Synthesis and solid state characterization of molecular rotors with steroidal stators: ethisterone and norethisterone†

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Received 4th March 2010, Accepted 20th April 2010
First published as an Advance Article on the web 12th May 2010
DOI: 10.1039/c003778h

In this article we describe the synthesis and dynamic behavior of two new molecular rotors with 1,4-diethynylphenylene rotators axially linked to two conformationally rigid steroidal norethisterone acetate or ethisterone frames. The resulting 1,4-bis(19-nor-17α-ethynyltestosterone-17β-acetate)benzene (**1**) and 1,4-bis(17α-ethynyltestosterone)benzene (**2**) were fully characterized in solution and in the solid state, and the rotational dynamics of the central phenylene were explored with the help of ^{13}C NMR with cross polarization and magic angle spinning (CPMAS), and with quadrupolar echo variable temperature (VT) ^{2}H NMR in the case of **1**. Splitting of signals from the aromatic ring on the ^{13}C CPMAS NMR and a broad quadrupolar spin echo ^{2}H spectrum of polycrystalline samples indicated that the rotation of the central aromatic ring in these compounds was limited at ambient temperature in the solid state. Variable temperature ^{2}H NMR experiments at 350 K in the case of **1**-d_4 suggested a 2-fold rotational exchange with upper frequency limit of *ca.* 10 kHz. Single crystal X-ray analysis of this compound revealed that a crowded environment around the prospective phenylene rotator is responsible of the restricted rotation in the solid state.

Introduction

The development of organic solids with addressable physical properties for smart materials and artificial molecular machines has become a field of intense research during the past few years.[1] Our group has been particularly interested in the design and characterization of compounds that emulate the structure and dynamic properties of macroscopic gyroscopes,[2] which may be useful for applications that take advantage of individual and collective rotary motions in the solid state.

One of the short-term goals of our own investigations is to explore the structural features and supramolecular architectures that facilitate fast motion and reorientation in the solid state, and to implement the analytical tools that will aid the study of such phenomena. The most basic design explored to date consists of two bulky triarylmethane or triptycyl groups linked to a central 1,4-diethynylphenylene (Fig. 1a). The two bulky groups constitute a shielding stator that allows for Brownian rotation of the central phenylene rotator along the periodic potential of its 1,4-axis.[3,4]

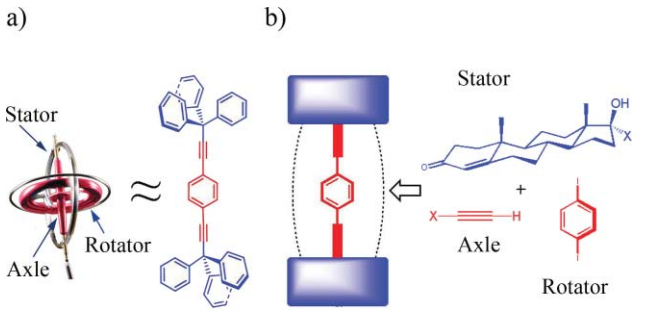

Fig. 1 (a) A macroscopic gyroscope with its rotator, axle and stator indicated, along with a schematic representation of a molecular analog. (b) A 1,4-phenylene group (in red) acting as a rotator linked by two alkyne linkages to bulky steroidal groups (in blue) acting as the stator.

While crystals of molecular gyroscopes built with unsubstituted trityl groups displayed rotation of the central phenylene with an exchange frequency of *ca.* 6 kHz at 300 K,[5] the attachment of shielding *tert*-butyl groups on the stator sped the process up to >100 MHz.[6] Similarly, structures based on triptycene stators ranged from static, in a structure with no substituents, to rotational frequencies approaching the gigahertz regime in crystals of a structure with twelve shielding methyl groups on the periphery of the stator.[7] It has been shown that structural modifications with rotary dipolar units[8] may have applications as dielectric materials,[9] and it is expected that homochiral structures will provide opportunities to take advantage of chiroptical signals. We envision electrooptic materials where changes in the orientation of the central rotator in response to external fields will affect the dichroism, birefringence and intrinsic optical activity of the sample.[10] Homochirality will help assure noncentrosymmetric crystal structures that may be used for second order nonlinear

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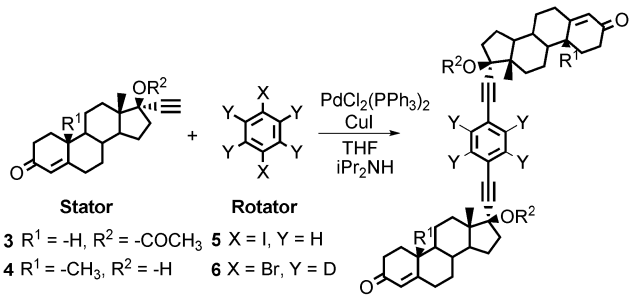
† Electronic supplementary information (ESI) available: Spectroscopic data ^{1}H, ^{13}C and 2D solution NMR, HRMS of compounds **1**, **1**-d_2 and **2**; solid state ^{13}C CPMAS NQS of compounds **1** and **2**; X-ray diffraction data for compound **1** (table of parameters and CIF), spectroscopic data of norethisterone acetate and ethisterone. CCDC reference number 768383. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c003778h

effects that may be further modulated by changing the orientation of the rotator.

