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# Conformational Analysis of Spiro-bis-dithiepins: A Peculiar Case of Axial Chirality

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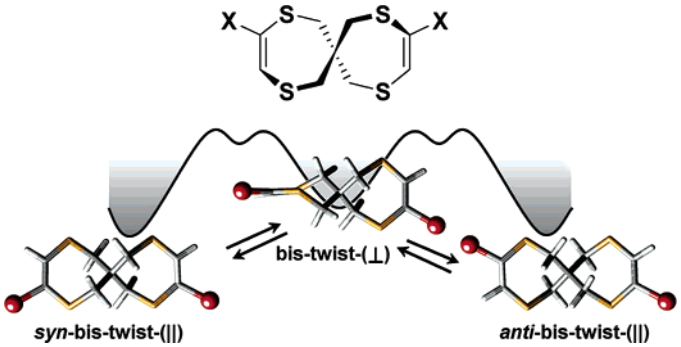
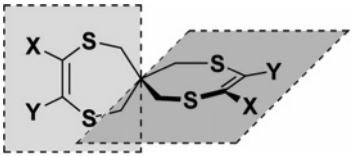
## ABSTRACT




**Spiro-bis-dithiepins are synthesized via dehydrative ring expansion in α-hydroxyalkyl spiro-bis-dithianes. Atypical of spiranes possessing axial chirality, the two most stable conformers of substituted spiro-bis-dithiepin have virtually colinear double bonds; i.e., each enantiomer exists in a form of two energy degenerate syn and anti conformations. Because of the high polarizability of the vinyl sulfide moiety, spiro-bis-dithiepins bearing electron-withdrawing substituents offer access to two-state systems possessing large dipole moments, which can be modulated by conformational events.**

A photoinduced 1,3-hydrogen shift in substituted 6,7-dihydro-5*H*-[1,4]dithiepins and associated modulation of the electronic properties of this highly polarizable system make dithiepins a promising framework for advanced materials.[1] Conjoining two dithiepin moieties via a spiro connection offers an even more sophisticated framework, with the potential for photoinduced modulation of the properties of both local $\pi$-systems, which are aligned according to the conformational bias of the two seven-membered heterocycles. Since the original Gerlach account[2] of axial chirality in spiro-[4.4]nonane-1,6-dione, the predominate description of these spiranes included their two cycles residing in perpendicular planes, with the symmetry of each lifted by asymmetric substitution in the opposite ring. Although this depiction is always valid for a time-averaged structure, we find that the actual conformational preferences in the dihydrodithiepin moiety produce a rather peculiar picture. In this Letter, we




report on synthesis and experimental and theoretical conformational analyses of spiro-bis-dithiepins.

As outlined in Scheme 1, the target bis-dithiepins **5** were synthesized via a two-step process: the addition of lithiated spiro-bis-methyldithiane **1** to aromatic aldehydes followed by dehydrative ring expansion, catalyzed by toluenesulfonic acid.[3] The first addition step produces up to 7% of monoad-

(1) Wan, Y.; Kurchan, A. N.; Kutateladze, A. G. *J. Org. Chem.* **2001**, *66* (5), 1894.
(2) Gerlach, H. *Helv. Chim. Acta* **1968**, *51*, 1587.

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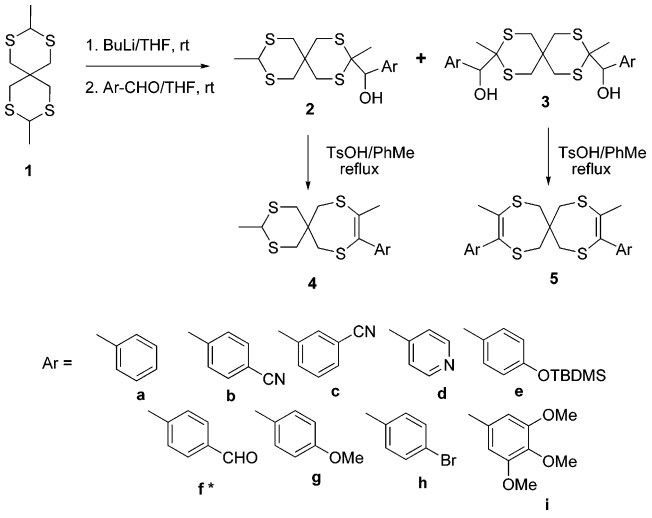
**Scheme 1**

