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Facile preparation and isolation of neutral organic electron donors based on 4-dimethylaminopyridine

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Abstract

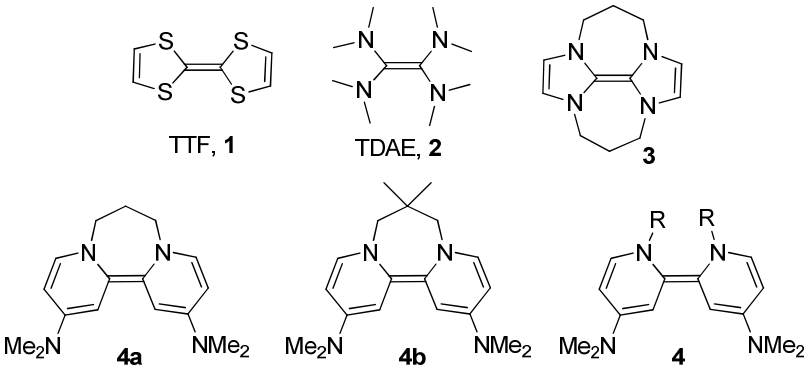
A number of new neutral bis-2-(4-dimethylamino)pyridinylidene electron donors featuring N-akyl groups of varying lengths (propyl, butyl, hexyl, dodecyl) have been prepared from 4-dimethylaminopyridine by means of a simple two step procedure. Each derivative could be isolated in high yield, and could be stored indefinitely under inert atmosphere. The electron donors were chemically oxidized to the corresponding bipyridinium ions, and all compounds were characterized by NMR spectroscopy and cyclic voltammetry. As an emerging class of electron transfer agents, the availability of the isolated neutral bispyridinylidenes should be beneficial for cases that are incompatible with generating the electron donor *in situ*.

Keywords

4-DMAP; bis-2-pyridinylidenes; electron donor; electron transfer; reduction

Introduction

There are a large variety of reducing agents available to the synthetic chemist, most of which are based on metals or their complexes. Recently, there has been increasing interest in developing neutral organic molecules as alternatives for metal-based reducing agents.[1-4] In principle, the neutrality of these organic compounds should lead to high solubility and should open up the possibility of homogeneous reduction reactions in conventional media at low temperatures, unique selectivity, and new synthetic methodologies. Early work in this area involved reagents such as tetrathiafulvalene (TTF, **1**)[5] and tetrakisdimethylaminoethylene (TDAE, **2**),[6] but the substrate scope is limited by the redox potentials of the reagents [TTF: $E^1_{1/2}$ (CH_3CN) = 0.32 V/ $E^2_{1/2}$ (CH_3CN) = 0.74 V; TDAE: $E^1_{1/2}$ (CH_3CN) = -0.78 V/ $E^2_{1/2}$ (CH_3CN) = -0.61 V all vs SCE] which are much more positive than those of common metal reagents like lithium or sodium metal [-3.01 V and -2.71 V vs NHE (-3.25 V and -2.95 V vs SCE), respectively]. One of the major challenges in this area is the development of neutral organic electron donors that can reduce increasingly challenging substrates.



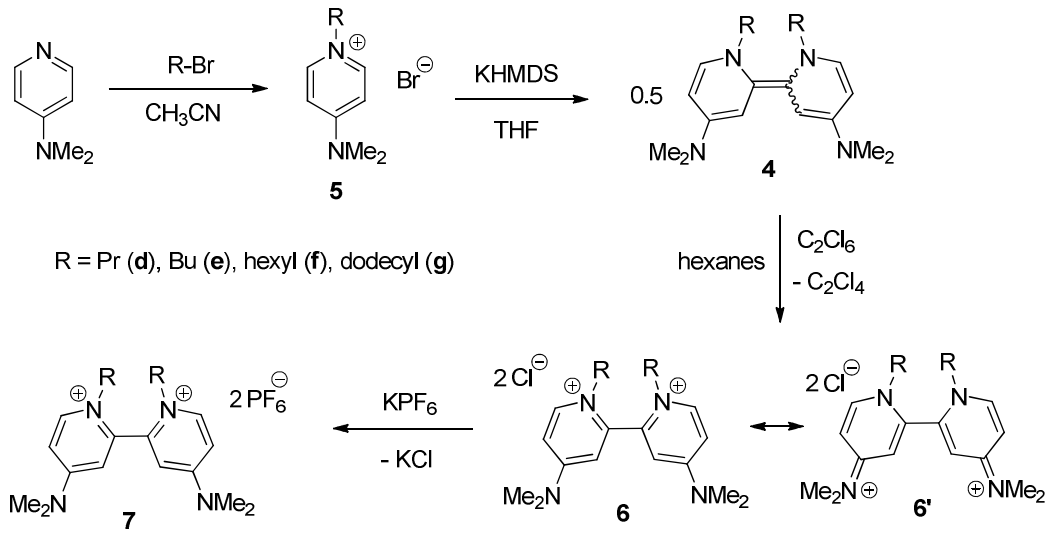
It was in searching for increasingly powerful neutral organic electron donors that Murphy discovered that compound **3** ($E_{1/2}$ (DMF) = -1.20 V vs SCE),[7] originally