As illustrated by recent results,[4] the primary role of the stator in the solid state is to prevent close packing interactions with neighboring molecules. This facilitates the dynamics of the rotator about the dialkyne axle, which, in the absence of steric hindrance in the gas phase is essentially barrierless.[11] While a current approach for the removal of steric interactions in the solid state is to take advantage of a close topology for the encapsulation of the rotator, the local environment of the rotator can also be determined by supramolecular factors. Recognizing that rigid dumbbell-like structures with a relatively narrow middle and bulky ends tend to form relatively low-density crystals,[12] we decided to explore a new set of architectures based on rigid steroidal frames (Fig. 1b).[13] In this article we investigate the relationship between the molecular and supramolecular structure and the dynamic behavior for two steroid-based molecular rotors. Steroidal compounds offer a series of nearly inflexible scaffolds with fused rings that can be coplanar or bent, and in addition to their shape persistent tetracyclic cores, naturally occurring steroidal structures are homochiral and many tend to be polymorphic and mesogenic.[14] Structures such as those illustrated in Fig. 1 equipped with a polar rotator may be used for the design of liquid crystals with negative dielectric anisotropy. These materials are expected to have a fast response to external fields in a direction perpendicular to the principal molecular axis.[15,16] A mechanism that relies on segmental reorientation of a small polar segment rather than rotation of the entire molecule has been a promising target for liquid crystal displays that operate in the vertical alignment mode.[17]

Furthermore, having been studied heavily for a variety of biological and therapeutic applications, the steroid chemistry has been developed extensively[18] and they can be functionalized at several points along their four ring structures. Steroids have been used in hybrid materials with novel applications.[19] From steroid-doped liquid crystalline polymers,[20] functionalized-nanotubes,[21] to gels,[22] the use of steroidal compounds in materials science has been gradually increased while searching for desirable physical properties. An interesting feature of steroidal structures would be their use in crystal engineering, which would take advantage of their tendency to occur in different crystal forms.[23] Accordingly, we believe that the development of organic materials based on these natural products may provide us with opportunities from a crystal engineering perspective. The compounds selected for this study are two widely used steroids, norethisterone acetate and ethisterone, which we set out to explore as rigid stators in potential molecular rotors. The selection of these steroids was based on their commercial availability and their convenient functionalization with a terminal acetylene at position C17, which is ideally positioned to link a variety of aromatic rotators. Norethisterone acetate **3** (Scheme 1) is used for birth control and for the treatment of menstrual symptoms. Ethisterone **4** is a derivative of testosterone used as an intermediate in the synthesis of drugs for the treatment of urinary tract and cardiovascular system diseases. The main difference between the two structures relates to the presence or absence of the angular methyl group at C-10.

In the following sections we describe the synthesis of compounds **1** and **2**, and their characterization in solution and in the solid state. To explore their rotary dynamics and in order to determine the



Scheme 1

formation of polymorphs[24] we carried out a series of solid state NMR experiments.[25] Measurements carried out with powdered samples at ambient temperature (296 K) using ^{13}C NMR under cross polarization and magic angle spinning (CPMAS) with the norethisterone acetate rotor **1** and ethisterone rotor **2** showed a splitting of signals of the central phenylene suggesting that rotary exchange is very slow. A single crystal X-ray structure of **1** showed tightly packed layers of rotors that restrain the motion of their central rings. Analysis by ^{2}H NMR at 350 K in the case of **1**-d_4 with a deuterium-labeled phenylene gave a spectrum in the slow exchange regime, suggesting that motion of the central phenylene in this compound is hampered and occurs with a frequency that is less than 10 kHz. DSC and TGA studies in the range from 20 to 300 °C showed the loss of solvent in molecular rotors before melting with no crystal phase transitions.

Results and discussion

Synthesis of molecular rotors

Compounds **1**, **1**-d_4 and **2** were obtained by Sonogashira cross coupling[26] between the appropriate steroid **3** or **4** (1 eq) and 1,4-diiodobenzene **5** or 1,4-dibromobenzene-d_4 **6**, (0.5 eq) as outlined in Scheme 1. The desired compounds were obtained in good (*ca.* 70%) and moderate (*ca.* 40%) isolated yields from 1,4-diiodobenzene and 1,4-dibromobenzene-d_4, respectively, along with small quantities of aryl-alkyne (5–15%) and diyne (2-4%) coupling[27] products.

Spectroscopic characterization

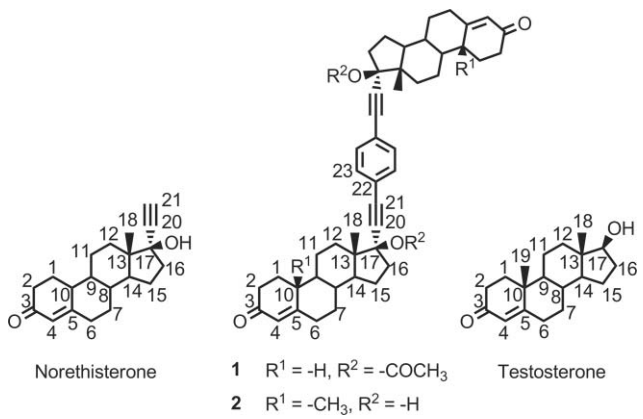
The infrared spectrum of compound **1** showed strong bands at 1725 and 1673 cm^{-1} corresponding to the acetate and the α,β-unsaturated carbonyl groups, respectively. Compound **2** showed bands at 3400, 2167 and 1655 cm^{-1}, in agreement with the expected hydroxyl, alkyne and carbonyl functional groups, respectively. The high resolution mass spectrometric (HRMS) data was in accordance with the exact masses expected from the molecular formulas of compounds **1**, **1**-d_4 and **2**. The molecular rotors **1** and **2** were fully characterized by solution ^{1}H and ^{13}C NMR. Despite the commercial availability of the starting materials, only references dealing with their syntheses were found.[28]

