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Abstract: Stereogenic silicon centres in functionalized tetracoordinated organosilanes generally exhibit very high configurational stability under neutral conditions. This stability drops completely when higher coordination states of the silicon center are reached due to rapid substituent exchange. Herein we describe the synthesis of chiral and neutral pentacoordinate silicon derivatives with high configurational stability. The zwitterionic nature of these air and water tolerant species allows for the first time their direct and efficient optical resolution using chiral HPLC techniques. By means of this method, pentacoordinate silicon compounds exhibiting high Si-inversion have been obtained as single enantiomers. A rationalisation of the enantiomerisation pathways has been also carried out using DFT calculations.

More than 170 years after the first optical resolution of racemic tartrate salts by Louis Pasteur, chirality still remains a topic of great fascination and the significance of chirality in modern molecular chemistry is indisputable.[1] In this context, the discovery and the quest of new chiral objects based on emerging concepts are fundamental to keep pushing the limits further. Organosilicon compounds have emerged quite lately thanks to the chemists who succeeded in making non-natural carbon–silicon bonds which paved the way of a nowadays extremely rich realm.[2] Conversely to carbon, silicon allows to reach coordination higher than four[3] and some of the great achievements developed in organosilicon chemistry over the last decades involve transient hypercoordinated intermediates.[4] In sharp contrast to the related tetravalent species,[5] the configurational stability is much weaker in pentacoordinate silicon(IV) compounds, which are mainly found as non-rigid structures.[6] Pentacoordinate species usually adopt a trigonal bipyramidal (TBP) geometry with two axial and three equatorial sites that are highly prone to configurational isomerism through a fast substituent interchange (Berry pseudorotation mechanism).[7] This stereodynamism can be judiciously utilised to form stable diastereoisomers by transferring the chiral information of remote stereogenic centres to the silicon atom.[8] To the best of our knowledge, the synthesis of relatively rigid pentacoordinate silicon compounds with silicon as the only stereogenic element remains extremely rare.[9-12]

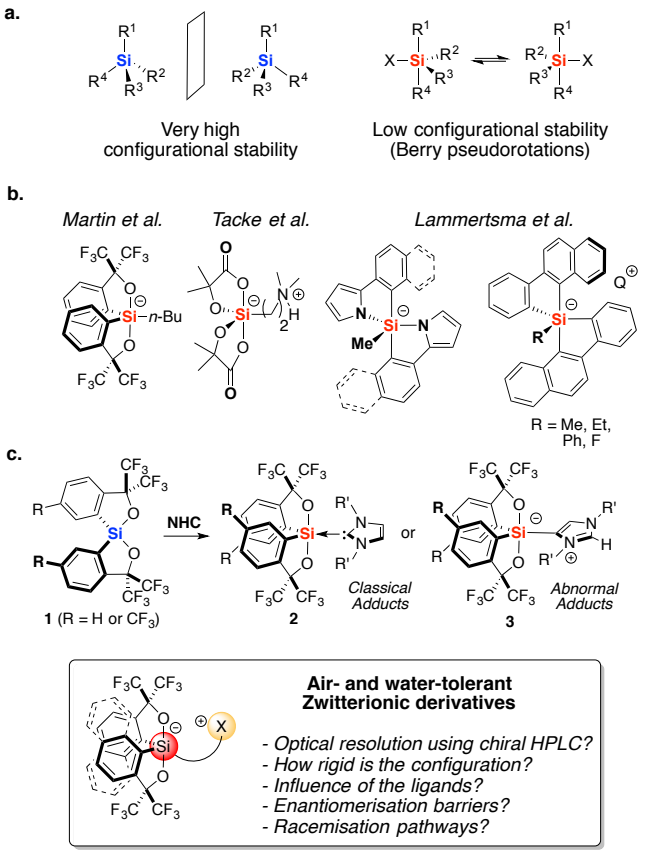

Figure 1. a) Configurational stability of tetracoordinated *vs* pentacoordinate silicon compounds. b) Towards configurationally stable pentacoordinate compounds. c) Formation of zwitterioic adducts featuring a pentacoordinate silicon atom obtained from spirosilanes of type **1** and the present study.