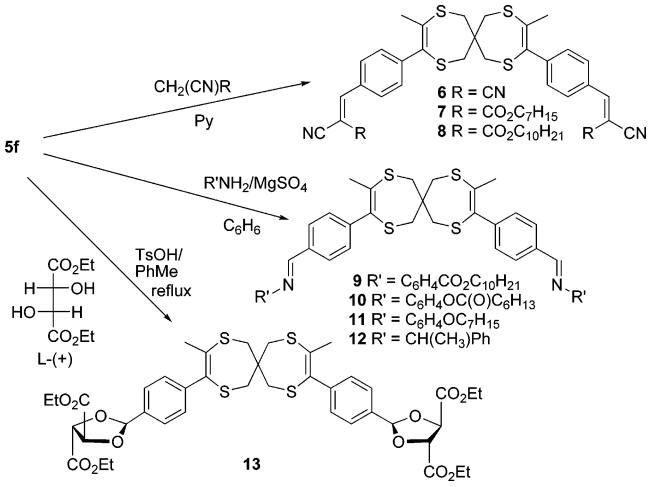



*Starting from the monoacetal of terephthalaldehyde.

ducts **2**, which also are readily converted into spiro-dithianodithiepins **4**.

Bisaldehyde **5f**, synthesized from the monoacetal of terephthalaldehyde, is a primary synthon for the facile post modifications shown in Scheme 2. It is readily condensed

**Scheme 2**




with nitriles to yield tetraenes **6**−**8**, possessing polarized $\pi$-systems, or converted into imines **9**−**11** in reactions with substituted anilines.[4] Imine **12** was synthesized with enantiopure *S*-(−)-α-phenylethyl amine in an attempt to separate the enantiomers of **5f**. For the same reason, diethyl L-(+)-tartrate was used in preparation of bisacetal **13**. In both cases, the resulting diastereomers showed insufficient differences in physical properties for their separation. However, direct separation of enantiomers **5f** on a chiral chromatography column, Chiracel OD, was successful (Figure 1).

According to our DFT computational studies, the half-twist conformer (from here on "twist") of the parent

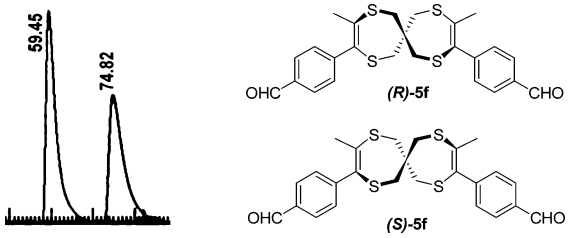



**Figure 1.** HPLC trace for enantioseparation of **5f** on a Chiralcel OD chiral chromatography column.

unsubstituted 6,7-dihydro-5*H*-[1,4]dithiepin is 0.9 kcal/mol more stable than the chair conformer. It was therefore not unexpected that in the spiro-bis-dithiepin the most stable conformers have both rings in the twist conformation. What

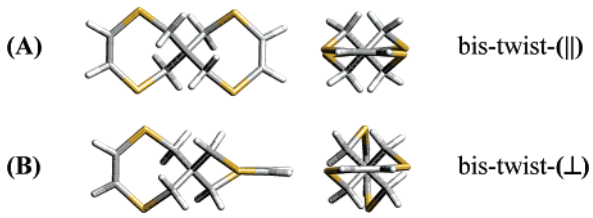



**Figure 2.** DFT structures of the two bis-twist conformers of the unsubstituted spiro-bis-dithiepin: (**A**) the coplanar conformer (||) and (**B**) the cross conformer (⊥). Bis-twist-(||) is 1.7 kcal/mol more stable than bis-twist-(⊥) at the B3LYP/6-311++G(3df) level of theory.

