RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2025, **15**, 870

Mechanistic insights into the base-mediated deuteration of pyridyl phosphonium and ammonium salts†

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Received 22nd October 2024
Accepted 6th January 2025

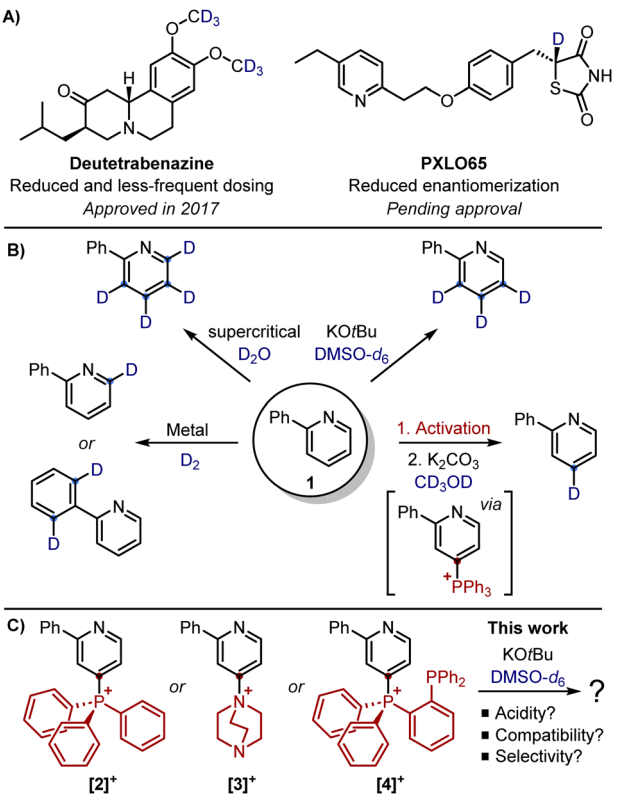
DOI: 10.1039/d4ra07557a

rsc.li/rsc-advances

Pyridines can be deuterated at the remote sites by treatment with KO*t*Bu in DMSO-d_6, although without discrimination between the *meta*- and *para*-position. Herein, base-catalyzed deuterations have been studied, computationally and experimentally, using a series of pyridyl phosphonium salts with a temporary electron-withdrawing group to block the *para*-position while increasing the acidity in the other positions.

The past decade has witnessed spectacular progress in the field of "deuterium switching", a strategy based on the replacement of hydrogen with deuterium.[1,2] Indeed, while the H-to-D substitution is one of the most conservative examples of bio-isosterism, the C–D bond is associated with greater activation energy for cleavage (with a difference of 1.2–1.5 kcal mol^{-1}), thus resulting in a more robust C–D bond.[3] As a result, the metabolic stability of a drug can improve as well as its efficacy and safety compared with the non-deuterated counterparts (Scheme 1A). Nevertheless, the deuterium switch in drugs is still in its infancy, with the first deuterated drug Austedo (deutetrabenazine) approved by FDA only in 2017.[4] Furthermore, deuterium is mainly installed on sp^3-hybridized carbon atoms (*e.g.* a –CD_3 group), whereas incorporation of deuterium on sp^2-hybridized carbons of drugs has been less explored.[5] This is particularly true for pyridines, for which only a handful of strategies are available for the deuteration of the aromatic ring (Scheme 1B).[6,7] For instance, taking 2-phenyl-pyridine **1** as a model substrate, deuteration has been achieved at the *ortho*-position (of the pyridine or the phenyl ring) using transition metal-catalysis[8–12] or at the *para*-position upon conversion into the corresponding pyridyl phosphonium triflate.[13] Alternatively, complete deuteration has been possible with supercritical D_2O,[14,15] whereas a base-mediated deuteration (KO*t*Bu in DMSO-d_6) has allowed for remote labelling at the *meta*/*para*-positions.[16,17]

Given that pyridines are some of the prevailing N-heterocycles in drugs,[18] novel methodologies that can give



Scheme 1 (A) Examples of deuterated drugs. (B) Most relevant modes of deuteration of 2-phenyl-pyridine **1**. (C) Mechanistic insights into the base-mediated deuteration of pyridyl phosphonium and ammonium salts.