Table 1 Chemical shifts of steroidal molecular rotors **1** and **2**, and analogous compounds in solution

^{13}C signal	Norethisterone[a]	Compound **1**[b]	Testosterone[c]	Compound **2**[b,d]
1	28.0	26.8	36.1	35.8
2	37.6	36.7	34.1	34.1
3	203.1	200.1	198.0	199.8
4	125.1	124.9	124.2	124.1
5	170.9	166.5	170.4	171.4
6	36.8	35.6	32.8	33.0
7	32.4	30.9	32.2	31.7
8	42.6	41.0	36.1	36.4
9	51.2	49.3	54.6	53.6
10	44.1	42.8	39.0	38.8
11	27.7	26.4	21.2	20.9
12	34.1	33.4	37.1	32.9
13	*n.r.*	48.4	43.2	47.4
14	50.8	48.2	51.1	50.4
15	24.1	23.7	23.8	23.4
16	40.1	37.6	30.7	39.2
17	80.5	85.1	81.3	80.3
18	13.5	13.8	11.3	13.1
20	89.0	90.8		94.6
21	75.1	86.6		85.7
22		122.9		122.9
23		131.8		131.7

[a] Data in CD_3OD ref. 30. [b] Data in $CDCl_3$ at 500 MHz. [c] Data in $CDCl_3$ ref. 29*a*. [d] C19, 17.6 ppm. [n.r.] Not resolved

Thus, in order to ascertain the assignment of the molecular rotors, the starting materials were characterized with an appropriate selection of 1D and 2D solution NMR experiments (ESI†), and the results were compared with those available in comprehensive NMR reviews of analogous steroids.[29] Having assigned the starting materials, we corroborated the assignment on the steroidal molecular rotors where, as expected, only the alkyne moiety showed significant changes. In this section we use the norethisterone acetate rotor **1** as an example of the reasoning behind the assignment of the frequencies to the corresponding carbon atoms. Selected ^{13}C signals of **1** and **2** (Scheme 2) are compiled and compared with those of analogous compounds in Table 1. The numbering scheme used for the steroidal rotors follows the standard convention, with the carbons of the central phenyl ring labeled consistently for comparison purposes. In molecular rotor **1**, a single aromatic proton signal (H-23) at δ = 7.32 confirms the formation of a symmetric rotor. The assignment



Scheme 2

of the vinylic proton H-4 at δ = 5.82 was straightforward. Additionally, H-10 (δ = 2.18–2.00) in compound **1** could be located with the help of COSY experiment despite severe overlap with signals corresponding to the acetate methyl group and to proton 16β. In this compound, the acetate group at C-17 deshields a proton signal (δ = 2.80) that could be assigned to 16α on the basis of geminal (^2J = 15 Hz) and vicinal (16α-15α, ^3J = 9.5 Hz and 16α-15β, ^3J = 5.4 Hz) couplings.[30]

The solution ^{13}C NMR spectrum of **1** showed a total of 24 carbon mirror-averaged signals, with two methyl carbons in the aliphatic region readily assignable with the help of a ^{1}H–^{13}C heteronuclear (HETCOR) correlation. The signal at δ = 13.8 is assigned to C-18 and the other one at δ = 21.7 to the acetate methyl. The quaternary carbons C-3 (δ = 200.1), C-5 (δ = 166.5), C-13 (δ = 48.4) and C-22 (δ = 122.9), and that from the carbonyl of the acetate group (δ = 169.7) were easily assignable from APT experiments.

Using the HMBC technique (Fig. 2) we identified the remaining quaternary carbons, C-17 (δ = 85.1) by a three-bond correlation with H-18. The signal of C-20 at δ = 90.8 was identified by the three bond correlation with H-16α, allowing us to differentiate the signal from C-21 at δ = 86.6. A DEPT 90° experiment revealed six methine carbon atoms. The signal of C-4 at δ = 124.9 was identified by a heteronuclear correlation with the vinylic proton H-4 and the peaks of C-8 at δ = 41.0 and C-10 at δ = 42.8 were differentiated by the three-bond HMBC correlation of the latter with H-4. The signal of C-14 at δ = 48.2 also showed a three bond correlation with H-16α and was distinguished from the one assigned to C-9 at δ = 49.3. Finally, the only aromatic signal in the molecule at δ = 131.8 was assigned to C-23. This signal was very distinct from the rest of the steroid, suggesting that it could be suitable for examination using high resolution solid state CPMAS ^{13}C NMR.