To be considered as potentially isolable in a stereochemical form, a stereoisomer must display a half-life time ($t_{1/2}$) higher than one thousand seconds (16.7 min) at 25°C which corresponds to an enantiomerisation barrier of 22.3 kcal.mol^{-1}.[13] In a pioneering work, the group of Martin reported the use of the bis-deprotonated form of hexafluorocumyl alcohol as bidentate

ligand for the synthesis of pentaorganosilicate derivatives.[9] Some dynamic NMR experiments suggested that these species could exhibit enantiomerisation barriers of up to 29 kcal.mol^{-1}.[10] Other strategies have been undertaken to tackle the synthesis of configurationally stable pentaorganosilicates. Whereas the group of Tacke used β-hydroxyacid ligands,[8a,11] the group of Lammertsma focused on phenylpyrrole and naphthylpyrrole bidentate ligands[12] but despite their configurational stability at the NMR timescale, most of these species possess corresponding enantiomerisation barriers too low (less than 21.5 kcal.mol^{-1}) to expect any isolation and applications. Recently, the latter group reported on the first enantiomerically-enriched pentaorganosilicates[12c] *via* the addition of nucleophiles to an optically pure tetravalent spirosilane featuring two all-carbon bidentate ligands (Figure 1). Interestingly, the corresponding fluorosilicate possesses a very good configurational stability but the enantiomeric purity could not be analytically measured.

Recently, we have studied the interactions of Lewis acidic spirosilanes featuring Martin type ligand with NHC Lewis bases of imidazolylidene type which lead to classical or abnormal adducts according to the NHC steric demand and the strength of both Lewis partners.[14] All these adducts are zwitterionic[15] and according to the data on Martin type silicates previously mentioned, the energy barriers corresponding to the ligand interchange should fall in a range where the racemisation might become slow enough to allow the separation of enantiomers at room temperature. Moreover, adducts **2** and **3** are neutral, air- and water-tolerant and, for most of them, can be purified by standard chromatography on silica gel. Prompted by these unique specifications, we envisioned to study their configurational stabilities and to resolve the racemic mixtures using chiral HPLC.[16]

In the first place, we focused on the analysis of abnormal adduct **3a** that exhibits two *tert*-butyl groups on the imidazolium ring. To our delight, the two enantiomers of compound **3a** could be nicely separated under standard conditions using a Chiralcel® OD-3 chiral column with a heptane/isopropanol (90/10) mixture as eluent (Figure 2). Circular Dichroism (CD) detection unambiguously confirmed that the two peaks corresponded to both enantiomers.[17]

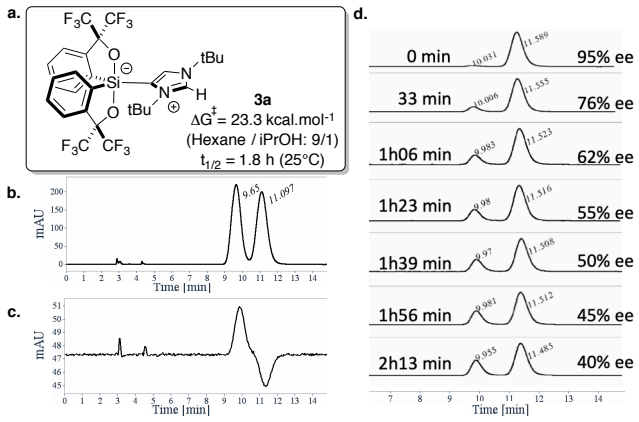

Figure 2. a) Neutral adduct **3a** with the corresponding enantiomerisation barriers and half-life times at 25°C. b) UV chromatogram of zwitterion **3a** using the Chiralcel ® OD-3 column, heptane/iPrOH (90/10) as eluent at a 1mL/min flow (220 nm). c) Circular dichroism (CD) chromatogram (254 nm). d) Racemisation of the second eluted enantiomer over the time.

