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1,1′-Bipyrroles: Synthesis and Stereochemistry

Sanjeev K. Dey and David A. Lightner*

Department of Chemistry, University of Nevada, Reno, Nevada 89557

lightner@scs.unr.edu

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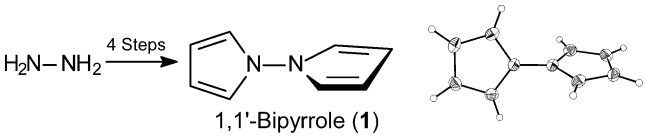

1,1′-Bipyrrole is synthesized in four steps from hydrazine. A colorless solid, mp 52 °C, it sublimes readily at room temperature and forms X-ray quality crystals in which the rings are not coplanar but are nearly orthogonal.

Bipyrroles[1] are *N*-heterocyclic analogs of biphenyl, although far less well studied. Bipyrrole articles entered the literature only about a dozen times during the first half of the last century; yet, in the past 25 years, there has been a relative explosion of interest in bipyrroles and bipyrrole-based more complex structures with more than 400 citations. Bipyrroles are found in nature as components of clinically interesting and important natural products for the treatment of cancer and viral and bacterial infection;[2] (in reduced form) in vitamin-B_{12};[3] in marine natural products;[4] in macrocyclic oligopyrroles for use as ionophores[5] and in medicine;[6] and in synthetic linear oligopyrrole conductive polymers.[7]

There are six different bond connections that can be drawn between two pyrrole molecules, leading to six constitutionally isomeric bipyrroles: 3 symmetric (1,1′; 2,2′; and 3,3′) and 3 nonsymmetric (1,2′; 1,3′; and 2,3′). All but one, 1,1′-bipyrrole, have C−C or N−C bonds linking the two pyrrole rings. Four of the six parent, unsubstituted bipyrroles (1,1′, 2,2′, 3,3′, and 2,3′) have been synthesized in 1976[8] and 1977,[9] and subsequent spectroscopic[10] and theoretical analyses[11,12] were reported in only a few publications. Unlike biphenyls and other biaryls, rotational stereochemistry (atropisomerism) about the interconnecting bond of the six possible bipyrrole isomers is not well understood.[1,12]

In contrast to the well-studied atropisomeric stereochemistry of biaryls,[13] there are only two known optically active bipyrroles: a 1,1′-bipyrrole (2,2′,5,5′-tetramethyl-1,1′-bipyrrole-3,3′-dicarboxylic acid)[14a] and a 2,2′-bipyrrole (1,1′,2,2′,5,5′-hexamethyl-2,2′-bipyrrole-3,3′-dicar-boxylic acid).[14b] Molecular orbital calculations and photoelectron spectroscopy have indicated a preference for orthogonal rings in 1,1′-bipyrrole.[10] *Ab initio* calculations on 2,2′-bipyrrole show it adopting preferentially an *anti*-clinal (*ac*) conformation at the global minimum with an N-2−2′-N′ torsion angle ∼148° and a 3−4 kcal/mol greater stability than the *sc* local minimum conformation, where the N-2−2′-N′ torsion angle is ∼46°.[11,12b] Theory also predicts the *ac* conformations of 3,3′- and 2,3′-bipyrrole to be the most stable.[11a,c]

Such theoretical predictions do not necessarily relate to the solid phase: an X-ray structure of 2,2′-bipyrrole shows it to adopt an *ap* planar conformation in the crystal.[12] There are no crystal structures available of any of the other parent constitutional isomers of bipyrrole. And although crystallographic structures of octa-substituted 1,1′-bipyrroles may not reflect that

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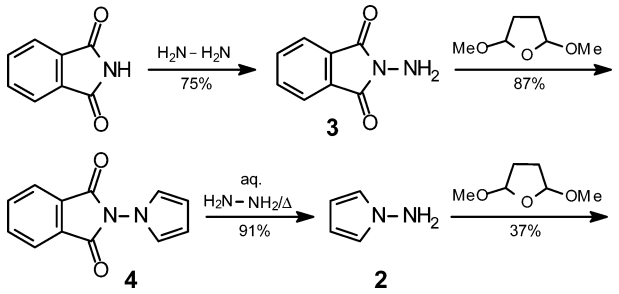
SCHEME 1



of the parent, octamethyl- and octa(trifluoromethylthio)-1,1′-bipyrrole were found to have orthogonal rings (92.4 and 92.8°, respectively).[15] Given the differences between the predicted conformation of 2,2′-bipyrrole and that found in its crystal, and the general prediction that bipyrroles are twisted, we were attracted to determine the crystal structure conformation of 1,1′-bipyrrole, which is a solid with a reported mp 57 °C.[9]