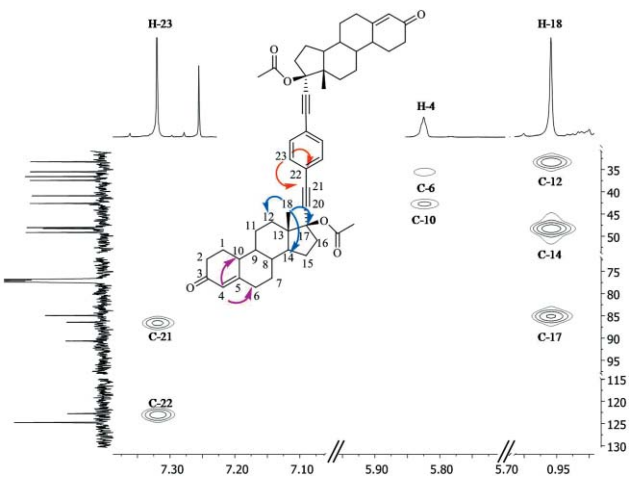


Fig. 2 Portion of the 2D HMBC spectrum of **1** illustrating long-range ^{1}H–^{13}C correlations.

Signals corresponding to the eight methylenes in the structure were confirmed with the help of a DEPT 135° experiment, where they occurred with the expected negative phase. Among them, the assignment of C-6 at δ = 35.6 was straightforward because of its three-bond (HMBC) and through space (COSY) correlation with vinylic hydrogen H-4. The signal of C-12 at δ = 33.4 correlates

with H-18 in the HMBC experiment, and that of C-16 at δ = 37.6 correlates with the greatly shifted H16α in the HETCOR spectrum. From the latter, the assignment of C-2 at $\delta = 36.7$ was done with ease. Finally, signals of C-1 at δ = 26.8 and C-11 at $\delta = 26.4$ were differentiated by the three-bond correlation of H-1β with C-3.

A clear distinction between the two rotors can be seen in the ^{13}C NMR where the carbon atom C-10 in compound **2** (δ = 38.8) is shielded due to the presence of the methyl group, in contrast with the corresponding signal in **1** (δ 42.8). The methyl group C-19 in **2** deprotects the α-carbon atoms C-1 ($\Delta\delta = 9$), C-5 ($\Delta\delta = 4.9$) and C-9 ($\Delta\delta = 4.3$), while protecting the β-carbon atoms C-2 ($\Delta\delta$ = -2.6), C-8 ($\Delta\delta$ = -4.6) and C-11 ($\Delta\delta = -5.5$) as compared to compound **1**. The acetate group in **1** shifts the C-17 signal by $\Delta\delta = 4.8$ with respect to that in **2**. However, their structural differences had a very small effect on the chemical shifts of the aromatic carbons of the central rotator, as can be seen in Table 1.

X-Ray studies

Although polymorphism and pseudopolymorphism in steroidal compounds is a frequent phenomenon,[31] only one crystal form of compound **1** suitable for single crystal X-ray diffraction analyses was obtained by slow evaporation from saturated chloroform. Both starting materials have had their crystal structures reported,[32,33] and only one polymorph is known in each case. Crystallographic acquisition and refinement data for the crystal structure of the norethisterone rotor **1** is listed in the ESI,† and its ORTEP diagram illustrated in Fig. 3. Rotor **1** crystallizes in the chiral monoclinic space group C2, with cell constants and angles a = 19.2269(6), b = 10.7806(4), c = 12.2170(4), $\alpha = \gamma = 90°$, β = 94.89°. The asymmetric unit consists of only half a molecule as a result of coincident molecular and crystallographic 2-fold axes, which in Fig. 3 are orthogonal to the plane of the paper.

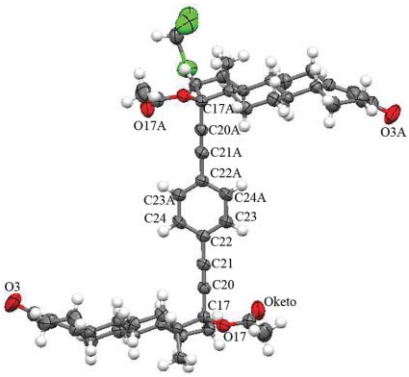
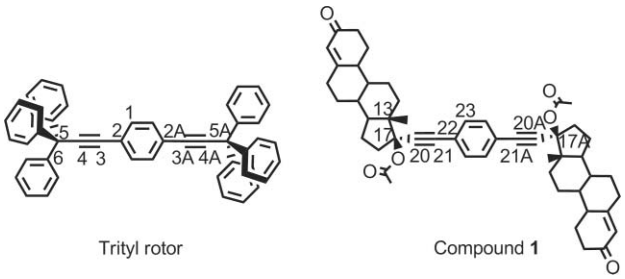


Fig. 3 Molecular structure of rotor **1** crystallized with $CHCl_3$ with thermal ellipsoids at the 50% probability level.

With very limited conformational degrees of freedom, the structure of the steroidal components in rotor **1** is very similar to the reported structure for the norethisterone. Despite lacking the ananchomeric properties of the angular C-19 methyl group,[34] the A-ring occurs in the more favorable 1α,2β half-chair conformation with C-1 below and C-2 above of the plane formed by C-3, C-4, C-5 and C-10.[35] Interestingly, the acetate group has a nearly identical conformation in the starting material and in rotor **1**, despite its expected rotational freedom: the dihedral angle C17–O17–C_{keto}–O_{keto} in the crystal structure of the starting material is –0.6° and that in the molecular rotor **1** is –0.8°. Additionally, the dihedral angle C13–C17–O17–C_{keto} in norethisterone acetate is 172.9° while in compound **1** it is 173.0°.