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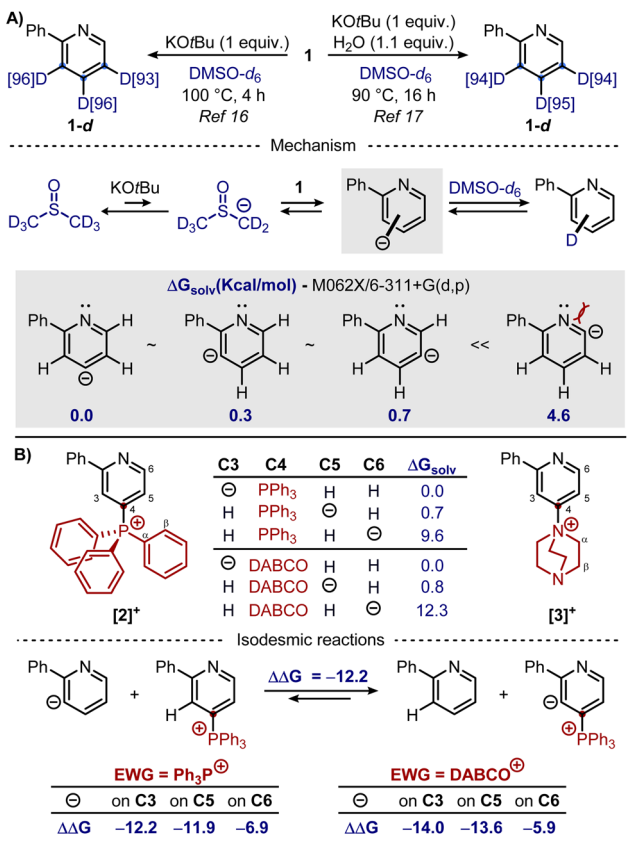
† Electronic supplementary information (ESI) available. CCDC 2352491. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d4ra07557a

access to diverse patterns of deuteration are still highly desirable. Inspired by the base-mediated *meta*/*para*-deuteration,[16,17] we wondered how the deuteration of **1** could be modified to allow for a different labelling selectivity. In particular, we envisaged that the temporary installation of an electron-withdrawing group (EWG) on the *para*-position could block this position and increase the relative acidity of the adjacent positions (Scheme 1C). In this work, we report our investigation of the base-promoted deuteration of pyridyl phosphonium and ammonium salts, hoping to reverse the selectivity reported for these activated pyridines. The use of **1** as a benchmark allowed the direct comparison with the literature as well as avoiding alternative deuterations not induced by the EWG group but rather by the stereoinductive effects of other substituents (as observed for pyridines containing halogens or methyl groups).[16]

In 2022, the base-promoted deuteration of **1** was reported in two related studies, as shown in Scheme 2A.[16,17]

Gao and co-workers showed that treatment of **1** with 1 equiv. of KO*t*Bu in DMSO-d_6 at 100 °C for 4 hours resulted in high deuterium incorporation in distal positions 3, 4 and 5 (>90%), with neglectable deuteration in the *ortho*-positions of the pyridine or the phenyl ring. Similar results were obtained by Beller and co-workers running the reaction at 90 °C for 16 hours in the presence of 1.1 equiv. of H_2O (to slightly decrease the overall basicity of the reaction mixture). While the reaction conditions were marginally different, both studies showed that this reaction proceeded *via* a pyridyl anion mechanism, with the latter obtained upon the deprotonation of **1** by the *in situ* generated dimsyl anion. Indeed, the distribution and degree of deuteration could be explained by the relative thermodynamic stability of the pyridyl anions, whereas isotopic studies suggested a reversible reaction, with the rate-determining step not involving C–H cleavage but rather the deuteration of the pyridyl anions or the generation of the dimsyl anion (in DMSO, pK_a(-*t*BuOH) = 32 *vs.* pK_a(DMSO) = 35).[19] Furthermore, kinetic studies showed that the *para*-position underwent a slightly faster deuteration compared to the *meta*-positions, although deuteration of the latter was reached within one hour. Based on these premises, we envisaged that phosphonium $[2]^+$ or ammonium $[3]^+$ could promote *ortho*/*meta*-deuterations by increasing the corresponding acidity in these positions while blocking the *para*-position. Our investigation started evaluating the stability of pyridyl anions deriving from the deprotonation of $[2]^+$ and $[3]^+$ (Scheme 2B). In analogy with previous theoretical studies on **1**,[17] we chose M062X functional with 6-311+G(d,p) basis set for optimization in DMSO-d_6 solvent based on solute electron density (SMD). For compounds $[2]^+$ and $[3]^+$, being the *para*-position substituted, the most stable anions derive from the deprotonation in *meta*-positions, as reported for **1**. Interestingly, the deprotonation in *ortho*-position, to give the least stable pyridyl anion, could now compete with the deprotonation of the EWG (in β for $[2]^+$ and in α for $[3]^+$, with $\Delta G = 4.0$ kcal-mol^{-1} and 10.1 kcal mol^{-1}, respectively). To assess the variation in acidity going from **1** to $[2]^+$ and $[3]^+$, isodesmic reactions were calculated too. These hypothetical reactions, in which the number of bonds of each type remains the same on each side of the equation, are useful to compensate for potential systematic errors in the modelling of each species.[20] It was found that introducing both electron-withdrawing groups in *para*-position should increase the acidity in *meta*-positions, and, to a lesser extent, in *ortho*-position too, thus supporting our starting hypothesis. From the computational analysis, we can therefore conclude that going from **1** to $[2]^+$ and $[3]^+$ deprotonation at any position of the pyridine ring should become easier, but there should be more discrimination between the favored *meta*-positions and the unfavored *ortho*-position. Nevertheless, the modelling was purely based on thermodynamics (*i.e.* the anion stability), therefore the effect of sterics could dramatically affect the predictions. With this in mind, base-mediated deuterations were performed in the laboratory. Initially, the deuteration of **1** with KO*t*Bu in DMSO-d_6 (as reported by Gao and co-workers) was repeated, confirming indeed, upon an aqueous work-up, isolation of **1-*d*** in 88% yield with deuteration occurring at the distal positions. Interestingly enough, conducting the same reaction in a J-Young tube to monitor its progression by *in situ* ^{1}H NMR (not done in previous studies), showed the expected disappearance of the signals of distal protons, along with a partial loss (up to 50%) of the diagnostic signal at 8.68 ppm of the *ortho*-proton. Yet no deuteration at this position was observed in **1-*d*** upon an aqueous work-up, even repeating the reaction and quenching it with D_2O, followed by extraction with $CDCl_3$. While this could be attributed to a severe broadening of

