Chirality at phosphorus in pentacoordinate spirophosphoranes: stereochemistry by X-ray structure and spectroscopic analysis†

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Two pairs of enantiomers of stable chiral pentacoordinate spirophosphoranes with two bonds from the amino and two bonds from the carboxyl groups of amino acids have been synthesized and analysed. The results show that differences in chirality at phosphorus are linked to distinct differences in physical properties.

Protein phosphorylation/dephosphorylation is a mechanistic switch between active and inactive states for the majority of proteins and plays a central role in regulating biological processes.[1] For example, there are over one hundred human kinases that catalyze transfer of the γ-phosphate group of ATP to amino acid residues on target proteins.[2] In enzymatic phosphoryl transfer processes, pentacoordinate phosphorus species have been proposed as transient intermediates or transition states[3] and both steric and electronic effects undoubtedly influence the pathways of phosphoryl transfer.[4] Therefore, to explore the intrinsic character of these processes, many model pentacoordinate phosphoranes have been investigated.[5–10] Hitherto, most studies have focused on aspects of apicophilicity,[11] anti-apicophilicity,[12] and pseudorotation[13] of phosphoranes but there has been only limited investigation of the absolute configurations of pentacoordinate phosphoranes with an asymmetric phosphorus atom.[14] Therefore, we supposed chiral pentacoordinate spirophosphoranes with bis-α-amino acid bonds might be interesting prototype model complexes for studying the stereochemistry of pentacoordinate phosphoranes. We here describe the synthesis and characterisation of two pairs of enantiomers of chiral pentacoordinate spirophosphorane model compounds having two bonds from the amino and two from the carboxyl groups of amino acids. Physical properties and absolute configurations of these four isomers are reported.

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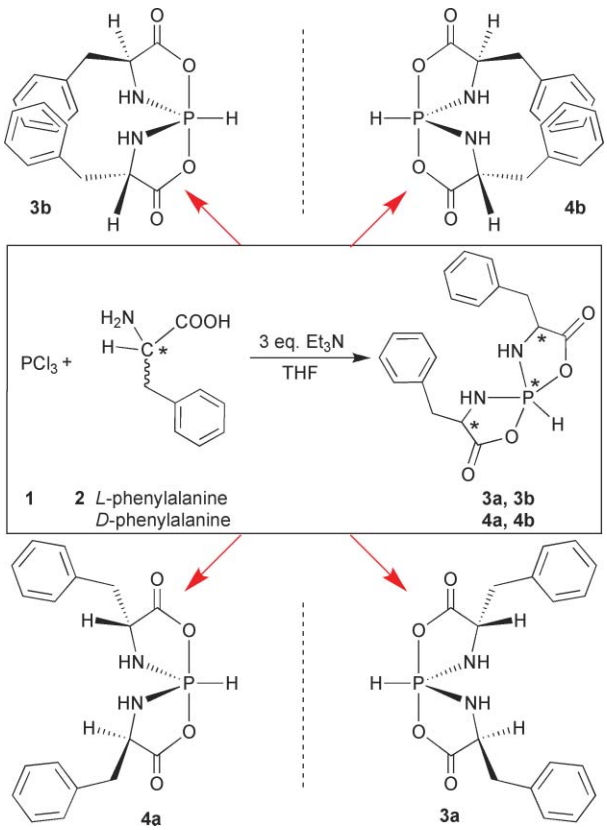
Four stereoisomers of pentacoordinate spirophosphoranes were synthesized[9b] and isolated, **3a**,**b** derived from *L*- and **4a**,**b** derived from *D*-phenylalanine (Scheme 1). The two **b** isomers are soluble in dichloromethane, methanol, acetone, and chloroform. By contrast, the **a** isomers are virtually insoluble in these solvents, but are soluble in polar solvents such as dimethyl sulfoxide.



Scheme 1 Structures of spirophosphoranes **3a**, **3b**, **4a** and **4b**.

Isomers **3a** and **4a** have essentially the same retention times on TC-C_{18}, reverse-phase high-performance liquid chromatography (HPLC) (15.63 min), while isomers **3b** and **4b** are retained longer (18.00 min) (methanol and deionized water v/v = 3:2 as eluent). Hence, it is evident that **3a**/**4a** and **3b**/**4b** are two pairs of enantiomers.

In order to confirm this stereochemical relationship between the two pairs of isomers, solid-state circular dichroism (CD)

spectra were measured (Fig. 1). The CD spectra of **3a** and **4a** are virtually mirror images of each other. Similarly, mirror-image symmetric CD spectra confirm the enantiomeric nature of **3b** and **4b**. Hence it is established that **3a**/**4a** and **3b**/**4b** are two pairs of enantiomers.