Scheme 3

Table 2 Selected distances, angles and dihedral angles from crystal data of parent, and norethisterone acetate molecular rotors

Trityl Rotor (C_6H_6)		Compound **1** ($CHCl_3$)	
C5-C5A (Å)	11.027	C17-C17A (Å)	10.975
C5-centroid-C3 (°)	1.7	C17-centroid-C21 (°)	2.1
C5-centroid-C1 (°)	58.68	C17-centroid-C23 (°)	59.71
C1-C2-C5-C6 (°)	5.39	C23-C22-C17-C13 (°)	12.38

In order to compare the structural features of rotor **1** with those previously reported, relevant features of its crystal structure are compared in Table 2 with those of the analogous rotor with trityl groups in the stator (Scheme 3). The distance between carbons that bear the alkynyl groups in compound **1**, d(C17–C17A)=10.975 Å, is slightly shorter than that in the trityl rotor, d(C5–C5′) = 11.027 Å. The angle described by C17-phenylene centroid-C21 in the second row of the table (2.1°) is a measure of the deviation from the linearity of the diethynylphenylene moiety. A modest deviation is accompanied by a minimal distortion in the arrangement of the central ring, as indicated by the angle C17-phenylene centroid-C23 (59.71°), which is very close to the ideal 60°. Even though the rotation of the phenylene ring in the steroidal rotors with these molecular structures would be permitted for isolated molecules, intermolecular contacts can impede internal motion as described below.

The packing structure of compound **1** is characterized by an arrangement of one-dimensional layers propagating along the plane formed by the a and c crystallographic axis (Fig. 4a). The solvent of crystallization ($CHCl_3$) trapped between neighboring rotors interacts through hydrogen bonds (indicated by blue arrows) with the carbonyl of the acetate group attached to C-17, as suggested by an $O_{keto} - Cl_{solv}$ distance of 3.13 Å and $O_{keto} \cdots H_{solv} \cdots Cl_{solv}$ angle of 167.2°. A second intermolecular interaction of the same molecule of the solvent with a contiguous C-9′ was observed with a C9′ $\cdots$ H9′ $\cdots$ Cl_{solv} angle of 161.4° and a C9′–Cl_{solv} distance of 3.82 Å. Intermolecular hydrogen contacts between the adjacent stators were observed between the acidic H16β and the oxygen O3′ atom of a neighboring molecule, with a C16 $\cdots$ H16β $\cdots$ O3′ angle of 163.5°, and a C16 – O3′distance of 3.51 Å. With the steroidal stators in *anti* conformation, additional 1D layers of flat norethisterone acetate rotor (*i.e.* those propagating above and below the plane of the paper) stack close to each other, limiting the available space around the aromatic ring. As indicated by solid state NMR results in the following section, this arrangement

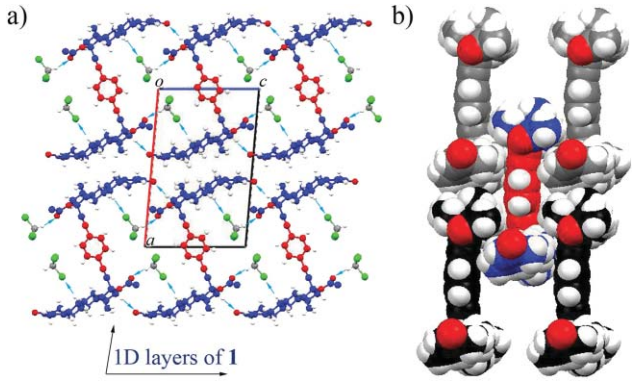


Fig. 4 (a) Packing diagram of compound **1** viewed down the crystallographic *b*-axis. (b) Space-filling representation of close-packing interactions between neighboring molecules viewed down the crystallographic *c*-axis. Space-filling contacts between the central rotator (shown in red) and neighboring molecules result in a high barrier for rotation.

restricts the motion of the central phenylene to a considerable extent (Fig. 4b).

Solid state characterization

Samples for solid state analysis were obtained from solutions of $CHCl_3$ in the case of **1** and ethyl acetate/hexanes in the case of **2**. Visual melting point analyses of compound **1** showed gradual softening above 40 °C and complete melting over 140 °C. In contrast, samples of compound **2** showed a relatively narrow melting point range of 234–238 °C. Weight changes and thermal stability upon heating of solid samples were also monitored by open pan thermogravimetric analysis (TGA) and sealed pan differential scanning calorimetry (DSC),[36,37] respectively, with a slow heating rate of 5 °C min^{-1}.[38]

In the case of compound **1**, a broad endothermic transition was observed by DSC between 26 °C and 90 °C, with a maximum at *ca.* 53 °C, which coincided with a loss of mass on the TGA experiments that was attributed to the loss of chloroform. In the case of compound **2**, DSC analysis up to 300 °C showed small endothermic transitions from 37 °C to 88 °C and from 140 °C to 180 °C prior to melting (236.7 °C). These transitions coincide in temperature with little perturbations in the thermogravimetric analysis indicating that compound **2** may occlude ethyl acetate.