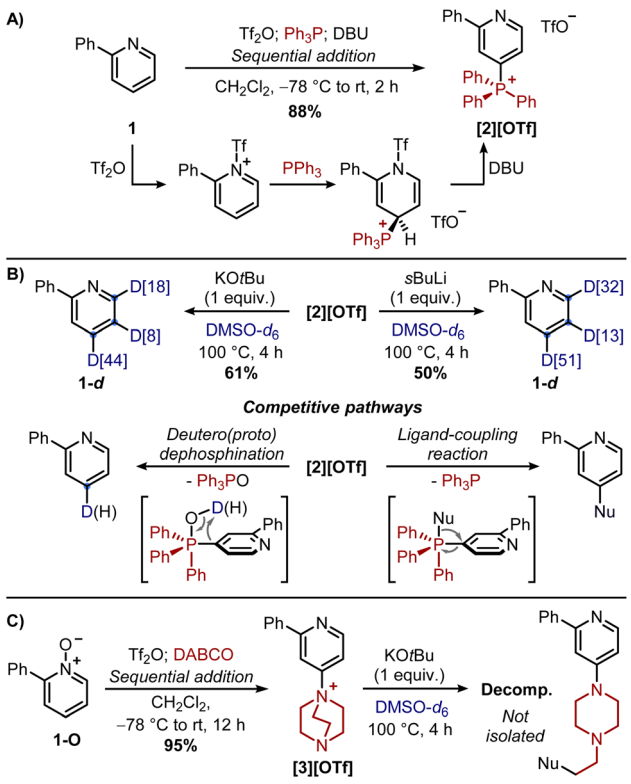


Scheme 2 (A) Base-mediated deuteration of **1**. (B) DFT calculations of the stability of carbanions deriving from the deprotonation of $[2]^+$ and $[3]^+$.

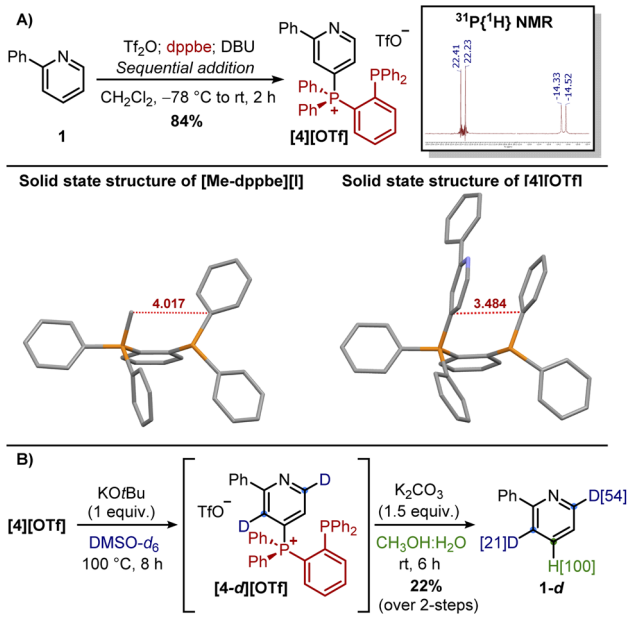
the signal of the *ortho*-proton (confirmed by NMR analysis with longer acquisition times),[21] this effect, caused by the coupling with the quadrupolar ^{14}N and ^{2}D nuclei, should be considered when following the reaction by *in situ* NMR analysis. The deuteration was then explored on pyridyl phosphonium salt **[2][OTf]**, obtained in one-pot by the sequential addition of Tf_2O, Ph_3P, and DBU to **1** (Scheme 3A).[22]