This promising finding indicated that: i) the product **3a** is not sensitive to hydrolysis, ii) it presents a strong affinity with the chiral phase and iii) the racemisation is not too fast at the HPLC timescale. After the separation and isolation of both enantiomers using semi-preparative chiral HPLC, it was then possible to study the kinetics of the racemisation of **3a**, by injecting a part of the thermostated optically active sample onto the chiral column at different times. The decrease of the ee of the eluted enantiomer was then monitored. From these set of data, an energy barrier of enantiomerisation of 23.3 kcal.mol^{-1} corresponding to a half-life time of 1.80 h at 25°C in a hexane/iPrOH mixture, was found for zwitterion **3a**.[18] Other pentacoordinate silicon derivatives were analysed by chiral HPLC and their enantiomerisation barriers were calculated either by determining their enantiomeric purity after a preparative separation, or by dynamic chiral chromatography.[19] Half-life times at 25°C were used to compare the enantiomeric stability and the results are reported in Figure 3. The classical adduct **2a** presents a slightly higher configurational stability than **3a** with an enantiomerisation energy barrier of 23.8 kcal.mol^{-1}.

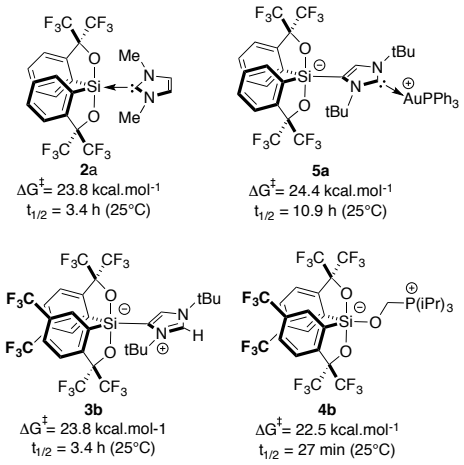

Figure 3. Neutral adducts that could be separated by chiral HPLC with the corresponding enantiomerisation barriers (25 °C, Heptane/iPrOH) and the corresponding half-life times at 25°C.[18]

The same barrier was obtained for the abnormal adduct **3b** bearing *tert*-butyl groups on the imidazolium ring as for **3a**, but with additional trifluoromethyl groups on the substituted benzene rings attached to the silicon.[14b] The higher barrier can be attributed either to an increased steric hindrance slowing down the Berry pseudorotations or to an electronic effect of the withdrawing groups on the silicon atom. Interestingly, neutral gold(I) complex **5a**, easily accessed by deprotonation of abnormal adduct **3a**, exhibits a higher enantiomerisation barrier than its imidazolium silicate parent (24.4 kcal.mol^{-1}). On the other hand, replacing the imidazolium ring by a more electronegative oxygen atom has a dramatic effect since a decrease of the half-life time to less than 30 min at 25°C is observed for adduct **4b**. At this stage, we decided to vary two parameters to access pentacoordinate silicon derivatives with a higher configurational rigidity. Firstly, the nature of the ligand connected to the spirosilane was switched from an imidazolium ring (C_{sp}^2) to a functionalised methylene (C_{sp}^3) and, secondly, the steric hindrance brought by the aromatic system on the

spirosilane scaffold. For that purpose, we added the deprotonated form of tetramethylammonium triflate[20] to simple spirosilane **1a** and the more congested analogue **1c**[21] bearing two naphthyl groups (Figure 4).