Solid state CPMAS ^{13}C NMR experiments

High resolution ^{13}C NMR spectra in the solid state can be obtained using the cross polarization in the magic angle spinning technique,[39] which is ideal to observe dilute nuclei with low sensitivity, such as ^{13}C, due to the transfer of magnetization from the abundant ^{1}H nucleus under the Hartmann–Hahn matching condition.[40,41]

For crystalline molecular rotors, ^{13}C CPMAS NMR spectroscopy has been used to analyze rotary motion in the kilohertz regime by variable temperature analysis of signals corresponding to magnetically non-equivalent sites that are related by a dynamic rotary site exchange process. Solid state NMR of crystalline natural products[42] has also been used to determine changes in average molecular symmetry, conformational parameters, the number of non-equivalent molecules in the unit cell, and the presence and/or loss of solvent.[43] The ^{13}C CPMAS NMR spectra of polycrystalline samples of **1** and **2** are shown in Fig. 5. It is well known that assignments from solution NMR are qualitatively similar to those obtained in the solid state by ^{13}C CPMAS NMR, and we found a good agreement between the two. In accordance with the molecular symmetry revealed by the X-ray data, the spectrum of **1** (Fig. 5a) showed a single peak for each steroidal carbon and only two C–H signals for the central aromatic group. A broad peak at $\delta = 79$ was assigned to chloroform and some peaks were readily assigned due to their shift similarity with solution NMR: C-3 ($\delta = 197.3$), C-5 ($\delta = 161.9$), C-4 ($\delta = 124.9$), C-22 ($\delta = 123.9$), C-20 ($\delta = 91.2$), C-21 ($\delta = 86.1$), C-17 ($\delta = 84.8$), C-13 ($\delta = 48.1$), C-8 ($\delta = 41.2$), and C-18 ($\delta = 13.7$). In contrast to the simplicity of **1**, most signals in the ^{13}C CPMAS of compound **2** appeared in pairs (Fig. 5b). This includes signals tentatively assigned to C-3 ($\delta = 200.0$ and 198.2), C-4 ($\delta = 124.9$ and 124.2), C-20 ($\delta = 97.8$ and 95.9), C-9 ($\delta = 57.0$ and 55.6), C-13 ($\delta = 48.2$ and 47.5), C-18 ($\delta = 13.3$ and 12.5) and C-19 ($\delta = 18.6$ and 16.6). The substantial number of resolved pairs of signals can be attributed to a molecular conformation and/or packing environment where the two halves of the molecules are different.

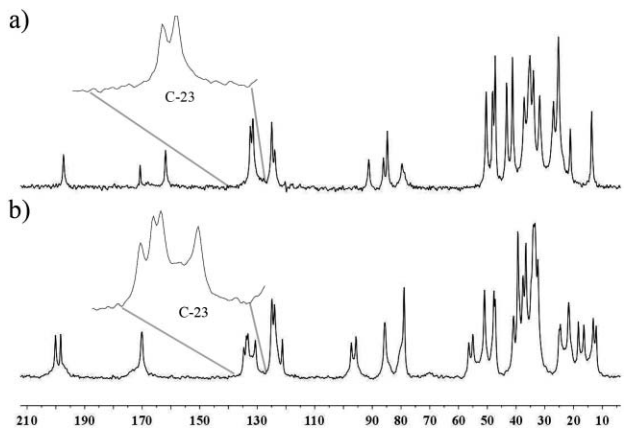


Fig. 5 (a) ^{13}C CPMAS NMR spectrum of compound **1** showing phenylene signal at $\delta = 132$ as a doublet. (b) ^{13}C CPMAS NMR spectrum of compound **2** displaying a multiple signal from the C-23 carbon atom.

As illustrated in Fig. 5, there are interesting differences in the signals of the aromatic rings of rotors **1** and **2**. While the aromatic C–H signals of compound **1** appear as two signals centered at $\delta = 132$, the spectrum of compound **2** exhibits four distinguishable signals in a range from $\delta = 136$ to $\delta = 128$. The two signals in **1** are consistent with crystallographic and magnetic non-equivalence of C-23 and C-24, and their splitting indicates that there is no site exchange occurring at ambient temperature. The greater complexity of the corresponding signals in the case of **2** suggests a lower molecular symmetry, with all carbons being magnetically non-equivalent, and a relatively static structure.

Additional experiments with the "non quaternary suppression" (NQS) pulse sequence[44] were carried out to confirm some assignments and the static nature of the two crystalline samples. The NQS sequence includes a brief (*ca.* 30 μs) interruption of ^{1}H decoupling after cross polarization to dephase the signals of static ^{13}C atoms attached to ^{1}H nuclei, such as most methines and methylenes. Spectra acquired with this sequence allows for a

simple identification of quaternary carbons, and of carbons that are protonated but highly mobile, such as CH_3 groups, and some CH carbon atoms from highly dynamic rotators. NQS experiments in the case of **1** and **2** showed complete disappearance of the signals corresponding to the central phenylene carbons, indicating that rotation of this group must be much slower than the range of the aromatic ^1H–^{13}C dipolar coupling of *ca.* 20–30 kHz.

