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Configurational Lability at Tetrahedral Phosphorus: *syn/anti*-Isomerization of a P-Stereogenic Phosphiranium Cation by Intramolecular Epimerization at Phosphorus

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Abstract: Tetrahedral main group compounds are normally configurationally stable, but P-epimerization of the chiral phosphiranium cations *syn*- or *anti*-[Mes*P(Me)CH_2CHPh][OTf] (Mes* = 2,4,6-(*t*-Bu)$_3C_6H_2$) occurred under mild conditions at 60 °C in CD_2Cl_2, resulting in isomerization to give a *syn*-enriched equilibrium mixture. Ion exchange with excess [NBu_4][Δ-TRISPHAT] (Δ-TRISPHAT = Δ-P(*o*-$C_6Cl_4O_2$)$_3$) followed by chromatography on silica removed [NBu_4][OTf] and gave mixtures of *syn*- and *anti*-[Mes*P(Me)CH_2CHPh][Δ-TRISPHAT]•x[NBu_4][Δ-TRISPHAT]. NMR spectroscopy showed that isomerization proceeded with epimerization at P and retention at C. DFT calculations are consistent with a mechanism involving P–C cleavage to yield a hyperconjugation-stabilized carbocation, pyramidal inversion promoted by σ-interaction of the P lone pair with the neighboring β-carbocation, and ring closure with inversion of configuration at P.

Tetrahedral carbon with four different substituents is the textbook example of a chiral molecule (Scheme 1).[1] Analogous four-coordinate main group compounds including silanes,[2] quaternary ammonium salts,[3] and P-stereogenic phosphine oxides,[4] phosphine-boranes,[5] and phosphonium salts[6,7] are also configurationally stable. Because tetrahedral-planar interconversion is unfavorable,[8] epimerization requires reversible cleavage of a bond between the central atom and a substituent. This process can be promoted by strain in cyclopropanes, leading to epimerization of one C-stereocenter or two (racemization) on heating (Scheme 1).[9] We hypothesized that P–C cleavage in the isoelectronic phosphiranium cations would occur under mild conditions, since their ring strain is comparable to that in cyclopropane,[10] and the neutral phosphine would be a good leaving group.[11] However, phosphiranium cations are rare,[12] and little is known about their reactivity,[13] despite their "spring-loaded" nature.[14] To probe the stereochemistry of ring opening, we targeted derivatives **A** containing both P- and C-stereocenters, which have not yet been prepared in enantiomerically enriched form.12[a] Proposed ring-opening intermediate **B**, with a pyramidal phosphine and a trigonal planar carbocation, could lead to isomerization via two pathways (Scheme 1). In route 1, rotation about the C–C bond, normally a fast process, followed by nucleophilic cyclization, would yield diastereomer **C** with retention at P and inversion at C. Alternatively, phosphorus pyramidal inversion in **B**, usually slow,[15] and subsequent ring closure would give diastereomer **D** with inversion at P and retention at C (route 2). We report here that isomerization of enantiomerically enriched **A** occurred under mild conditions, as expected, but, surprisingly, with the stereochemistry of route 2, preserving the configuration of the normally labile C-stereocenter, while inverting the usually configurationally stable phosphorus.[16] To rationalize this unexpected behavior, we propose an intramolecular mechanism in which an intermediate pendant β-carbocation promotes low-barrier pyramidal inversion at phosphorus, while hyperconjugative stabilization from a P–C σ-bond preserves the cation's C-chirality.[17]