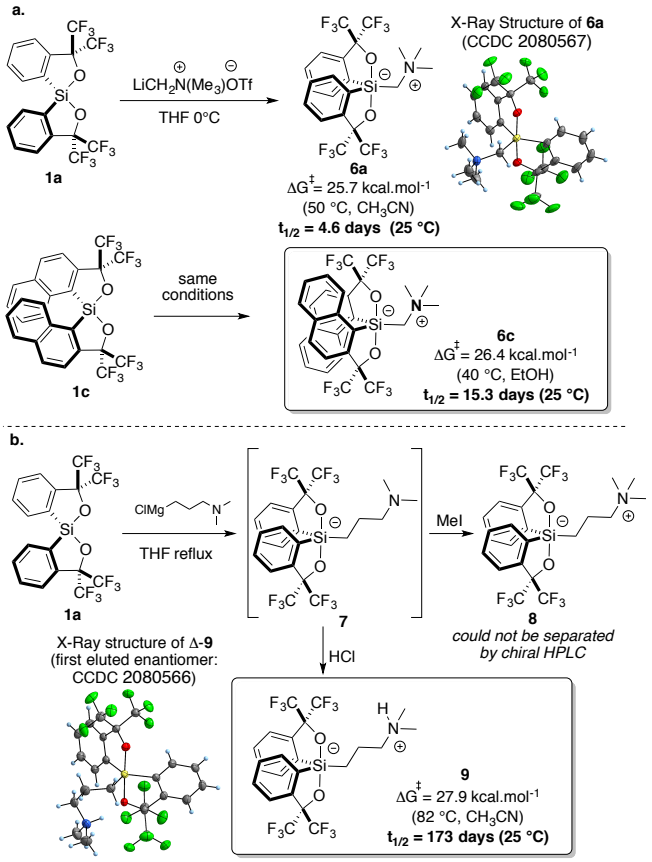

Figure 4. Synthesis of zwitterions **6a**, **6c, 8** and **9** and their corresponding enantiomerisation energy barriers and half-life times. For X-ray structures, ellipsoids are shown with 50% of probability.

In both cases neutral adducts **6a** and **6c** were obtained and the X-Ray Diffraction (XRD) analysis[22] of **6a** crystals confirmed its zwitterionic structure. The enantiomerisation energy barriers were determined after chiral HPLC separation and that of **6a** is of 25.7 kcal.mol^{-1} in CH_3CN at 50 °C. This barrier corresponds to a half-life time of 4.6 days at 25 °C, which is about fifty times higher than that of previously analysed **3a**. Furthermore, the rigidity brought by the two naphthyl groups proved to be also considerable since a barrier of 26.4 kcal.mol^{-1} (40 °C, EtOH), was reached for **6c** which corresponds to a half-life time of about 15 days at 25°C. This high configurational stability of zwitterion **6c** allowed us to record the CD spectra for both enantiomers and to measure their specific rotation.[18] Finally, we surmised that a longer link between the silicate moiety and the ammonium part would have some beneficial effects. Therefore, zwitterionic compound **8** featuring two extra methylene groups in the tether compared to **6a** was synthesised by addition of a *N*-containing Grignard reagent[23] to spirosilane **1a**[24] followed by a subsequent methylation (Figure 4b). Unfortunately, despite many attempts, we were not able to find conditions to separate the compound **8** by chiral HPLC. However, the corresponding tertiary ammonium **9**, obtained by a simple acidic treatment of intermediate **7**, could in turn be efficiently separated. It presents a very high enantiomerisation energy barrier of 27.9 kcal.mol^{-1} in acetonitrile at 82 °C, which corresponds to a half-life time of almost 6 months at 25 °C in solution. X-Ray crystal structure of the first eluted enantiomer of **9** allowed the determination of the absolute configuration[25] (Δ-enantiomer[26]).