1,1′-Bipyrroles were apparently first synthesized in 1904,[16] the first bipyrroles (2,2′,5,5′-dimethyl-1,1′-bipyrrole-3,3′-dicarboxylic acid) to have been synthesized, by condensing 1,4-dione (ethyl 3-acetyl-5-oxohexanoate) with hydrazine in a reaction that proceeded stepwise through 1-aminopyrrole. Our syntheses of the parent 1,1′-bipyrrole (**1**) follows a similar path, as outlined in Scheme 1. It differs from the most recently published synthesis of **1**[9] in two ways: (1) improved yields at each step shown and (2) a shorter synthesis. The published synthesis converts 1-aminopyrrole (**2**)[17] to its succinimide derivative by reaction with succinic anhydride (50% yield), followed by treatment with pyrocatechol-phosphorus trichloride to give 2,5-dichloro-1,1′-bipyrrole in 59% yield and, finally, dechlorination by *n*-Bu_3SnH in 30% yield. The overall yield was 1.6−2.3% in the longer route vs 22% in a new shorter route shown below. The authors[9] indicate that a direct reaction of 1-aminopyrrole with 2,5-diethoxytetrahydrofuran to produce 1,1′-bipyrrole was not possible, that TLC of the reaction mixture showed two spots that gave the expected color reaction with Ehrlich's reagent. In our route (Scheme 1), we too converted phthalimide in 3 steps to 1-aminopyrrole, via **3** and **4**, in an overall yield of 49%. We found that the key final step, direct reaction of **2** with 2,5-dimethoxytetrahydrofuran, gave an acceptable yield of **1**. However, this low-melting solid sublimes easily at room temperature and low yields can result from such losses during isolation.

A crystal grown by sublimation proved suitable for an X-ray crystallographic determination that showed (Figure 1A) **1** to be twisted in the crystal, with an ∼80° interplanar angle. This result stands in stark contrast with that from the crystal structure of the 2,2′-bipyrrole isomer, in which the two rings lie coplanar.

The bond lengths and bond angles of the pyrrole rings of **1** (Figure 1B) find good correlation with those of pyrrole itself. Microwave spectroscopic analysis gave the following for pyrrole: N−C2, C2−C3, and C3−C4 bond lengths of 1.370, 1.382, and 1.417 Å, respectively; and C2−N−C5, N−C2−C3, and C2−C3−C4 bond angles of 109.8, 107.7, and 107.4°,