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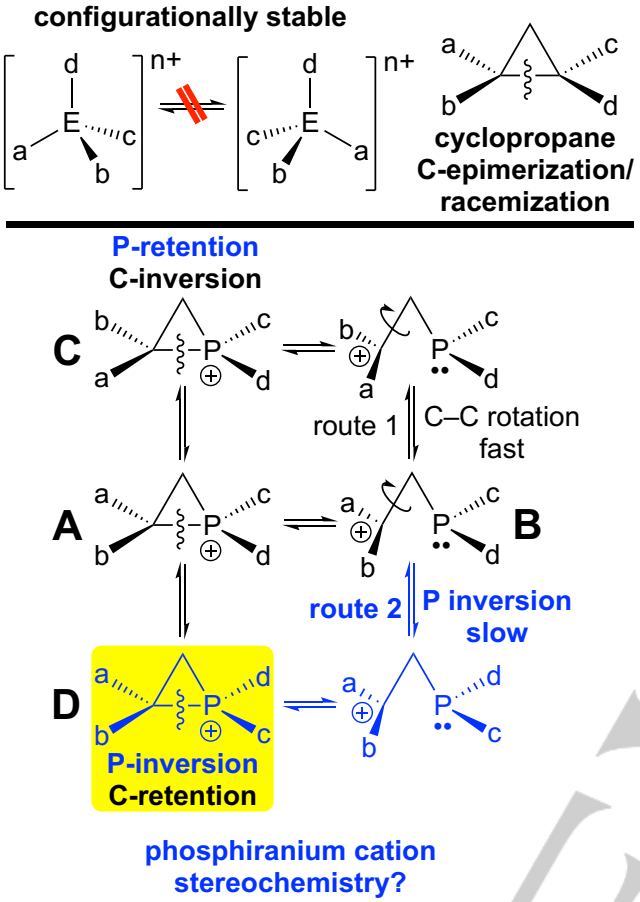
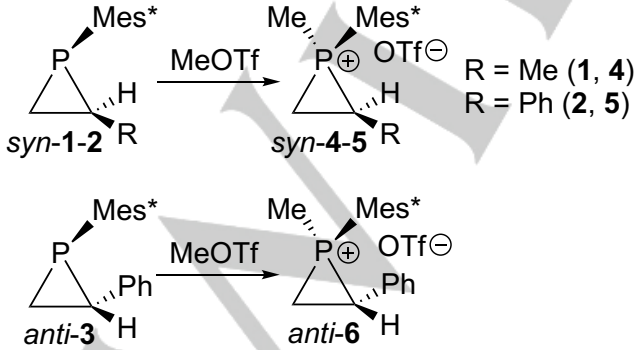


Scheme 1. Configurationally Stable Tetrahedral Main Group Compounds (E = C, Si, n = 0; E = N, P, n = 1) and Stereochemistry of Isomerization in Cyclopropanes (Known) and Phosphiranium Cations (New, This Work)

Treatment of the racemic or enantiomerically enriched phosphiranes *syn*- or *anti*-Mes*PCH$_2$CHR (Mes* = 2,4,6-(*t*-Bu)$_3$C$_6$H$_2$, R = Me (**1**) or Ph (**2-3**))[18] with methyl triflate gave the phosphiranium cations **4-6** as air-stable white solids (Scheme 2).



Scheme 2. Synthesis of P-Stereogenic Phosphiranium Cations

The crystal structures of **4-6**, in comparison to those of related phosphiranes,18 showed that methylation resulted in shorter P–C bonds and increased exocyclic angles at phosphorus (Figure 1 and Supporting Information). These structural changes are consistent with a change in phosphorus hybridization on quaternization, from essentially unhybridized in the phosphiranes to approaching sp^3 hybridization in the cations. This increase in s-character is consistent with the P–C bond shortening,[19] as also seen upon quaternization of **5** and **6** as ligands in metal complexes.[20]

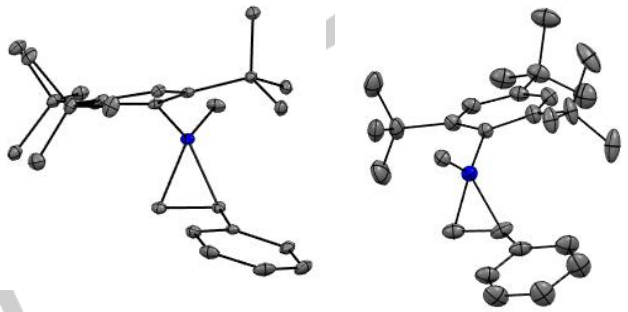
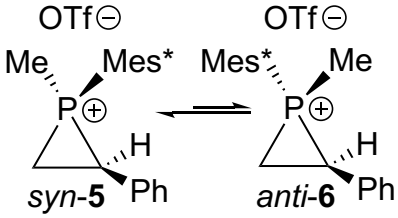