Usually, pentacoordinate compounds adopt a trigonal bipyramidal (TBP) geometry (with two axial and three equatorial ligands) more or less distorted towards a square pyramidal (SP) geometry.[7] The total number of TBP structures is highly dependent on the nature of the ligands and for pentacoordinate silicon derivatives substituted by two identical bidentate Martin's type ligands, only ten (five pairs of enantiomers) can be drawn on paper. As the axial positions are preferentially occupied by electron-stabilising ligands, all of the TBP isomers are not necessarily stable intermediates. To grasp the whole picture of the racemisation mechanisms operating in such pentacoordinate systems, we performed DFT calculations at the B3LYP-D3/6-311G(2d,p) level of theory that has already proved to be suitable for similar studies.[13b,13c] The impact in terms of geometry and energy when naphthyl groups are present was studied as well. We first determined the stable TBP intermediates for silicate **I** (two Martin's ligands and a methyl). Not surprisingly, the most stable isomer is **IA** (Δ and Λ enantiomers) with the two oxygen atoms in axial positions (Figure 5a). Isomer **IC** (Δ and Λ enantiomers), lying at 9.3 kcal.mol^{-1} above **IA** and displaying one oxygen and one aryl group in axial positions, was the only other stable TBP intermediate we could compute. On the Figure 5b is represented an energy diagram of all the possible connections (black and blue arrows for silicate **I**) between the stable isomers through Berry pseudorotation (BPR) steps (with SP-like transition states) or Turnstile Rotation (TR with TBP-like transition state) which is a single-step double BPR.[7] The highest transition states for silicate **I** are TBP geometries displaying the methyl ligand in axial position, **[TBPI$_{BC}$]‡** (both enantiomers *A* and *C* at 28.1 kcal.mol-1) and **[TBPI$_{AC}$]‡** (both enantiomers *A* and *C* at 30.0 kcal.mol^{-1}). Interestingly, silicate **I** can racemise avoiding the highest transition state **[TBPI$_{AC}$]‡** since **Λ-IC** is easily converted into its enantiomer **Δ-IC** through **[SPI$_{C}$]‡** lying at 15.2 kcal.mol^{-1} (5.9 kcal.mol^{-1} from Λ- and Δ-**IC**). Therefore the privileged racemisation pathway for the silicate **I** is **Λ-IA⇔Λ-IC⇔Δ-IC⇔Δ-IA** with an energy barrier calculated at 28.1 kcal.mol^{-1}. Interestingly, the naphthyl analogue silicate **II**, is involved in a very different scenario (black and red arrows on Figure 4b). As a matter of fact, in this case TBP isomer **IIB**, with the two naphthyl rings in axial positions turns out to be a computationally stable intermediate and is almost isoenergetic with **IIA**. Both TBPs **IIA** and **IIB** readily interconvert through **[SPII$_{AB}$]‡** (only 4.8 kcal.mol^{-1}). Isomer **IIC** is also a stable intermediate (9.1 kcal.mol^{-1} above **IIB**) however the direct equilibrium between both enantiomers (Λ and Δ forms) through a SP-like transition state is this time not feasible due to the very high steric constraints brought by the additional aromatic rings. As a consequence, no shortcuts are possible and therefore to racemise, silicate **II** must go through the two TBP transition states with the methyl in axial position, **[TBPII$_{AC}$]‡** and **[TBPII$_{BC}$]‡**, lying at 30.6 and 31.2 kcal.mol^{-1} respectively. Accordingly, the preferential racemisation pathway for naphthylsilicate **II** is **Δ-IIB⇔Λ-IIA⇔Δ-IIC⇔Λ-IIB** with the highest energy barrier evaluated at 31.2 kcal.mol^{-1}.

