpies ($\Delta H = -1.0$ to -1.7 kcal mol⁻¹) and the experimental enthalpy of the benzene dimer reported by Krause et al.¹¹ ($\Delta H = -1.6 \pm 0.2$ kcal mol⁻¹), Jennings^{4a,9} ($\Delta H = -1.2$ to -1.5 kcal mol⁻¹) and Furuta¹² ($\Delta H = -1.3$ kcal mol⁻¹). We interpret an entropy change in the range of -3.3 to -5.1 cal mol⁻¹ K⁻¹ as reflecting the difference between a small number of CH/ π bound states and a larger number of unbound rotational states, as suggested in Figure 1.

Supporting Information. Syntheses and characterization of new compounds and solid state CP-MAS ¹³C analysis. Computational procedures, Cartesian coordinates, electronic energies, entropies, enthalpies, Gibbs free energies, and lowest frequencies of the calculated structures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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