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Macrobicyclic Phosphanes

Dibridgehead Diphosphines that Turn Themselves Inside Out**

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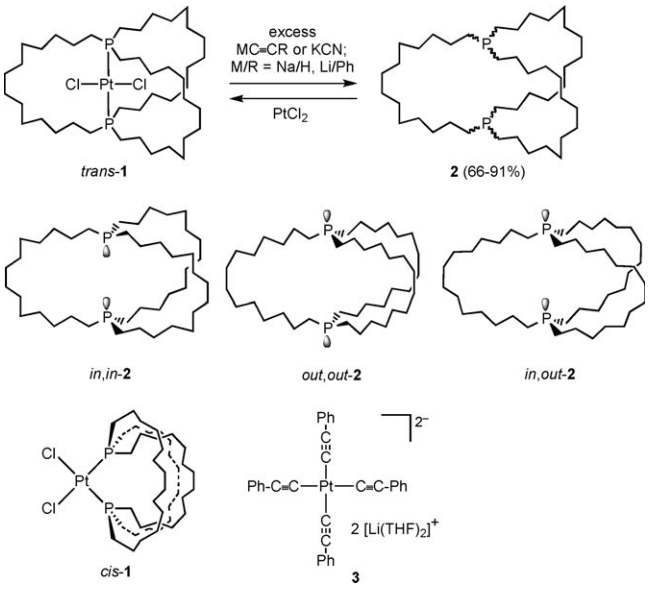
Molecules and macromolecules that undergo topologically complex dynamic processes—such as knot-forming[1] and multistep folding[2] sequences—have attracted considerable attention from numerous standpoints. However, there is much less awareness that certain types of molecules, including but not limited to macrocyclic bicyclic (macrobicyclic) compounds, are able to turn themselves inside out.[3] This has been termed "homeomorphic isomerization",[4] even though the process can be degenerate. At the time of a 1996 review,[3] only four (degenerate) cases had been rigorously established by spectroscopic means.[5] Although we are unaware of additional confirmed examples since, such equilibria have been invoked to rationalize the NMR spectroscopic properties of other macrobicyclic compounds.[6]

Herein we demonstrate this type of dynamic behavior—in both degenerate and nondegenerate manifestations—with three stereoisomers of a macrobicyclic aliphatic dibridgehead diphosphine (*in*,*in*, *out*,*out*, and *in*,*out*, referring to the orientations of the lone pairs of electrons on the phosphorus atoms[3]). In the nondegenerate case, the lone pairs of electrons are alternately directed in a convergent manner towards an interior domain (*in*,*in*) or directed externally (*out*,*out*). Thus, such processes can potentially mediate the sequesterization, transport, and delivery of Lewis acid guests. Analogous dynamic behavior has recently been proposed for a hexaaryl dibridgehead diphosphine[6b] and other types of aromatic dibridgehead diphosphorus compounds.[6a,c]

Our story begins with the platinum dichloride complex *trans*-**1** (Scheme 1), in which three $(CH_2)_{14}$ chains connect the *trans*-arranged phosphorus atoms.[7] This complex exemplifies a class of compounds termed "gyroscope like", because of the rapid rotation of the caged ML_n moieties in suitably sized systems on the NMR time scale, and their structural similarities to common toy gyroscopes.[7–9] Treatment of *trans*-**1** with an excess of the nucleophiles NaC≡CH, LiC≡CPh, or KC≡N afforded the macrobicyclic dibridgehead diphosphine **2** as an analytically pure, moderately air-sensitive white powder in 66–91% yield. The dianionic platinum tetrakis(acetylide) complex **3** could also be isolated (35%) when LiC≡CPh was employed.



Scheme 1. Synthesis and complexation of the dibridgehead diphosphine **2**.