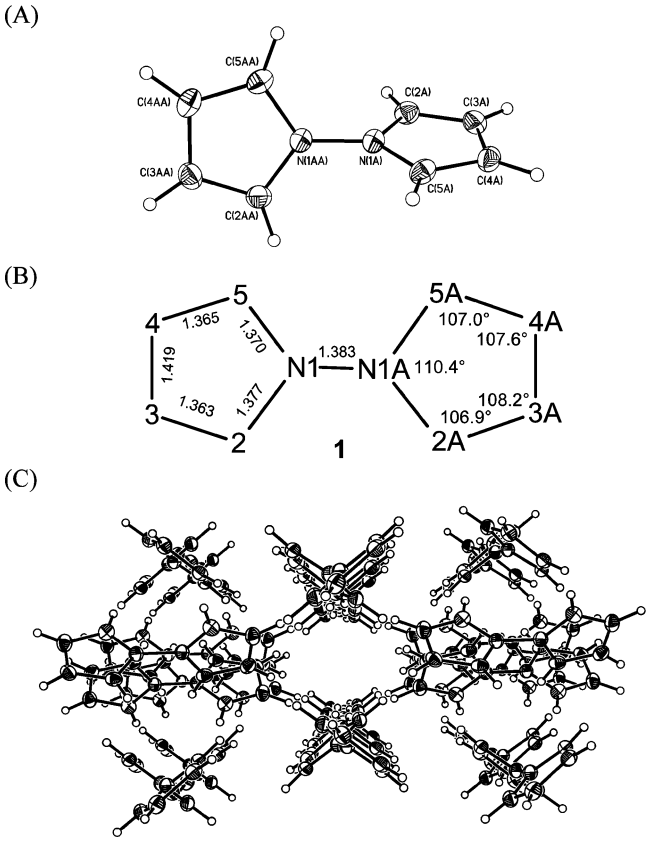


FIGURE 1. (A) Structural drawing of **1** in the crystal showing the atom numbering system. (B) Bond distances (Å) and angles (deg) found in the X-ray crystallographic structure of 1,1′-bipyrrole (**1**) with the numbering system used. The atoms of the leftmost pyrrole ring lie in a plane, as do those of the rightmost. The C(2)−N(1)−N(1A)−C(5A) torsion angle was found to be ∼80°, and the C(5)−N(1)−N(1A)−C(5A) torsion angle is ∼100°. (C) Packing arrangement of **1** in the crystal.

respectively.[18] Molecular mechanics calculations[19] agree reasonably well: 1.300, 1.335, and 1.469 Å; and 113.9, 107.6, and 105.4°, respectively, and predict a 1.393 Å N−N bond length. The N−N bond length of crystalline **1** is shorter than that of hydrazine (1.449 Å), determined by electron diffraction,[20] where the nitrogen geometry is pyramidal. A plot of the energy barrier[19] to rotation about the N−N bond of **1** is shown in Figure 2. Here, the minimum energy conformation also lies near a 90° interplanar angle. The higher barrier (∼7 kcal/mol above the minimum) corresponds to coplanar rings with the nitrogen lone pairs syn; the lower barrier (∼2 kcal/mol above the minimum) corresponds to coplanar rings with the nitrogen lone pairs anti. They are similar to the calculated (HF/6-31G*) barriers to rotation about the N−N bond of hydrazine.[21] From hydrazine's energy-minimum conformation, where the lp-N−N-lp torsion angle is 90°, the two barriers to rotation are: 0° (∼10.5 kcal/mol), where the lone pairs are syn, and 180° (∼3.3 kcal/mol), where the lone pairs are anti.[21]

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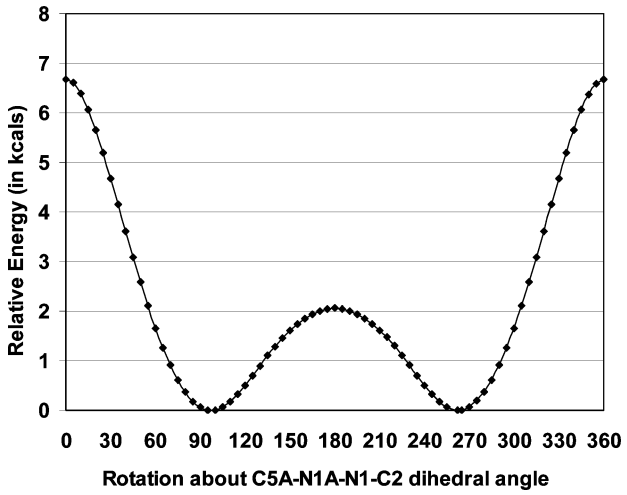

FIGURE 2. Plot of total energy (kcal/mol) vs angle of rotation about the N−N bond of **1**. The minima lie at 95 and 265°. The maxima corresond to the planar molecule, with syn (0° rotation angle) and anti (180° rotation angle) nitrogen lone pairs.

The synthetic methodology of the current work suggests the possibility of making 2,2′-di-*t*-butyl-1,1′-bipyrrole for studies of atropisomerism and possible chiral resolution.

Experimental Section

For general procedures of the synthesis, see ref 12.