is unique about the spiro-bis-dithiepin framework is that there are two ways in which the bis-twist arrangement can be realized (Figure 2): (i) with the two double bonds perpendicular to each other, which we denote as (⊥), and (ii) with

(3) At the first addition step, some amount of monoadduct is always formed together with bisadduct **3**. To improve the bis/mono ratio, we deviated from the classic Corey−Seebach procedure for preparation of dithiane anions (Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231) by generating the bisanion at room temperature for 30 min, before quenching the reaction with a carbonyl compound to furnish **2**. (a) General Procedure for Preparation of **3**: Butyllithium (5 mL, 8 mmol, 1.6 M) was added to 0.5 g (2 mmol) of 3,9-dimethyl-2,4,6,10-tetrathiaspiro[5.5]undecane, and the mixture was stirred at room temperature for 30 min. A solution of a substituted benzaldehyde (4.4 mmol) in 10 mL of freshly distilled THF was added to the mixture, and the solution was stirred for 2 h at room temperature, quenched with 20 mL of saturated $NH_4Cl$(aq), and extracted with dichloromethane (20 mL × 2). The organic layers were combined and dried over anhydrous sodium sulfate. The solvent was removed under a vacuum, and the crude product was purified by column chromatography (**3f** was synthesized starting from the monoacetal of terephthalaldehyde and deprotected with AcOH before dehydrative ring expansion into sprio-bis-dithiepin; for details refer to Supporting Information). (b) General Procedure for Preparation of **5**: 0.1 g (0.2 mmol) of bisadduct **3** was dissolved in toluene, and a catalytic amount of *p*-toluenesulfonic acid (0.1 equiv) was added. The reaction mixture was refluxed with a Dean−Stark trap for 12 h, then allowed to cool to room temperature. The remaining toluene was removed under a vacuum. The resulting oil was washed with saturated $NH_4Cl$(aq) and extracted with dichloromethane (15 mL × 2). The organic extracts were combined and dried over anhydrous sodium sulfate. The solvent was removed under a vacuum, and the crude residue was chromatographed.

the double bonds nearly coplanar (||). The latter—in cases when the dithiepin moieties carry nonsymmetrically substituted double bonds—gives rise to syn and anti conformations. Another feature is that the conformational equilibrium is hardly affected by substitution at the double bond but rather is governed by the intrinsic properties of the parent (i.e., unsubstituted) spiro-bis-dithiepin (Table 1). Among other

**Table 1.** B3LYP/6−31G(d) Relative Energies and Dipole Moments of **5f** and **18**

| | | dipole moment (D) | | | |
|---|---|---|---|---|---|
| bis-twist: | rel energy[a] | *X* | *Y* | *Z* | total |
| *syn*-(\|\|)-**5f** | 0.06 | 0.00 | 5.07 | 0.00 | 5.07 |
| *anti*-(\|\|)-**5f** | (0.0) | 0.00 | 0.00 | 2.16 | 2.16 |
| (⊥)-**5f** | 1.55 | 0.47 | 1.75 | 2.06 | 2.75 |
| *syn*-(\|\|)-**18** | 0.35 | 0.00 | 7.19 | 0.00 | 7.19 |
| *anti*-(\|\|)-**18** | (0.0) | 0.00 | 0.00 | 0.53 | 0.53 |
| (⊥)-**18** | 1.77 | −0.19 | 2.76 | 4.35 | 5.16 |

[a] In kcal/mol.

things, this implies that the syn and anti conformations are nearly energy degenerate for various spiro-bis-dithiepins substituted at the double bond.

B3LYP/6-311++G(3df) computations reveal that the bis-twist-(||) to bis-twist-(⊥) conformational flip occurs via a twist-chair intermediate (Figure 3). The highest-energy