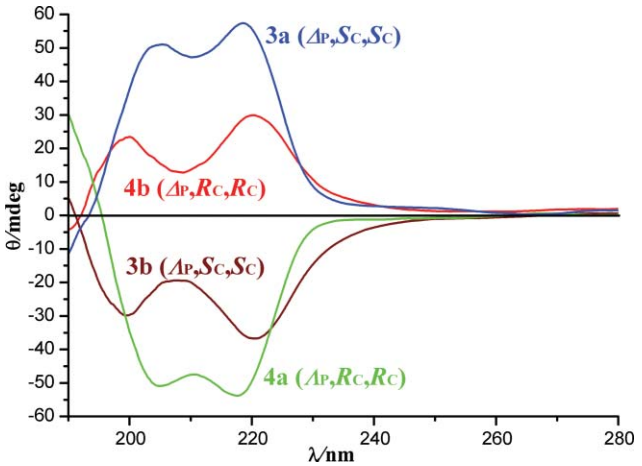


Fig. 1 Solid-state CD spectra of compounds **3a**,**b** and **4a**,**b** (KCl disk).

Although both **3a** and **3b** are synthesised from *L*-phenylalanine, they have very different CD Cotton effects. Likewise the same phenomenon is seen for **4a** and **4b**, both derived from *D*-phenylalanine. It is to be noted that the sign of the CD Cotton effect does not follow the chirality of the parent amino acid. The absolute configuration at the phosphorus center is the controlling factor for the optical asymmetry of the four isomers **3a**–**4b**.

The four isomers were also characterized by ^{1}H NMR solution spectroscopy. The epimeric **a**/**b** pairs of the enantiomers **3a**/**4a** and **3b**/**4b** show significantly different spectra (Fig. 2) while the spectra of enantiomers **3a**/**4a**, likewise of **3b**/**4b**, are identical. Whether the proton bound to nitrogen is deuterated or not, the proton bound to phosphorus in **3a** and **4a** gives a double triplet signal from coupling to phosphorus and to two magnetically-equivalent protons (δ = 5.64 ppm, dt, $^{1}J_{(H,P)}$ = 810.2 Hz, $^{4}J_{(H,H)}$ = 2.4 Hz). However, the P-H proton in **3b** and **4b** shows a doublet signal split only by phosphorus (δ = 7.09 ppm, d, $^{1}J_{(H,P)}$ = 804.9 Hz). This phenomenon was further confirmed by the ^{1}H-^{1}H COSY spectra of **3a** and **4a** identifying an interaction between the P-H proton and the α-hydrogen of phenylalanine, thus establishing unusual coupling through four bonds for these species. There is no such ^{1}H-^{1}H COSY effect for the epimeric **3b**/**4b** isomers. Also, the P-H proton signal of the **3b**/**4b** pair appears at lower field than for **3a**/**4a**, likely because of deshielding effects of the π–π semi-stacking.

Potential epimerization of these isomers was monitored by ^{1}H and ^{31}P NMR at 30 °C in DMSO-d_6 as solvent. No epimerization was observed over a period of one month, establishing the high configurational stability of these isomers. This stability will be very important for the further investigation of these compounds as simple models for pre-biological activity.

While solid-state CD spectra and ^{1}H-NMR data are consistent with the assignment of **3a**/**4a** and **3b**/**4b** as two pairs of enantiomers, their absolute configurations were proven by

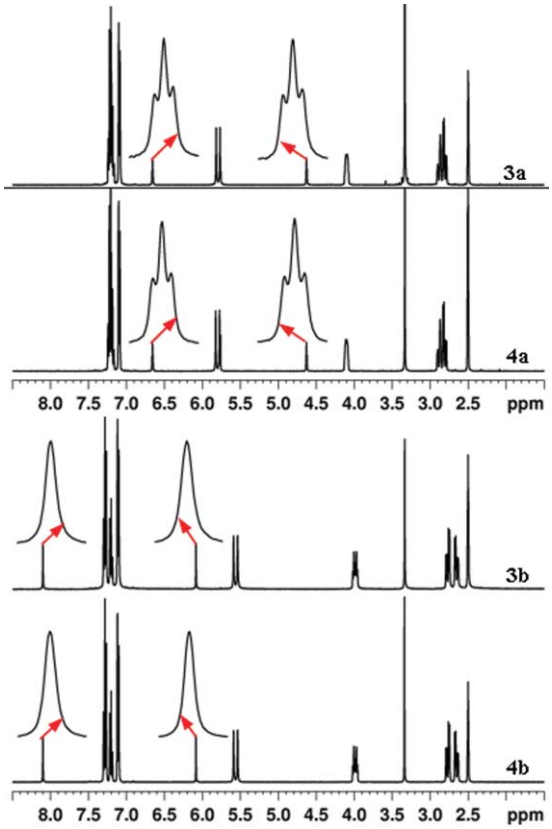


Fig. 2 ^{1}H NMR spectra of compounds **3a**,**b** and **4a**,**b** (solvent peaks at 2.50 ppm from DMSO and at 3.38 ppm from H_2O in DMSO-d_6).