Figure 1. ORTEP diagrams of *syn*-(R_P,S_C)-**5** (left) and *anti*-(S_P,S_C)-**6**•CH_2Cl_2 (right), with the triflate anions and solvent and disorder in **6** omitted.

Heating either *syn*-**5** or *anti*-**6** in CD_2Cl_2 at 60 °C resulted in slow isomerization (days) to give a *syn*-enriched equilibrium mixture (Scheme 3). Determination of K_{eq} (1.4(1)) starting with pure *syn*-**5** or *anti*-**6** was complicated by decomposition at long reaction times, but mixtures of the diastereomers reached equilibrium more quickly. These observations were consistent with the computed *syn*/*anti* free energy difference, 0.7 kcal/mol (gas-phase B3LYP-D3/6-311G**++/ZPE). The change in concentrations of *syn*-**5** and *anti*-**6** over time was consistent with a first-order approach to equilibrium.[21]



Scheme 3. *syn-anti* Isomerization Equilibrium (K_{eq} = *syn*-**5**/*anti*-**6** = 1.4(1))

To determine the stereochemical features of this isomerization, we used the commercially available chiral anion [Δ-TRISPHAT],[22] which has been applied previously to differentiate enantiomers of chiral phosphonium[23] and thiiranium cations.[24] Treatment of *syn*-**5**, *anti*-**6**, or their mixtures with one or more equiv of [NBu$_4$][Δ-TRISPHAT], followed by chromatography on silica, removed [NBu$_4$][OTf], as demonstrated by $^{19}F\{^1H\}$ NMR spectroscopy (Scheme 4). The resulting material had the