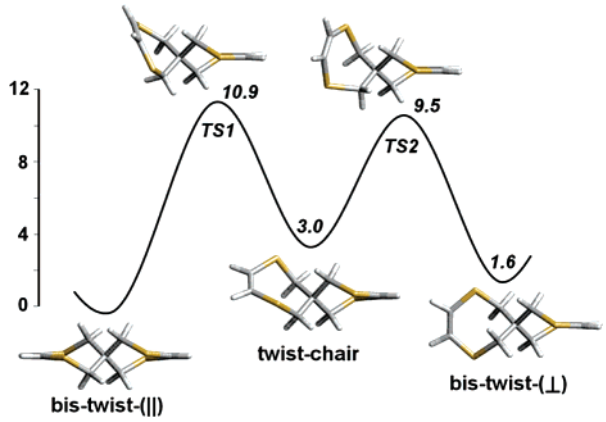



**Figure 3.** Energy profile (rel kcal/mol) for bis-twist-(||) to bis-twist-(⊥) interconversion at the B3LYP/6-311++G(3df) level of theory.

transition state (TS1) is found at 10.9 kcal/mol above the coplanar conformer, which is consistent with a previously reported 12.6 kcal/mol energy barrier for the conformational flip in a related benzodithiepin.[5] The bis-chair conformation (not shown) lies 3 kcal/mol above the bis-twist-(||); i.e., it is very similar in energy to the twist-chair intermediate.

To experimentally determine the barrier of the conformational equilibration in **5f**, a variable-temperature (VT) NMR experiment was carried out (Figure 4a). At 20 °C, confor-

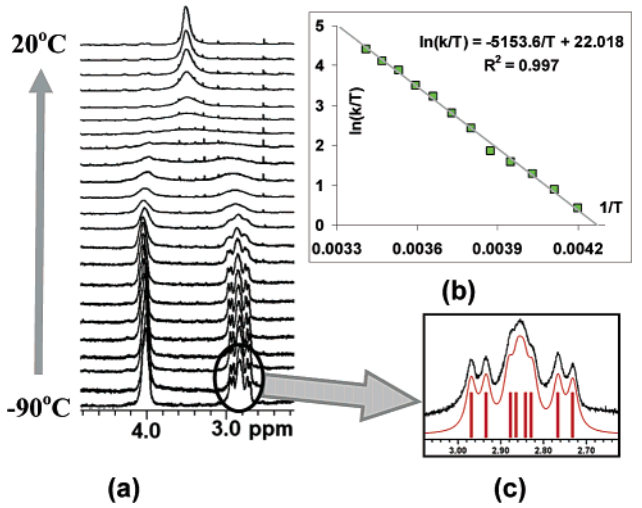



**Figure 4.** (a) VT-NMR for **5f**: 20 to −90 °C at $\Delta T = 5°$, $CD_2Cl_2$. (**b**) Eyring plot and (c) a 2.8 ppm multiplet (black) simulated with two pairs of doublets ($J = 14.1$ Hz) with equal intensity (red).

mational dynamics are fast and all four pairs of methylenic protons show as a broad singlet at 3.5 ppm. Lowering the temperature causes this peak to decoalesce into two resonances (*pseudoaxial* and *pseudoequatorial* methylene protons), approximately 1.2 ppm apart. At −90 °C, the higher-field 4H multiplet is best simulated as two pairs of doublets of equal intensity, with a geminal spin−spin coupling constant of 14.1 Hz (Figure 4c). This is consistent with two $C_2$-symmetric conformers, syn and anti bis-twist-(||), present in equal or nearly equal concentrations. Line shape analysis of the NMR data produced a set of rate constants, which were plotted according to the Eyring equation (Figure 4b) to yield the following activation parameters: $\Delta H^{\ddagger} = 10.2 \pm 1.2$ kcal/mol and $\Delta S^{\ddagger} = 3.5 \pm 2.4$ eu. This is in very good agreement with our DFT computational results for the spiro-bis-dithiepin core.