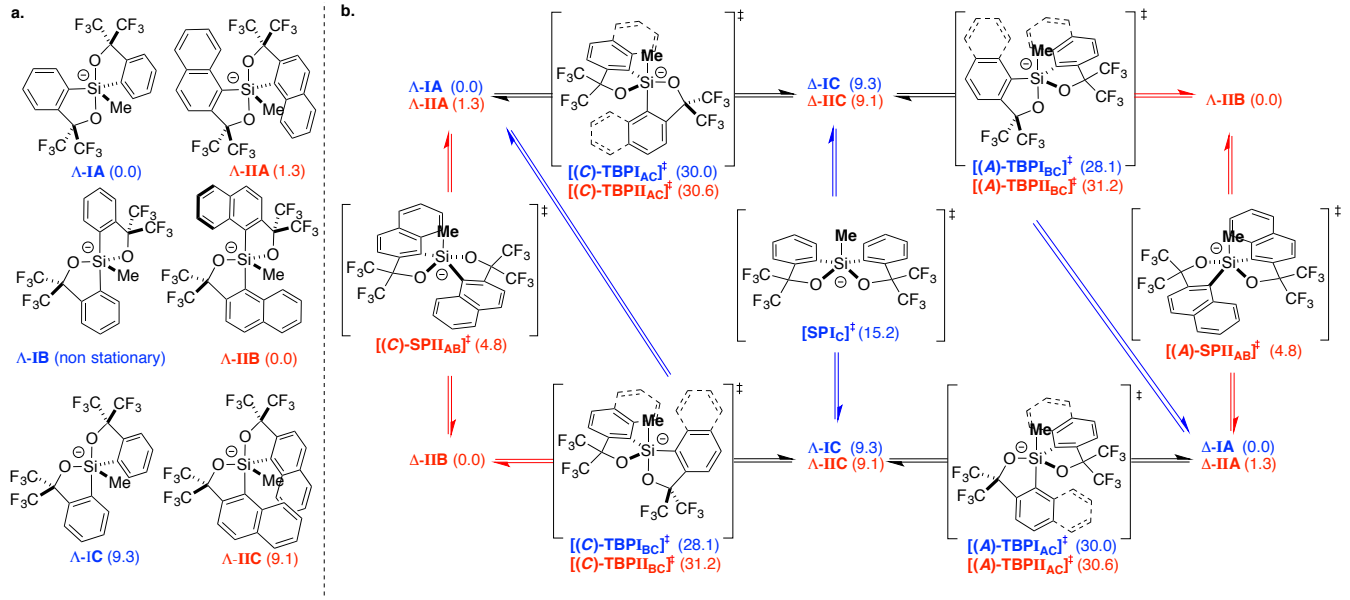

Figure 5. a) Computationally stable intermediates for silicate **I** and **II**. b) Racemisation pathways at the B3LYP-D3/6-311G(2d,p) level of theory (the blue pathway is specific to silicate **I** and the red one is specific to naphthylsilicate **II**). Prefixes *C* and *A* designate enantiomeric pairs of transition states.

This higher value than that of silicate **I** with the same methyl ligand implies a slower racemisation process when naphthyl groups are present which is in accordance with the experiment (**6a** *vs* **6c**, Figure 4a).Since the methyl ligand is in apical position in all the transition states in silicates **I** and **II**, its replacement by a more electron-stabilising *C*-ligand, like a methyl ammonium ligand, would stabilise the TBP-like transition states which explain the lower enantiomerisation barrier observed experimentally for zwitterions **6a** and **6c** (~ 26 kcal.mol^{-1}). In contrast, compound **9** featuring a propylammonium ligand with a comparable electronegativity than a simple methyl, possesses an enantiomerisation barrier in accordance with the calculation obtained for silicate **I** (27.9 kcal.mol^{-1}).

To conclude, we have described the first examples of enantiomerically pure pentacoordinate silicon compounds exhibiting high configurational stabilities. The zwitterionic nature of these chiral species and their robustness against hydrolysis were key points to enable their optical resolution by means of chiral HPLC. A DFT study rationalised the enantiomerisation pathways occurring in such systems and the influence of the substituents on the different transitions states. These enantiomerically pure pentaorganosilicates with such a high configurational stability can now be an ideal platform for designing new chiral objects that can be implemented for asymmetric applications.

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Keywords: silicon • chirality • zwitterion • chiral HPLC• optical resolution

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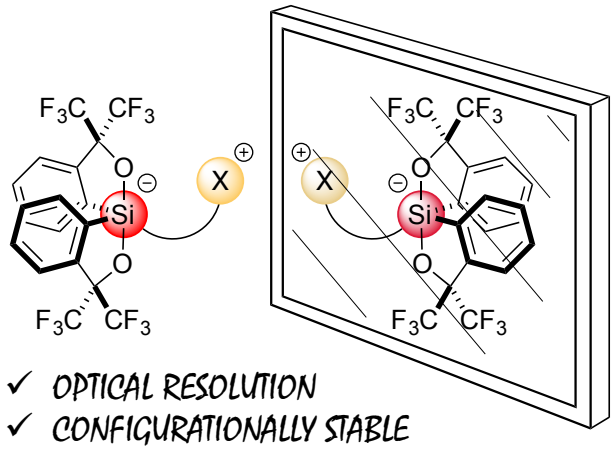

The synthesis of air- and water-tolerant zwitterions featuring a chiral pentacoordinate silicon moiety is described. Their stability toward moisture and aerobic conditions allowed their optical resolution by means of chiral HPLC, which constitutes a premiere in the chemistry of organosilicon compounds. Studies on the kinetics of racemisation of enantiomerically pure substrates attest for their high configurational stabilities in solution.