Variable temperature solid state spin echo ^2H NMR

Deuterium NMR spectroscopy is a valuable tool to determine the molecular dynamics of molecular rotators.[45–47] The method is based on the fact that changes observed in the spectrum of powder samples as a function of temperature can be analyzed in terms of a dynamic process that changes the orientation of the C–D bond with respect to the orientation of the external magnetic field. A single crystal with only one type of C–^{2}H bond with a symmetric quadrupolar tensor would give a doublet with a quadrupolar splitting $\Delta\nu$ that depends on the orientation angle β that the bond makes with respect to the external field.[48]

$$\Delta\nu = 3/4\ (e^2q_{zz}\ Q/\mathrm{h})\ (3\cos^2\beta - 1) = 3/4\ \mathrm{QCC}\ (3\cos^2\beta - 1)$$

The variable Q represents the electric quadrupole moment of the deuterium, e and h are the electric charge and Planck constant, and q_{zz} is the magnitude of the principal component of electric field gradient tensor, which lies along the C–^{2}H bond. A collection of doublets in all possible orientations in a powder sample gives rise to a broad symmetric spectrum known as a Pake pattern. As reorientation of the C–^{2}H bond vector results in predictable changes in the powder spectrum, line shape analysis of the deuterium NMR spectra acquired as a function of temperature can be used to characterize the frequency and trajectories of motion. Variations in the powder pattern of a solid sample are commonly related to reorientations of the C–^{2}H bonds with discrete jumps between different sites with observable exchange rates in the range of 10^3 to 10^8 s^{-1}.

The solid state spin echo ^2H NMR spectrum obtained with a polycrystalline sample of compound **1**-d_4 at 296 K in Fig. 6a produced a Pake pattern such as that expected for a static sample. A spectrum acquired at 350 K showed a very small variation, suggesting that any dynamic process in the sample must be close to the lower limit of the intermediate exchange regime of 10^3 s^{-1}. Given that the trajectories of motion of the phenylene C–D bonds in crystals of **1** are limited to rotation about the 1,4-dialkynyl axis, with a site exchange determined by the two degenerate minima determined by the orientation of its aromatic plane (Fig. 6d), we decided to estimate an upper limit of its rotary dynamics. To that effect, the spectrum in Fig. 6c was obtained with a model that considers a quadrupolar coupling constant QCC = 180 KHz, angular displacements of 180°, also known as two-fold flips, and an exchange frequency of 10 kHz. A comparison of the experiment at 350 K and the simulated spectra in Fig. 4b and c shows that the exchange dynamics in **1** are below the 10 kHz. This is in agreement with the ^{13}C CPMAS NMR, which shows two signals for the two sites of the relatively static phenylene.

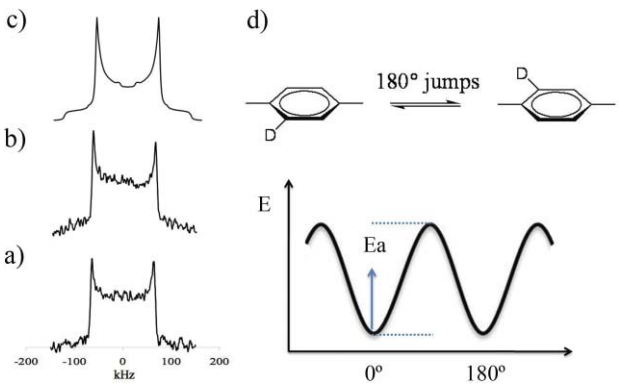


Fig. 6 VT ^2H NMR spectra of **1**-d_4 acquired at (a) 296 K, (b) 350 K and (c) line shape simulation for a model that assumes a quadrupolar coupling constant coupling QCC = 180 kHz and jumps between sites related by 180° with a frequency of 10 kHz. (d) Model of the corresponding potential energy diagram.

Conclusions

Molecular rotors prepared by transition metal catalyzed aryl–alkyne coupling reactions using readily available 17α-ethynyl-substituted steroids provide a novel structural platform to explore the dynamics of potential phenylene rotators in the solid state. The steroids selected for this study, ethisterone and norethisterone acetate, are structurally related to testosterone and have been widely studied for their pharmacological activities. Molecular rotors derived from these compounds were prepared by a double Pd(0)-coupling reaction with 1,4-diiodobenzene, or 1,4-dibromobenzene-d_4, in yields that varied from *ca.* 40–75%. The resulting 1,4-bis(19-nor-17α-ethynyltestosterone-17β-acetate)benzene **1** and 1,4-bis(17α-ethynyltestosterone)benzene **2** were characterized in solution by standard analytical techniques and in the solid state by ^{13}C CPMAS NMR and thermal analyses, as well as single crystal X-ray diffraction and VT ^2H NMR in the case of **1**. The results from ^{13}C CPMAS NMR dipolar dephasing and variable temperature ^2H NMR experiments in the solid state indicated that the internal dynamics of **1** are very slow in the crystalline state. The restricted motion of the central ring can be explained in terms of the packing structure determined by X-ray diffraction analysis, which revealed that the steroidal portion of four near neighboring rotors occupies the space surrounding each prospective phenylene rotator. The results with compound **1** suggest that functionalization of the α,β-unsaturated ketone in the A-ring and the 17-β-hydroxyl group in the D-ring should help prevent the close proximity between the prospective rotator and the steroidal stator of its close neighbors. Preliminary results with analogous steroids from the estradiol family present remarkably different packing motifs with low barriers to rotation. These studies are now in progress and their results will be reported in due course.