The three *in*/*out* stereoisomers of **2** are depicted in Scheme 1 (middle). In the $PtCl_2$ adduct **1**, both lone pairs of electrons of the dibridgehead diphosphine ligand are directed inwards. Treatment of **2** with $PtCl_2$ in C_6D_6 regenerated **1**, which constitutes an overall retention of configuration at the phosphorus atoms. For this reason, it was originally thought that only *in*,*in*-**2** was produced. For small bicycles, *out*,*out* isomers are energetically much more favorable, but computational data for analogous hydrocarbons indicate that *in*,*out* isomers become most stable at medium ring sizes, and that *in*,*in* isomers become most stable at larger ring sizes.[10] DFT calculations (see the Supporting Information) indicated (as did preliminary molecular mechanics calculations) that *in*,*in*-**2** was considerably more stable than *out*,*out*-**2** (6.98 kcal mol^{-1}), and somewhat more stable than *in*,*out*-**2** (1.59 kcal mol^{-1}). The longest aliphatic dibridgehead diphosphine reported previously features one $(CH_2)_3$ and two $(CH_2)_4$ chains, which are much shorter than the $(CH_2)_{14}$ linkers in **2**.[11]

The isomers of **2** can be regarded as configurational diastereomers that are interrelated by pyramidal inversions at

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the phosphorus atoms. In classic studies, Baechler and Mislow established that such inversions in simple trialkylphosphines require 29–36 kcal mol^{-1},[12] which corresponds to a very slow process at room temperature. This is consistent with the many chiral PRR′R″ species that can be generated in enantiopure form.[13] Thus, we did not expect to encounter any facile configurational equilibria involving **2**.

^{31}P NMR spectra of **2** were recorded in various solvents at low-temperature. After some time, we became convinced that a small signal reproducibly appeared in [D$_8$]toluene (area ratio 97:3; Figure 1).[14] A ^{31}P EXSY experiment established that the species responsible for the two signals are in equilibrium ($\Delta G_{193K} = 1.33$ kcal mol^{-1}). Line-broadening analyses indicated $\Delta G^{\neq}_{193K}$ values of 11.5 and 10.4 kcal mol^{-1} (major to minor and minor to major isomers, respectively), which are much lower than those for pyramidal inversions of trialkylphosphines.

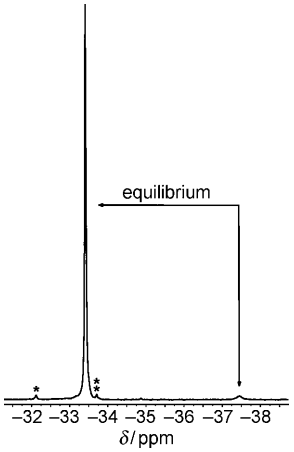


Figure 1. ^{31}P{^{1}H} NMR spectrum of **2** in [D$_8$]toluene at −80 °C (the arrows denote exchanging species; * and ** denote unknown and known impurities, respectively).

With the help of models, we then realized that *in*,*in*-**2** and *out*,*out*-**2** can be interconverted by a purely conformational process not involving phosphorus inversion or a "homeomorphic isomerization". This process corresponds to pulling one of the $(CH_2)_{14}$ chains connecting the phosphorus atoms through the macrocycle defined by the other two chains (Scheme 2, top left). The minor signal would correspond to *out*,*out*-**2**. This constitutes the first time such a process has been established for an *in*,*in*/*out*,*out* pair of isomers.[3] In this context, it is relevant that *cis*-**1** (Scheme 1) can be independently prepared.[15] The idealized 90° angle between the lone pairs of electrons on the phosphorus atoms demonstrates the inherent flexibility of **2**.[16]

This mechanistic model would be strengthened by a sample of *in*,*out*-**2**. If *in*,*out*-**2** were stable with respect to the other two isomers at room temperature, a pyramidal inversion sequence with anomalously low barriers would be definitively excluded.[17]

In the most direct approach, **2** was heated in mesitylene at 150 °C and monitored by ^{31}P{^{1}H} NMR spectroscopy. A new species, assigned as *in*,*out*-**2**, slowly formed. After 40 h, a 51:49 equilibrium mixture (*in*,*in*/*out*,*out* versus *in*,*out*) was present. The data gave a ΔG_{423K} value of 0.034 kcal mol^{-1} and a $\Delta G^{\neq}_{423K}$ value of 33.8 kcal mol^{-1}. The latter is in good agreement with the results of Baechler and Mislow.