McNally and co-workers have shown that the treatment of **[2][OTf]** with K_2CO_3 in $CD_3OD : D_2O$ allows the replacement of the phosphine with a deuterium atom upon elimination of Ph_3PO (a two-step deuterium switch from **1**).[13] In our case, **[2][OTf]** was dissolved in DMSO-d_6 and treated with 1 equiv. of KO*t*Bu (Scheme 3B). The *in situ* monitoring of the reaction by ^{1}H NMR and ^{31}P NMR revealed, a few minutes after the mixing, a small amount of Ph_3PO, suggesting initial dephosphination of $[2]^+$ probably caused by water traces deriving from hygroscopic KO*t*Bu. This process became prevalent upon heating the reaction mixture at 100 °C, with now significant Ph_3PO observed after 4 hours. Notably, partial loss of the signal of the *ortho*-proton was observed too. Upon an aqueous workup of the reaction mixture, isolation of **1-*d*** revealed 44% D-incorporation in *para*-position thus confirming deuterodephoshination (the other 56% H-incorporation was attributed to water traces or during the workup). Notably, **1-*d*** showed 18% deuterium switch in *ortho*-position, therefore highlighting a certain level of C2-deprotonation occurring directly on $[2]^+$ since deuteration of **1** occurs only at distal positions. In contrast with the computational predictions, minimal deuteration was observed in *meta*-positions, probably due to the steric shielding provided by the phosphonium moiety that favoured the *ortho*-position. These results suggest that slowing down the dephosphination reaction or accelerating the deprotonation of the *ortho*/*meta*-positions of $[2]^+$ may favour novel deuteration patterns. Therefore, the first strategy looked at the replacement of the KO*t*Bu with *s*BuLi with the hope of reducing adventitious protic sources (*vide supra*). As a control experiment, this change was also tested on **1** still confirming deuteration only at distal positions (**1-*d*** isolated in 86% yield). However, upon addition of **[2][OTf]** to a solution of *s*BuLi (1 equiv.) in DMSO-d_6, *in situ* monitoring by ^{31}P NMR of the reaction mixture revealed rapid (within 5 min) disappearing of $[2]^+$ with the formation of Ph_3PO and Ph_3P. While the former could be attributed to dephosphination, the release of the latter suggested a ligand-coupling reaction, a mechanism by which Ph_3P is replaced by a nucleophile (tentatively attributed to the dimsyl anion, formed quantitively with *s*BuLi, although we have not been able to characterize the corresponding product).[23–26] Upon workup, isolation of **1-*d*** revealed a similar level of deuteration in *para*-position (due to deuterodephosphination), but an increased deuterium switch in *ortho*/*meta*-position (45% in total). While modest, these increments highlight how the phosphonium moiety enhances the acidity of the adjacent positions (if sterically accessible), given the deprotonation of $[2]^+$ occurs before dephosphination. In this regard, ammonium salts have emerged as a valid alternative to phosphonium salts for selective functionalizations of pyridines with nucleophiles (*e.g.* alkoxides or halogens).[27] However, protodeamination is not predominant since not driven by the formation of Ph_3PO as in the case of phosphonium salts. A second approach we investigated was then based on the use of pyridyl ammonium salt **[3][OTf]**, a DABCO-derivative synthesized similarly to phosphonium salts but starting from *N*-oxide **1-O** (Scheme 3C).[28] However, the base-mediated deuteration of **[3][OTf]** resulted in an unproductive consumption of the starting material, with rapid ring-opening of the bicycle as judged by the desymmetrization of the signals associated with DABCO.[29] A third strategy we explored looked instead at the installation of a directing group on the Ph_3P^+ moiety to facilitate the approach of the base by pre-coordination of its cation. We identified phosphines as ideal directing groups since (i) phosphines are excellent ligands for cations, and (ii) symmetrical diphosphines (Ph_2P-linker-PPh_2), needed for the synthesis, are commercially available. The first diphosphine we targeted was 1,2-bis(diphenylphosphino)-benzene (dppbe) since its electronic properties should not dramatically differ from those of PPh_3. In the laboratory, pyridyl phosphine–phosphonium salt **[4][OTf]** was synthesized in 84% yield by treatment of **1** with Tf_2O, dppbe, and DBU (Scheme 4A). This salt, obtained in high purity by simple precipitation in cold ether, showed two diagnostic peaks in the $^{31}P\{^{1}H\}$ NMR, confirming the desymmetrisation of the starting dppbe. The peak at 22.32 ppm (d, $^{3}J_{P-P} = 30.3$ Hz) and the other at −14.43 ppm (d, $^{3}J_{P-P} = 30.3$ Hz) were assigned to the P(v) and P(iii) atoms, respectively.