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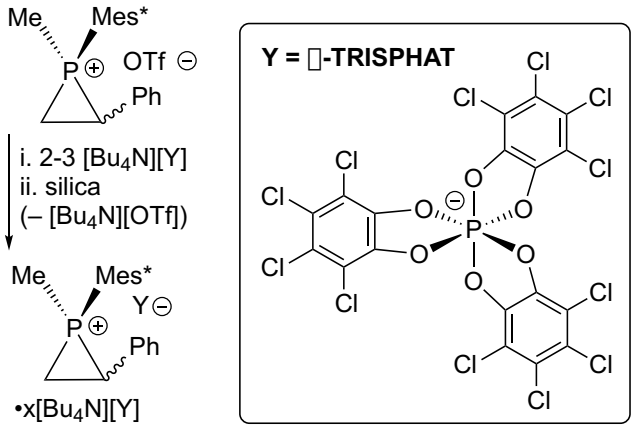
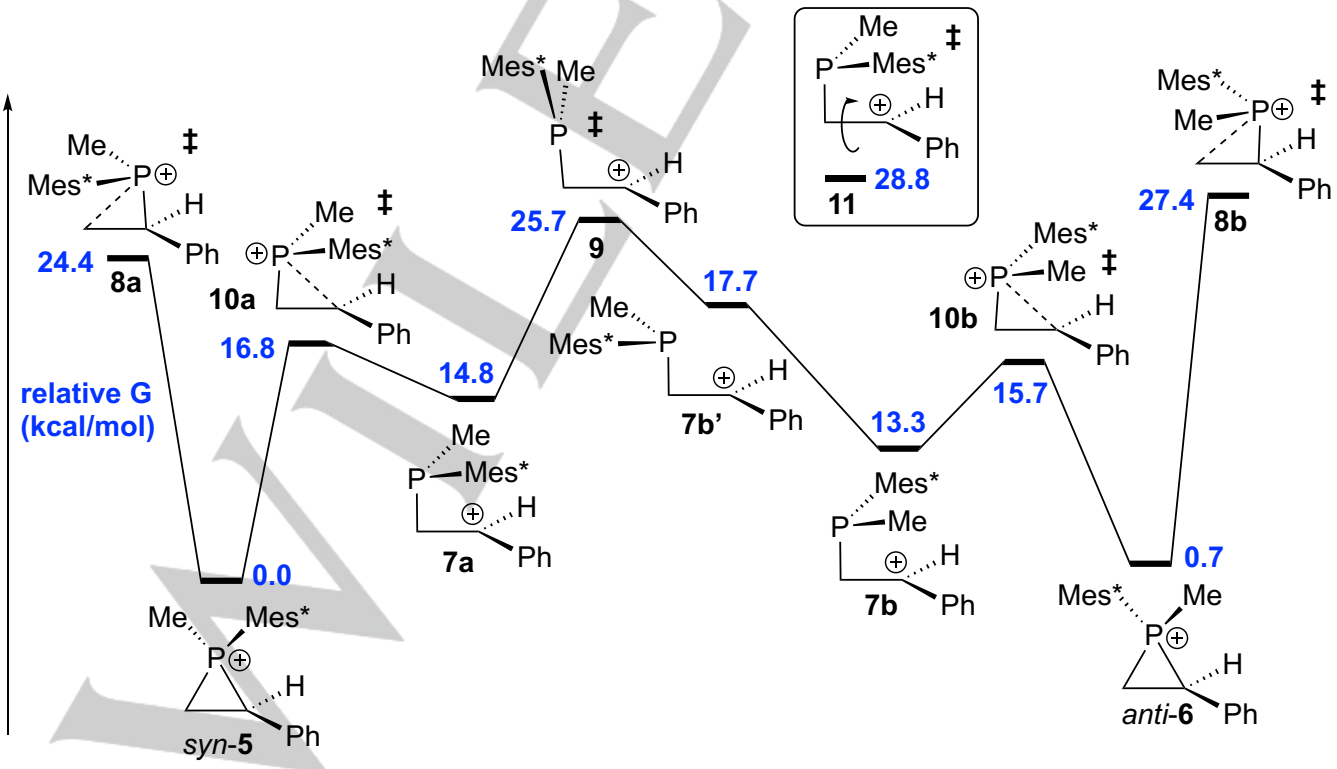
composition [phosphiranium][Δ-TRISPHAT]•x[NBu4][Δ-TRISPHAT], where x-values, determined by ^{1}H NMR integration and elemental analyses, depended on the excess of [NBu4][Δ-TRISPHAT] used. ^{31}P{^{1}H} and ^{1}H NMR spectroscopy on these mixtures in CD_2Cl_2 distinguished signals of the enantiomeric cations in the diastereomeric salts.



Scheme 4. Ion Exchange and Chromatography on Silica Removed [NBu4][OTf] and Gave Δ-TRISPHAT Phosphiranium Salts Containing Additional [NBu4][Δ-TRISPHAT]

Triflate salts of either racemic or enantiomerically enriched *syn*-**5** or *anti*-**6** were separately heated in CD_2Cl_2 at 60 °C to about 15% conversion, to minimize the decomposition observed at longer reaction times. Treatment with 3 equiv of [NBu4][Δ-TRISPHAT] and column chromatography on silica then gave [phosphiranium][Δ-TRISPHAT]•x[NBu4][Δ-TRISPHAT] in about 60-70% yield. Despite these losses of the phosphiranium cation on the column, the *syn*/*anti* ratio was maintained before and after ion exchange/chromatography, and the two enantiomers of enriched **5**, and those of **6**, behaved similarly, suggesting that this process did not lead to any diastereomeric enrichment. NMR spectroscopy showed that (S_P,R_C)-*syn*-**5** and (R_P,R_C)-*anti*-**6**, and (R_P,S_C)-*syn*-**5** and (S_P,S_C)-*anti*-**6**, were interconverted, i.e. the isomerization proceeded intramolecularly with epimerization at phosphorus and retention at carbon (Scheme 1, see the SI, including Figures S68-S69, for details). Partial isomerization of [phosphiranium][Δ-TRISPHAT]•x[NBu4][Δ-TRISPHAT] gave similar results, complicated by apparent TRISPHAT racemization (see the SI for details).