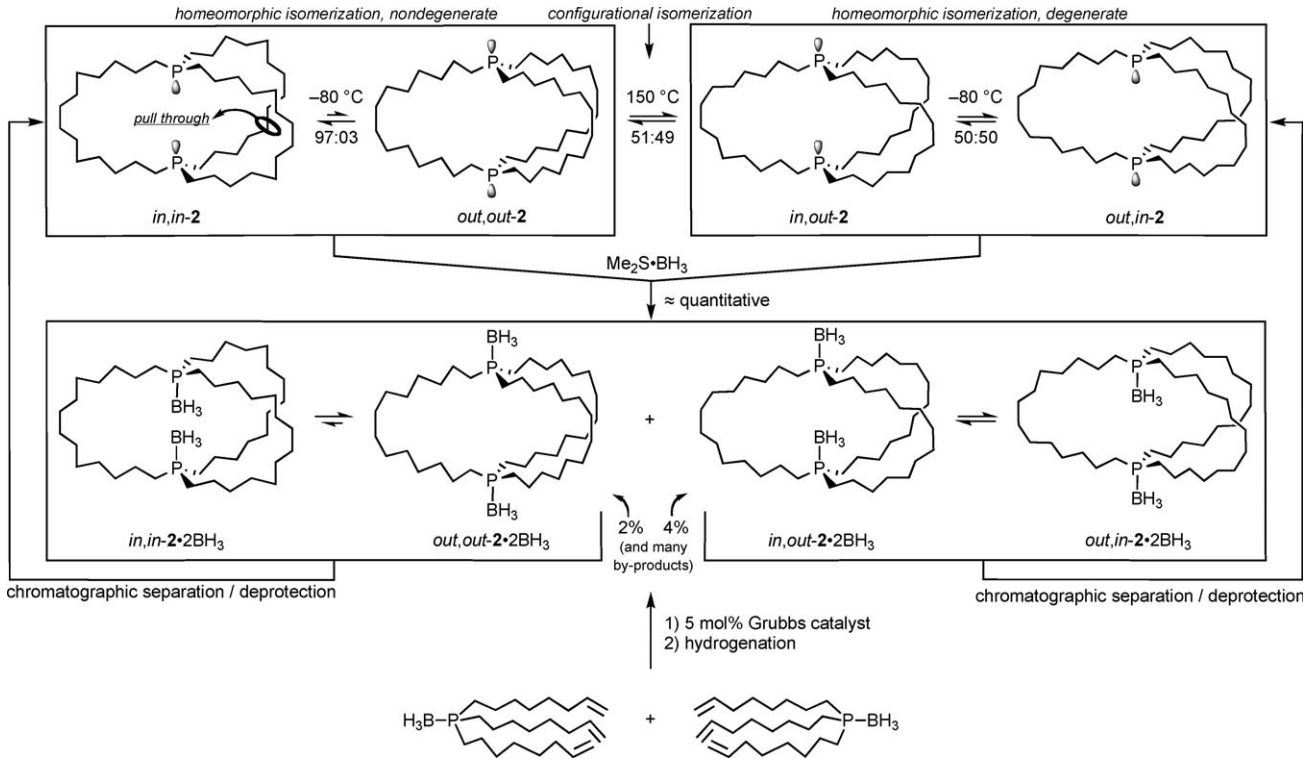
As shown in Scheme 2, this sample was treated with excess $Me_2S{\cdot}BH_3$. Chromatographic separation on silica gel gave the bis(borane) adducts (*in*,*in*/*out*,*out*)-**2**·2 BH_3 as a slowly solidifying oil and *in*,*out*-**2**·2BH_3 as a colorless viscous liquid in yields of 43 and 42 %, respectively. In a second route, the phosphine borane $H_3B{\cdot}P((CH_2)_6CH{=}CH_2)_3$[18] was treated with the Grubbs catalyst. Such an alkene metathesis would be expected to yield much oligomer, polymer, and other by-products. However, subsequent hydrogenation (Wilkinson catalyst) and column chromatography afforded (*in*,*in*/*out*,*out*)-**2**·2 BH_3 and *in*,*out*-**2**·2 BH_3 in yields of 2 and 4 %, respectively. Although these are poor yields, the route is not stoichiometric in platinum.