Crystals of **[4][OTf]** were obtained by slow evaporation from a $CHCl_3$ solution: the solid-state structure showed a π–π interaction between the pyridine and one of the phenyl rings on the P(iii) center, with the latter oriented toward the C5-proton.



Scheme 3 (A and B) Synthesis and reactivity of **[2][OTf]**. (C) Synthesis and reactivity of **[3][OTf]**.



Scheme 4 (A) Synthesis of **[4][OTf]** and its solid-state structure compared with [Me-dppbe][I][30] (anions omitted for clarity). (B) Reactivity of **[4][OTf]**.

We believe this arrangement is specific to $[\mathbf{4}]^+$ since in the solid-state of [Me-dppbe]$^+$, reported by Webster and co-workers and where the π–π interaction is missing,[30] the ligands attached to the two phosphorus centers are further away, probably to release steric destabilization. Attempts to replace dppbe with other diphosphines (*e.g.* linker = –CH_2–, –CH_2CH_2–, –CH_2-CH_2CH_2–) was not successful, with the corresponding phosphonium salts obtained as impure products, often with the pendant phosphine easily oxidized in air to its oxide. With compound **[4][OTf]** in hand, the base-mediated deuteration was explored on this novel pyridyl phosphonium salt (Scheme 4B). While the use of *s*BuLi as a base gave complete dephosphination within a few minutes, performing the reaction with KO*t*Bu gave interesting results. Specifically, a significantly slower dephosphination was observed, with the pyridyl phosphonium salt still present after prolonged heating (8 hours at 100 °C). Upon workup, a mixture of deuterated pyridines was obtained, but their isolation was complicated by similar polarities. The corresponding **[4-*d*][OTf]** could instead be isolated in 22%: this was then subjected to protodephosphination to reveal its level of deuteration. To our delight, deuteration at C6- and C3-position occurred in 54% and 21%, respectively, with the latter preferred over the other *meta*-position probably for steric reasons. While modest, this result suggests that the use of a temporary EWG group promotes *ortho*/*meta*-deuterations while blocking the *para*-position.

Conclusions

Pyridyl phosphonium and ammonium salts **[2][OTf]**–**[4][OTf]** were synthesized aiming for a diverse deuteration of model-pyridine **1**. Initial computational analysis validated the working hypothesis since, going from **1** to $[\mathbf{2}]^+$ and $[\mathbf{3}]^+$, deprotonation at the *meta*-position became thermodynamically favourable (due to electron-withdrawing effects), with the *ortho*-position being less convenient than the *meta* and with the *para*-position blocked. Nevertheless, sterics played an important role since the deuteration of **[2][OTf]** took place mainly at the *ortho*-position before the deutero(proto)dephosphination event occurred at the *para*-position. Deuteration of **[3][OTf]** was instead unsuccessful due to incompatibility with the use of bases. A final strategy (based on directing the base by coordination to its cation) brought to **[4][OTf]**, a novel phosphonium salt fully characterized by heteronuclear NMR and XRD analyses. Deuteration of **[4][OTf]** afforded indeed the highest level of *ortho*/*meta*-deuteration with phosphonium salts, although these temporary directing groups are not ideal when it comes to compatibility with bases, thus more robust directing groups are currently being developed in our laboratory.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We acknowledge Prof. Fabrizio Ortu (University of Leicester) for support in X-ray diffraction analysis and Giacomo W. Lombardo (University of Milan) for preliminary results. Dr Daniele Fiorito (Politecnico di Milano) is acknowledged for useful discussions. Computational resources provided by INDACO Core facility, which is a project of High Performance Computing at the University of MILAN **https://www.unimi.it**. We acknowledge Chiesi Farmaceutici for funding.

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