DFT calculations (B3LYP-D3/6-311G**++/ZPE) and literature precedents suggested a plausible mechanism for the isomerization, which rationalizes the observed stereochemistry (Scheme 5). [25] First, as in Scheme 1, ring opening gives intermediates **7a**-**b**, phosphines with a pendant benzylic β-carbocation. Like the related secondary phosphine cation [Mes*PHCH$_2$CHR]$^+$, a proposed intermediate in selective formation of phosphiranes **1**-**3**,18 cations **7** are stabilized by hyperconjugation from the P–CH$_2$ bond to the empty β-CHPh p-orbital, which also prevents loss of stereochemical information at carbon via rotation about the CH$_2$-CHPh bond (high-energy transition state **11**).17 As expected, cleavage of the P-CH$_2$ bond in **5** or **6** via transition states **8a**-**b** was much less favored, since these primary β-cations lack benzylic stabilization. We were unable to locate stable "open" forms of the cations resulting from this P-CH$_2$ cleavage, analogous to diastereomers **7a** and **7b**.



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Scheme 5. Proposed Mechanism of Isomerization, Including Computed Free Energies (B3LYP-D3/6-311G**++/ZPE) for Selected Intermediates and Transition States

Interconversion between **7a** and **7b** requires a combination of pyramidal inversion and P-CH_2 bond rotation. The (constrained: see SI) rotational barrier for conversion of **7b** to **7b'** was 7.5 kcal/mol; the lower free energy of **7b** arises from better directional overlap of the P lone pair with the β-carbocation.[17,18] We could not find a pathway for direct conversion of *syn*-**5** to **7b'**.

The higher-energy pyramidal inversion proceeded via planar-at-P transition state **9**, which is stabilized by σ-interaction of the P lone pair with the empty carbon p-orbital.[26] This interaction reduced the computed inversion barrier from 23.7 kcal/mol in the model phosphine PMes*(Me)(CH_2CH_2Ph), where the empty p-orbital has been formally replaced with a hydride, to only 10.8 or 12.4 kcal/mol for the two diastereomers of β-cation **7**, consistent with the observation of P-epimerization under mild conditions. Calculations on analogous β-cations and phosphines bearing the smaller aryl groups mesityl and phenyl showed that this stabilization was a general phenomenon,[27] but its magnitude increased with aryl group size, perhaps because of steric destabilization of the pyramidal ground state (Table 1).[28]

Table 1. Computed Inversion Barriers (kcal/mol) in the β-Cations [ArP(Me)CH_2CHPh]$^+$ and The Neutral Phosphines ArP(Me)CH_2CH_2Ph[a]

Ar	Barrier (cation)	Barrier (Neutral)	Difference
Mes*	10.8	23.7	12.9
Mes	19.9	28.8	8.9
Ph	23.5	28.9	5.4

[a] Only one diastereomer of the β-cations was considered

As required for microscopic reversibility, cyclization of cations **7** to complete the isomerization process must proceed with inversion of configuration at the phosphorus nucleophile, which is required for suitable orbital overlap in formation of the strained ring.[18,29] We described this behavior previously in cyclization of the proposed cationic intermediates [Mes*PHCH_2CH(R)]$^+$, which led after deprotonation to *syn*-phosphiranes **1-2**, and the computed P-Me transition states **10a-b** [Mes*PMeCH_2CH(R)]$^+$ are directly analogous.[18]