X-ray diffraction analysis of crystals of enantiomers of **3b** and **4b**. Crystals were grown from solutions in acetone/petroleum ether (v/v = 1:1) and ORTEP structures of **3b** and **4b** are shown (Fig. 3). The geometry of these two compounds are distorted trigonal bipyramids (TBP) with two apical oxygen atoms and two equatorial nitrogens. There is deviation of 5.79° and 5.90° from the ideal angle of 120° for the angles of N(4)-P(5)-N(9) in **3b** and **4b** respectively while the other angles of N(4)-P(5)-O(6), N(9)-P(5)-O(6), N(4)-P(5)-O(1), N(9)-P(5)-O(1) in **3b** and **4b** are all close to the ideal 90.00°. The crystal lattice is stabilized by intermolecular hydrogen bonds generating sheets parallel to (001). C-H$\cdots\pi$ interactions,[15] π–π semi-stacking and van der Waals interactions between the two sheets also provide stability for the crystal structure. The absolute stereochemistry of **3b** was determined from Flack parameter [–0.07(12)], hence the absolute structure of **4b** [which has a Flack parameter of 0.0(2)] can be clearly generated.

The crystals of **3b** and **4b** show an *endo*-configuration like a "resting butterfly" where the "wings" are the benzene rings of the phenylalanine ligands that semi-stack together. A similar crystal structure of an *L*-valine-derived pentacoordinate spirophosphorane has also been obtained.[9a] By contrast, the non-crystalline diastereomers **3a** and **4a** can be projected to have an *exo*-configuration like a "resting moth", with near coplanar "wings". A similar crystal structure of the corresponding *L*-alanine pentacoordinate spirophosphorane has been determined in our lab previously.[9c]

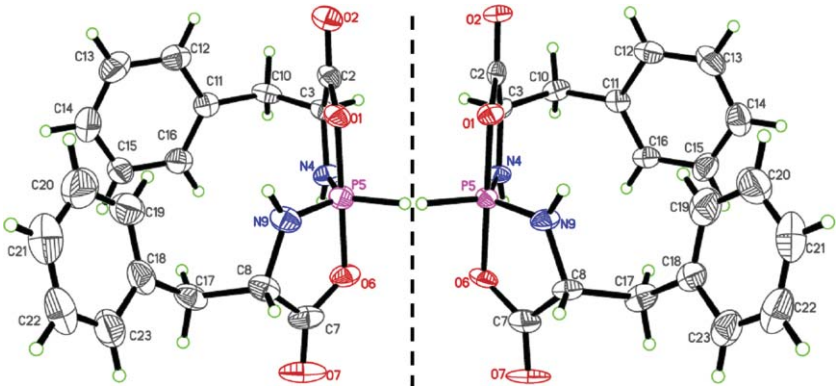


Fig. 3 ORTEP drawing showing 50% probability displacement ellipsoids of compounds **3b** (left) and **4b** (right) with atom numbering scheme.

Based on coordination stereochemistry, it is known that a complex $[MX(AB)_2]$ (AB = hetero-bidentate ligand) can have TBP or square-pyramidal (SP) geometry. When a monodentate ligand X occupies one equatorial position of a complex $[MX(AB)_2]$ in TBP geometry, the "chiral-at-metal" configuration is either *Λ* or *Δ*.[16] According to the above nomenclature, the X-ray diffraction data shows that the phosphorus center in **3b** is to be assigned as Λ_P, where both α-carbons of amino acid are in *S*-configuration. Thus, the absolute configuration of **3b** is (Λ_P,S_C,S_C). Likewise, **4b** is (Δ_P,R_C,R_C). Because **3a** and **4a** have not yet been crystallised, their absolute configurations cannot be assigned directly. However, since **3a** and **3b** are both derived from *L*-phenylalanine, the configurations of the two α-carbons are *S*. In addition, they have opposite CD signs, and therefore opposite configurations at phosphorus. We thus assign the configuration of **3a** as (Δ_P,S_C,S_C). Likewise, the configuration of **4a** is (Λ_P,R_C,R_C).

In summary, the relative spatial orientation of the chiral ligands around the phosphorus center induces distinct physical property changes and this clearly indicates that a small variation in the chiral environment at phosphorus can result in a large effect on the asymmetric behaviour of pentacoordinate phosphorus compounds. Since phosphoryl transfer processes in bio-systems are highly regio-selective and substrate specific, the present results suggest that pentacoordinate phosphorus is a very important structural feature relevant to chiral phosphoryl transfer pathways.

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