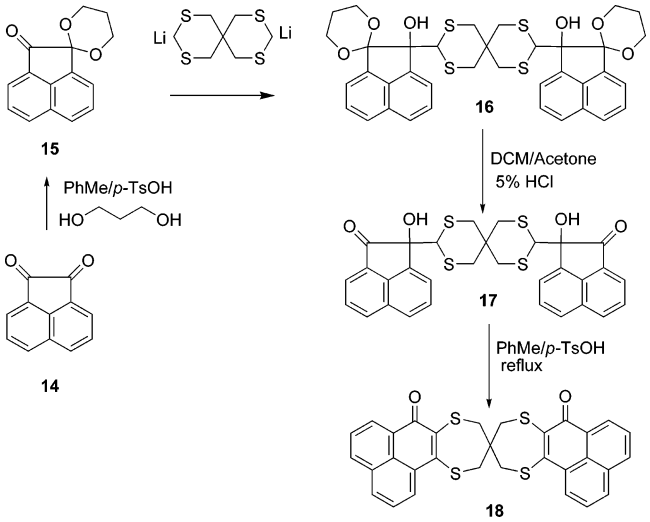
The long axis of the 4-formylphenyl moiety, primarily responsible for the direction of the local dipole in **5f**, forms a 148° angle with the chiral axis of the spiro-bis-dithiepin core. As a result, the dipole moments of the syn and anti bis-twist-(||)-**5f** conformers do not differ much from each other (Table 1).

The anti to syn conformational flip can more efficiently modulate the dipole moment of a system, in which local dipoles are more orthogonal to the long axis of the molecule. One solution, which potentially can achieve this objective, is to conjugate dithiepins' double bonds with a carbonyl directly. With this in mind, we have developed a straightforward synthetic approach to such α,β-unsaturated ketones starting with α-diketones (Scheme 3).

(4) This chemistry and related photochemical transformations will be reported in detail elsewhere.

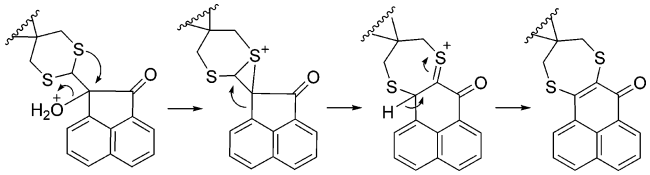
(5) Von Bredow, K.; Friebolin, H.; Kabuss, S. *Org. Magn. Reson.* **1970**, *2*, 43.

**Scheme 3**




A plausible mechanism of the **17** to **18** transformation involves a tandem ring expansion, i.e., (i) 1,2-sulfur migration producing the dithiepin ring, reciprocated by (ii) a 2,1-naphthyl migration furnishing fused six-membered cyclohexadienone (Scheme 4).[6]

**Scheme 4**



The carbonyl groups in **18** are perpendicular to the chiral axis of the molecule. The computed dipole moment of the syn conformer is rather large, 7.2 D, and directed almost exclusively along the *Y* axis (Figure 5 and Table 1). In the anti conformer, the dipole moment is 14 times smaller, due to canceling in the *XY* plane. Its residual value of 0.53 in the *Z* direction is primarily due to the slight deviation of the double bonds from coplanarity.

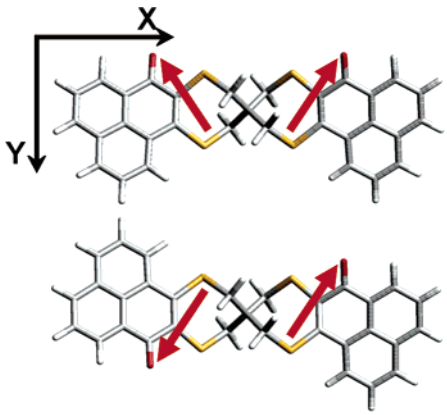



**Figure 5.** Local dipole alignment in syn (top) and anti (bottom) bis-twist-(ll)-**18**.

Experimental studies are underway to isolate individual enantiomers of **18** and to determine if solvent polarity or an external electric field could modulate their chiroptical properties. Changes in polarizability and hyperpolarizabilities in spiranes **6**−**11** and their photochromic properties, due to a photoinduced 1,3-hydrogen shift, are also being investigated.

**Acknowledgment.** We thank the National Science Foundation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for supporting this research.

**Supporting Information Available:** Spectral information and synthetic and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) A reviewer suggested an alternative mechanism: the alkene, formed via dehydration of the first species shown in Scheme 4, is protonated to give the S-stabilized cation which undergoes 1,2-naphthyl migration concomitant with $\beta$-sulfur participation. C−S cleavage followed by proton loss gives the observed product.