Natural Bond Orbital (NBO) analysis further clarified key contributions to the electronic structure of the intermediates and transition states (Scheme 6). NBO calculations were performed using the $CHOOSE option to mandate a common Lewis reference state (Scheme 6) in which P has three σ-bonds and a lone pair (lp) and the β-CHPh carbon also has three σ-bonds and a vacant p-orbital; the NBO occupancies (< 2.0e) of the P_{lp} and the P-C_α σ-NBOs reflect the extent of electron donation to the C_β carbocation in each species. For example, the P–CHPh bond in phosphiranium cation *anti*-**6** reflects strong interaction between these orbitals. The high p-character (sp^6) of the P electron pair is consistent with the geometrical requirement of p-enrichment in small rings, and the polarization $C_\beta^{\delta-}$–$P^{\delta+}$, expected from the electronegativities, is consistent with the computed orbital population (0.84e), compared to the expected 1e in a P–C bond with equal sharing.

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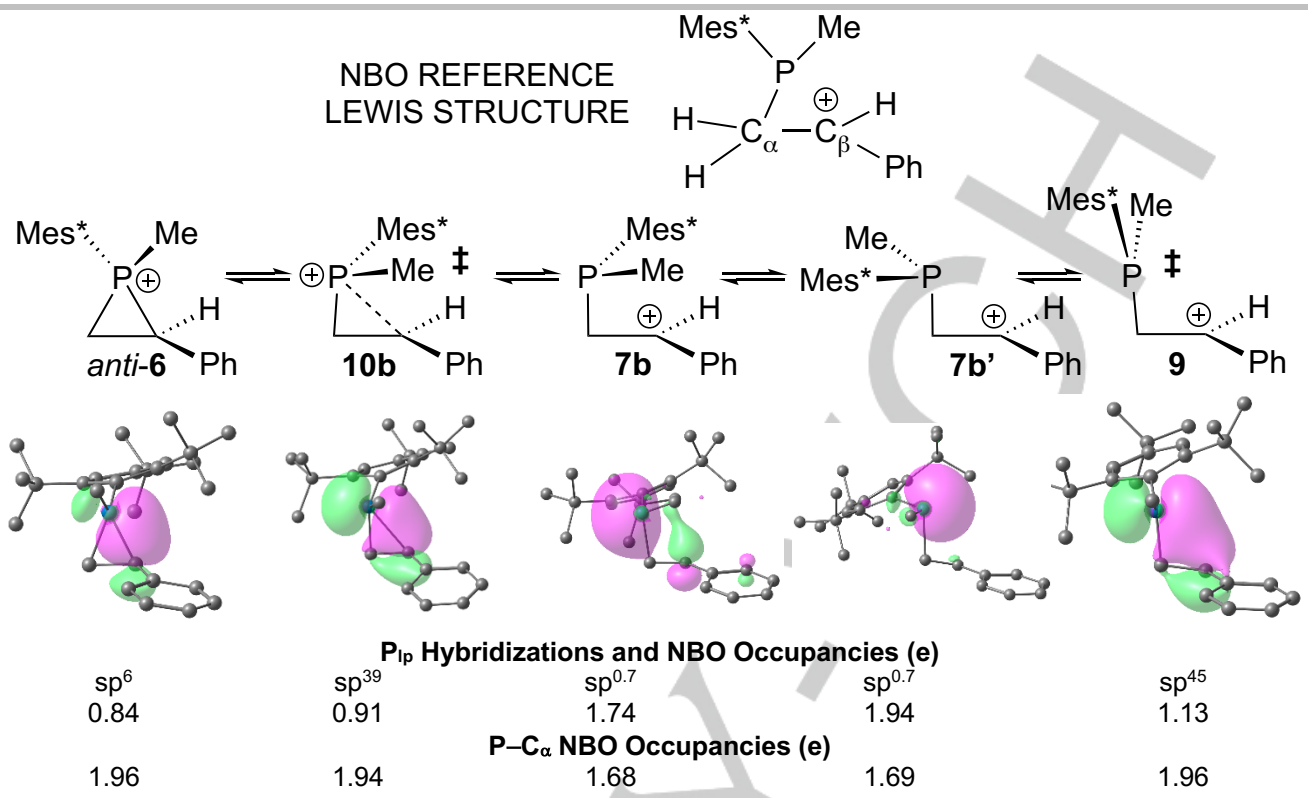