Experimental section

Synthesis of steroidal molecular rotor 1

In a round-bottom flask fitted with a Dean–Stark trap, the noresthisterone acetate was refluxed in toluene in order to remove traces of water. Dried steroid (0.500 g, 1.467 mmol), and 1,4-diiodobenzene (0.242 g, 0.734 mmol), were placed in a flame-dried round-bottom flask under nitrogen atmosphere;

then diisopropylamine (3 mL) and THF (6 mL) as the solvent were added. After the mixture was bubbled with nitrogen (15 min), dichloro-bis(triphenylphosphine)palladium(II), $PdCl_2(PPh_3)_2$ (0.052 g, 0.073 mmol), and copper(I) iodide (0.028 g, 0.147 mmol) were added. The mixture was refluxed 4 h and cooled to room temperature, the reaction was quenched with a saturated solution of ammonium chloride and the organic layer was extracted with methylene chloride. The aqueous compound was extracted with methylene chloride three times. The combined organic layers were dried over Na_2SO_4, and the solvent was removed under vacuum. A white powder (0.393 g, 71%, m.p. 142–146 °C) was obtained after flash column chromatography using hexanes : ethyl acetate (6 : 4) as eluent. $[\alpha]_D^{25} = -83.2$ (*c* 1.1, CH_2Cl_2), IR (ATR) ν_{max}/cm^{-1}: 2994, 2928, 2865, 1725 (-$COCH_3$), 1673 (C=O), 1619, 1508, 1448, 1365, 1243, 1015, 841, 742. δ_H (500 MHz, $CDCl_3$) δ: 7.32, 5.82, 2.80, 2.06, 0.96. δ_C (125 MHz, $CDCl_3$) δ: 200.1, 169.7, 166.5, 131.8, 124.9, 122.9, 90.8, 86.6, 85.1, 49.3, 48.4, 48.2, 42.8, 41.0, 37.6, 36.7, 35.6, 33.4, 30.9, 26.8, 26.4, 23.7, 21.7, 13.8. *m/z* HRMS (ESI-TOF) calculated for $[C_{50}H_{58}O_6+H]^+$: 755.4306; found: 755.4313.

Synthesis of steroidal molecular rotor 2

The procedure described above to prepare **1** was used with the following quantities. Ethisterone (1.001 g, 3.203 mmol), 1,4-diiodobenzene (0.528 g, 1.600 mmol), $PdCl_2(PPh_3)_2$ catalyst (0.112 g, 0.1596 mmol), CuI (I) (0.061 g, 0.320 mmol), 6.5 mL of diisopropylamine and 13 mL of THF were refluxed 4 h according to the previous methodology. The title compound was obtained as a white powder (0.805 g, 72%, m.p. 234–238 °C) after column purification using hexanes : ethyl acetate 8 : 2. $[\alpha]_D^{25} = +20.6$ (*c* 1.1, CH_2Cl_2). IR (ATR) ν_{max}/cm^{-1}: 3400 (OH), 2937, 2867, 2168, 1655 (C=O), 1615, 1508, 1449, 1380, 1331, 1272, 1232, 1125, 1063, 1013, 857. δ_H (500 MHz, $CDCl_3$) δ: 7.32, 5.71, 1.18, 0.92. δ_C (125 MHz, $CDCl_3$) δ: 199.8, 171.4, 131.7, 124.1, 122.9, 94.6, 85.7, 80.3, 53.6, 50.4, 47.4, 39.2, 38.8, 36.4, 35.8, 34.1, 33.0, 32.9, 31.7, 23.4, 20.9, 17.6, 13.1. *m/z* HRMS (ESI-TOF) calculated for $[C_{48}H_{59}O_4+H]^+$: 699.4407, found: 699.4401.

Synthesis of steroidal molecular rotor 1-d_4. 1,4-dibromobenzene-d_4. The procedure described above to prepare **1** was used with the following quantities: 1,4-dibromobenzene-d_4 (0.0176 g, 0.734 mmol), norethisterone acetate (0.500 g, 1.468 mmol), dichloro-bis(triphenylphosphine)palladium(II) catalyst (0.051 g, 0.073 mmol), CuI (0.027 g, 0.147 mmol), diisopropylamine (3 mL) and THF (6 mL) were refluxed 10 h according to the above methodology. After column chromatography purification eluting with a mixture of hexanes-ethyl acetate (6 : 4), a white solid (0.239 g, 43%) was obtained m.p. 139–142 °C. IR (ATR) ν_{max}/cm^{-1}: 2928, 2860, 2236, 2168, 1724, 1672, 1618, 1424, 1364, 1257, 1230, 1015, 921, 858, 722. δ_H (300 MHz, $CDCl_3$): 5.84, 2.82, 2.07, 0.97. δ_C (75 MHz, $CDCl_3$) δ: 200.0, 169.9, 166.7, 131.6 (triplet, $J_{CD} = 25$ Hz), 125.1, 122.9, 91.0, 86.7, 85.2, 49.4, 48.5, 48.3, 42.9, 41.2, 37.7, 36.9, 35.8, 33.6, 31.1, 26.9, 26.6, 23.9, 21.9, 14.0. *m/z* HRMS (ESI-TOF) calculated for $[C_{50}H_{54}O_6D_4+H]^+$: 759.4553; found: 759.4535.

Acknowledgements

This work was supported by CONACYT grant 45165, UNAM (PAPIIT IN-214010), and National Science Foundation grants DMR-0605688 and CHE 0844455. The authors thank M. A. Leyva for X-Ray diffraction experiments.

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