The bis(borane) adduct *in*,*out*-**2**·2 BH_3 could be deprotected in neat pyrrolidine at reflux. Workup afforded *in*,*out*-**2** in 56 % yield as an analytically pure, moderately air-stable, colorless oil. Importantly, *in*,*out*-**2** exhibited a single signal in the ^{31}P NMR spectrum, although from symmetry considerations two would have been expected. This implies that a degenerate *in*,*out*/*out*,*in* homeomorphic isomerization is rapid on the NMR time scale (Scheme 2, top right). Accordingly, a solution of *in*,*out*-**2** in CH_2Cl_2 was cooled, and ^{31}P NMR spectra were recorded. As shown in Figure 2, two signals of equal intensities separated ($T_c = -73$ °C). The data yielded a $\Delta G^{\neq}_{200K}$ value of 8.5 kcal mol^{-1}.

The adducts **2**·2 BH_3 illustrate additional nuances of these topological equilibria. First, the presence of progressively larger Lewis acids on the lone pairs of electrons of the phosphorus atoms should eventually render *out*,*out* isomers more stable than *in*,*in* isomers. Indeed, when samples of (*in*,*in*/*out*,*out*)-**2**·2 BH_3 were crystallized from hexanes or methylcyclohexane, *out*,*out*-**2**·2 BH_3 was obtained, but always with a guest molecule in the cavity. A representative structure, which features methylcyclopentane, a known component of hexanes, is given in Figure 3. The phosphorus–phosphorus distance expands to 13.22 Å, from 4.61 Å in *trans*-**1**, thereby underscoring the conformational flexibility of the diphosphine.

Similarly, progressively larger phosphorus-bound Lewis acids should eventually render an *in*/*out* isomer untenable. In this case, alternative conformations featuring *out*/*out* phosphorus substituents and crossed $(CH_2)_{14}$ chains may become preferred. The homeomorphic isomerization of *in*,*out*-**2** presumably involves crossed-chain species, illustrated by **IV** and **VI** in Scheme 3, which summarizes the principal equilibria in our system.[19] There remain many subtle unresolved issues, such as whether the equilibration of *in*,*in*-**2** and *out*,*out*-**2** involves a concerted disrotatory bridgehead motion or an intermediate with crossed chains generated by a "half turn". Experiments to address such points are in progress.

Various extensions of the above concepts are shown in Scheme 4. First, similar inside-out conformational equilibria should be possible with structures of the types **VII** and **VIII**. The former could operate in the case of 1,3,5-cyclophanes



Scheme 2. Isomerization of **2** and syntheses of BH_3 adducts.