Scheme 6. Hybridizations and Natural Localized Molecular Orbitals (NLMOs) for the P_{lp} and NBO Occupancies along the Pathway for Interconversion of *anti*-**6** and **9**

As P-C_β cleavage proceeds to give cation **7b**, the movement of this electron pair, from pointing at C_β to away from it, resembles pyramidal inversion, consistent with the higher p-character in transition state **10b** (sp^{39}), and an increase in the P_{lp} orbital population to 0.91e as fewer electrons are donated to the adjacent C_β p-orbital. The extent of delocalization of the P_{lp} into the C_β p-orbital can be visualized in the NLMOs shown in Scheme 6. On complete ring opening to form **7b**, the P_{lp} increases considerably in s-character ($sp^{0.7}$) and its orientation, pointing away from the C_β p-orbital, results in limited overlap, and significantly greater localization on P (1.74e). Interconversion of ring-opened cations **7b** and **7a** (Scheme 5) requires both P-C_α rotation and pyramidal inversion. First, rotation about the P-C_α bond yields **7b'**, in which, as for **7b**, the lone pair has even less overlap with the C p-orbital (1.94e) and $sp^{0.7}$ hybridization. Finally, in the planar-P inversion transition state **9**, the P lone pair is essentially a pure p-orbital (sp^{45}) strongly interacting with the C_β p-orbital (1.13e). The key role of P-C_α hyperconjugation in stabilizing the C_β carbocation is also illustrated by the NBO occupancies of the P-C_α orbital; as donation to C_β from P_{lp} decreases, especially in intermediates **7b** and **7b'**, hyperconjugation increases to stabilize the carbocation and preserve the stereochemistry at C_β.

The title stereospecific isomerization is an unusual exception to the standard configurational stability of tetrahedral main group compounds. The proposed mechanism includes two more surprises, in which inversion occurs at a normally configurationally stable pyramidal phosphorus, while the trigonal planar carbocation, usually labile, retains its configuration. This novel behavior stems from the specific structure of the phosphiranium cation, whose strain, along with benzylic stabilization of the resulting carbocation, results in ring opening. P-inversion, promoted by the steric bulk of the P-Mes* group, is accelerated by σ-interaction between the β-cation and the P lone pair, which stabilizes the planar transition state. Retention of C-configuration occurs because hyperconjugation from the P-CH_2 bond into the empty C p-orbital locks the CH_2-CHPh bond in place, slowing C-C rotation and maintaining the stereochemical integrity of the CHPh group.

Besides enabling these fundamental observations, the preparation of novel P-stereogenic phosphiranium cations **4-6** is potentially useful in asymmetric synthesis of bidentate or tridentate chiral phosphines by stereocontrolled nucleophilic ring opening, as recently reported for analogous achiral cations using anilines.[13a] We are currently investigating the regio- and stereochemistry of such processes with a range of nucleophiles.

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Keywords: configurations • phosphiranium • isomerization • reaction mechanisms • stereochemistry

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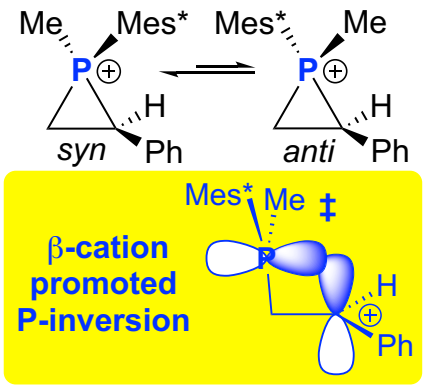

Tetrahedral carbon and analogous four-coordinate main group compounds are configurationally stable, but we report intramolecular P-epimerization of chiral phosphiranium cations under mild conditions. How? In the proposed mechanism, P–C cleavage yields an intermediate pendant β-carbocation which promotes low-barrier pyramidal inversion at phosphorus, while hyperconjugative stabilization from a P–C σ-bond preserves the cation's C-chirality.

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