***N*-Aminophthalimide (3).**[22] This variation of the reported procedure[17] avoids heating, which causes **3** to rearrange to the phthalhydrazide. To an ice-cold suspension of 14.7 g (0.1 mol) of phthalimide in 100 mL of 95% ethanol at 5 °C, with stirring, 3.6 mL (0.11 mol) of 99% hydrazine was added dropwise. A slightly exothermic reaction was observed, and the mixture was allowed to stir at 5 °C for 2 h. The mixture was then diluted with 200 mL of ice−water, stirred, filtered, washed with water, and dried in air to give 75% of pure product **3**, mp 199−200 °C (lit.[22] 199−202 °C). It had ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.57 (brs, 2H), 7.73 (dd, 2H, J = 5.0, 3.0 Hz), 7.85 (dd, 2H, J = 5.0, 3.0 Hz) ppm and ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.0(s), 134.5 (s), 130.5 (d), 123.4 (d) ppm.

***N*-Phthalimidopyrrole (4).**[17,23] A solution of **3** (2.5 g, 2.54 mmol) and 2.5 mL (19.3 mmol) of 2,5-dimethoxytetrahydrofuran in dioxane (25 mL) was heated at reflux until a yellow solution was obtained. While maintaining heating, 2.5 mL of 5 N HCl was carefully added, and the yellow solution became darker. The mixture was cooled, and the resultant precipitate was filtered and washed with a 1:3 mixture of dioxane−water to yield 87% of the product **4**, mp 208−209 °C (lit.[24] mp 218.5 °C). It had ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.37 (dd, 2H, J = 2.0, 2.5 Hz), 6.75 (dd, 2H, J = 2.0, 2.5 Hz), 7.86 (dd, 2H, J = 5.5, 3.0 Hz) and 7.99 (dd, 2H, J = 5.5, 3.0 Hz) ppm and ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.6 (s), 135.3 (s), 129.8 (d), 124.6 (d), 121.7 (d), 109.3 (d) ppm.

1-Aminopyrrole (2).[23,24] **4** (11.5 g, 54.2 mmol) was dissolved in ∼150 mL of CH_3OH, and to this solution was added ∼5 mL of 99% hydrazine monohydrate. The reaction was heated at reflux for 1 h and after cooling was treated with AcOH (3 mL). The mixture was further heated at reflux for 15 min, then it was filtered, and the resultant white precipitate was washed with CH_3OH. The filtrate was evaporated *in vacuo*, and the solid residue was treated with an excess of 40% aq. NaOH until the solid residue dissolved. The aqueous layer was evaporated *in vacuo* to give 4.00 g of pure product (91%). It had ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.86 (brs, 2H), 6.05 (dd, 2H, J = 2.0, 2.5 Hz) and 6.70 (dd, 2H, J = 2.0, 2.5 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 106.6 (α-C) and 122.2 (β-C) ppm.

1,1′-Bipyrrole (1). 2 (0.5 g, 6.1 mmol) was dissolved in 10 mL of 1,4-dioxane and to this solution was added ∼0.9 g (6.9 mmol) of 2,5-dimethoxytetrahydrofuran. The solution was heated at reflux for 72 h; then, while keeping it warm, ∼2 mL of 5 N HCl was added, and the entire solution turned brown. The solution was then cooled and extracted (6 × 50 mL) with *n*-hexane. The organic layer was dried over anh. Na_2SO_4 and evaporated to a volume of ∼10 mL by a stream of air. Colorless 1,1′-bipyrrole crystallizes out but goes back to solution. The reduced volume of hexane-containing product was transferred to a sublimator. The cold finger was cooled to −30 °C, and the sublimator was connected to a high vacuum pump and the bipyrrole crystals were collected shortly on the cold finger. The cold finger was removed carefully, and the solid was scraped off and collected to give 295 mg (37% yield) of product **1** [mp 52 °C (sealed tube)] (lit.[9] mp 57 °C). (n.b.: product is very volatile; even keeping at RT reduces the weight of the product.) ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.20 (dd, 4H, J = 2.0, 2.5 Hz) and 6.91 (dd, 4H, J = 2.0, 2.5 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 107.6 (α-C), 121.6 (β-H) ppm.

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Supporting Information Available: NMR spectra and X-ray experimental data. This material is available free of charge via the Internet at http://pubs.acs.org.

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