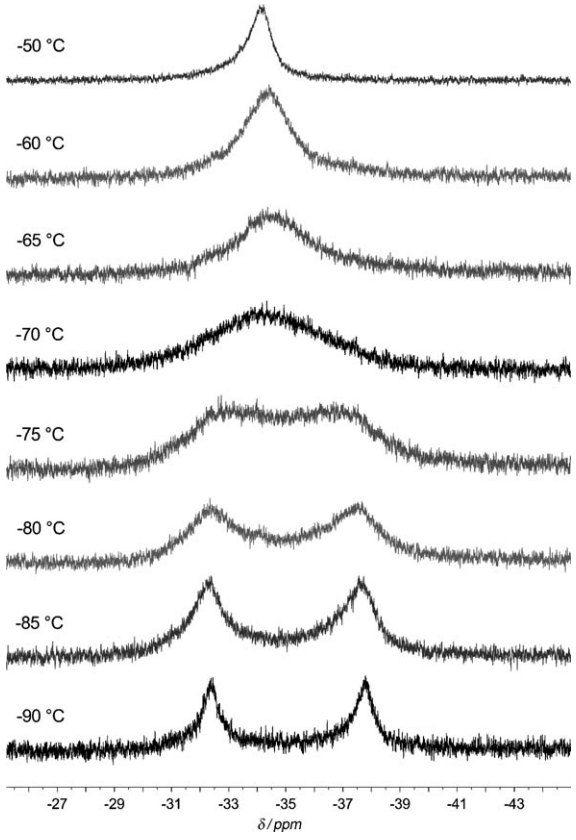


Figure 2. Low-temperature $^{31}P\{^1H\}$ NMR spectra of *in,out*-**2**.

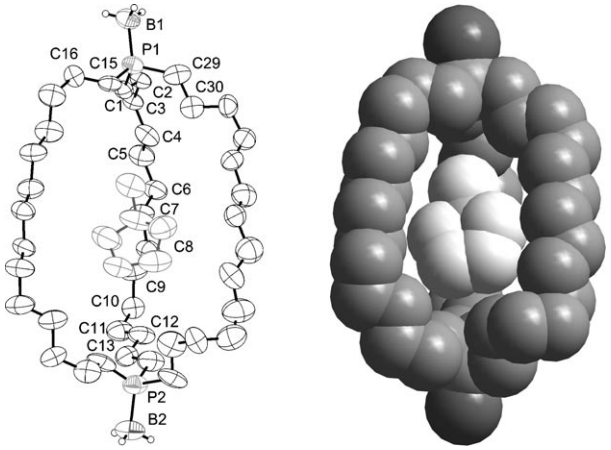
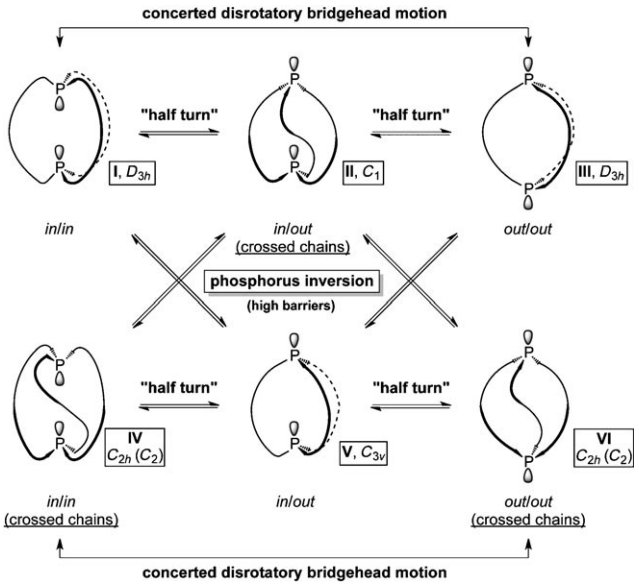
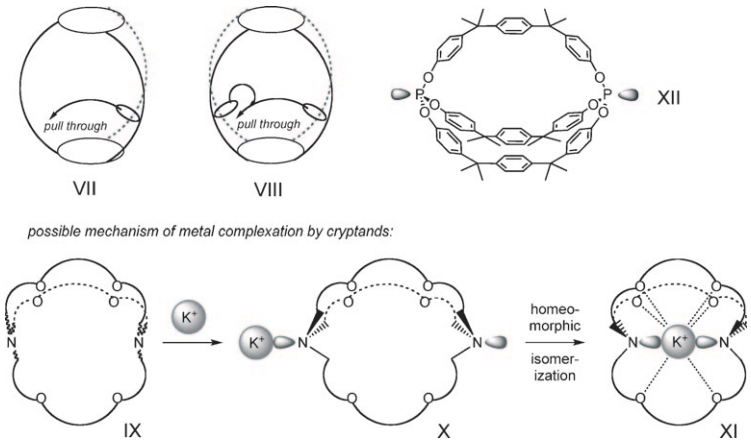


Figure 3. Crystal structure of *out,out*-**2**·2 BH_3·($C_5H_9CH_3$). The carbon atoms C1–C14 and C15–C18 exhibited disorder, which could be modeled; the dominant conformation is depicted.

with sufficient bridge lengths.[20] Type **VIII** structures have four bridges, with isomerization involving pulling two of them through the macrocycle defined by the remaining two. Many dibridgehead diamines exist, but *in*/*out* isomers preferentially interconvert through pyramidal inversion at the nitrogen atom, because of the much lower energy barriers. The corresponding protonated diammonium salts isomerize through deprotonation/inversion sequences.[3,4] However, the complexation of metal ions by cryptands may involve initial



Scheme 3. Summary of key equilibria.[19]



Scheme 4. Other relevant reactions and structures.

binding to an *out* lone pair of electrons, followed by a homeomorphic isomerization, as illustrated by **IX**–**XI**. To our knowledge, this pathway has not been considered previously in the literature. An analogous mechanism is likely for the reconstitution of *trans*-**1** from $PtCl_2$ and **2** (Scheme 1). Finally, other families of isomeric macrobicyclic dibridgehead diphosphorus compounds, as exemplified by **XII**, have been reported,[6] and it should be possible to demonstrate analogous dynamic behavior by appropriate NMR investigations and preparative experiments.

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[14] Analogous separation of the signals is not observed in $CDFCl_2$ at −100 °C (precipitation begins at lower temperatures, thus degrading the signal). Very slight signal broadening gradually occurs between −10 and −70 °C ($w_{1/2}$ = 7.6–22.2 Hz), which then drops (15.5 and 13.9 Hz at −80 and −100 °C). In contrast, the signal in [D_8]toluene broadens dramatically between 27 and −40 °C ($w_{1/2}$ = 5.8–93.0 Hz), and then sharpens (72.4, 26.2, 9.7, and 6.3 Hz at −50, −60, −70, and −80 °C). Thus, it is possible that solvent adducts analogous to that in Figure 3 might play a role in these equilibria.
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[16] Since *trans*-**1** and *cis*-**1** do not interconvert within 14 h at 180 °C, *trans*/*cis* isomerization cannot play a role in Scheme 1.
[17] Certain reactions of dibridgehead diphosphines based upon smaller rings can afford species with phosphorus–phosphorus bonds, for which inversions at phosphorus atoms have been documented: a) R. W. Alder, D. Read, *Angew. Chem.* **2000**, *112*,

3001 – 3004; *Angew. Chem. Int. Ed.* **2000**, *39*, 2879 – 2882; b) see also R. W. Alder, C. P. Butts, A. G. Orpen, D. Read, *J. Chem. Soc. Perkin Trans. 2* **2001**, 288 – 295.

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[19] The point groups given in Scheme 3 are a function of whether the phosphorus–carbon bonds, as viewed in Newman-type projections down the phosphorus–phosphorus vectors, are eclipsed (**I**, **III**, and **V**) or staggered (**II**, **IV**, **VI**). There is a C_2 axis in **IV** and **VI** that leads to exchange of the phosphorus atoms, which are inequivalent in **V**.

[20] For *in*/*out* isomers in 1,3,5-cyclophanes tethered to bridgehead atoms, see R. A. Pascal, Jr., *Eur. J. Org. Chem.* **2004**, 3763 – 3771.