prepared by Chen[8] and Thummel,[9] could effect the reduction of aryl halides via the intermediate formation of aryl anions.[10] Despite this, the significant time and synthetic challenges associated with the preparation of **3** are seen as limiting its utility as a commonplace reducing agent.[2] Electron donors based on alternate scaffolds, that are easier to prepare and offer similar, or even slightly increased, reducing power became available when Murphy described an elegant synthesis for amino-substituted bispyridinylidenes such as **4a** ($E_{1/2}$ (DMF) = -1.24 V vs SCE).[7, 11, 12] Their facile preparation has led these DMAP-derived electron transfer agents to find applicability in the polymerization of various activated alkene and cyclic ester monomers,[13] as well as the ground-state or photoexcited reduction of a variety of substrates including aryl halides,[11] Weinreb amides,[14] acyloin derivatives,[15] arenesulfonamides,[11] triflates and triflamides,[16] as well as benzylic C-O,[17] C-N,[18] and C-C bonds.[19] Most commonly, these reactions involve the *in situ* generation of the air and moisture sensitive electron donors via the reaction of easily handled pyridinium ion precursors with a strong base. In fact, of the seven bis-pyridinylidene derivatives prepared by Murphy,[7] only **4a**-**4c** have been spectroscopically characterized and only the propylene bridged derivatives **4a** and **4b** have been isolated (83 % and 71 % yield, respectively).[11, 12] More recently, we have been able to isolate some iminophosphorano-substituted bispyridinylidenes, which are even more powerful reductants.[20, 21] The availability of isolable reducing agents, free from by-products or excess base from their *in situ* generation, can be beneficial in increasing the utility of these reagents. Therefore, in order to facilitate the adoption of bispyridinylidenes as accessible and synthetically valuable reducing agents, we were interested in preparing and isolating a series of these compounds. In particular, since **4c** ($E_{1/2}$ (DMF) = -1.27 V vs SCE) was found to be a slightly (~30 mV) more powerful electron

donor than **4a**,[12] we focussed our studies on non-bridged derivatives of **4**. Herein we report the facile synthesis and characterization of new, isolable dimethylamino-substituted bispyridinylidenes **4c**-**4g**.

Results and discussion

Based on ease of synthesis, availability of starting materials and the expected favourable solubility of the products in a wide variety of solvents, our investigation was centred on the preparation of donors **4c-g** featuring alkyl chains of various lengths. These were prepared in two steps by slight modifications of Murphy's original preparation of **4a** and **4b**.[11, 12] Initially, 4-dimethylaminopyridine (DMAP) is alkylated with the appropriate alkylbromide in acetonitrile to form the N-alkylpyridinium bromides **5c-g** (Scheme 1). These compounds are readily precipitated from the reaction mixture by the addition of ether, and after subsequent recrystallization, were recovered in high yields (74-88%). These hygroscopic, colorless salts were then deprotonated with potassium hexamethyldisilazane (KHMDS) in dry THF at room temperature, ultimately affording the corresponding dark red electron donors **4c-g** as viscous oils in isolated yields of 66 to 84%. Although these compounds are air and moisture sensitive, they can be stored indefinitely under inert atmosphere, and they dissolve readily in all common organic solvents (except for acidic solvents like methylenechloride and chloroform, which react). As suggested previously,[11] the formation of derivatives of **4** likely involves initial deprotonation of **5** to form a pyridinylidene intermediate, which rapidly attacks the C-2 position of another pyridinium ring to form the new C-C bond, before a second deprotonation yields the final product.



Scheme 1: Preparation of electron donors **4d**-**g**, and their oxidation to the corresponding chloride salts **6d**-**g**, followed by metathesis to the corresponding hexafluorophosphate salts **7d**-**g**.

Although reaction times of 16 hours are used prior to workup, the rapid color change to red, and in situ NMR monitoring indicate that the reaction is largely complete upon mixing of the pyridinium ion and the base. Indeed, proton NMR spectroscopy shows the absence of characteristic doublets for the pyridine rings of **5** (~7.0 and 8.5 ppm) and appearance of peaks in the alkene region at approximately 5.2 (doublet), 5.4 (singlet), and 6.0 (doublet) ppm for the protons on C3, C5 and C6 of the C_5N rings. At the same time the α-hydrogens of the NMe_2 substituents shift from ~3.2 ppm in **5** to ~2.5 ppm upon formation of **4**.

Upon careful inspection, it becomes clear that the NMR spectra show an unequal mixture of *E*/*Z* isomers for each derivative of **4d-g**, with the minor isomer constituting only 13-16% of the mixture. Similar stereoisomers were observed in unbridged iminophosphorano-substituted bispyridinylidenes.[20, 21] Further support for the occurrence of isomers, rather than a mixture of unrelated compounds, is given by the

chemical oxidation of the bispyridinylidenes **4d-g** with hexachloroethane to produce only a single product, **6** (Scheme 1), in high isolated yields (79-96%). It is worth noting that trace amounts of **5** could be observed in some cases, and was believed to occur by decomposition of **4** during the exothermic oxidation reaction.

The minor constituent is assigned to the *E* isomer of **4**. This assignment is indirectly supported by theoretical studies by Clennan *et al.* who found that the *Z*-anti conformation of **4c** to be the most stable isomer by 1.59 kcal/mol over the lowest energy *E* conformation,[22] and by the fact that NOE-type NMR experiments validated the *E* isomer as the minor isomer for related iminophosphorano-substituted bispyridinylidenes.[20, 21] Unlike derivatives of **6**, which showed substantial double bond character of the N-$C_{pyridyl}$ bond, as evidenced by two distinct methyl groups for the $N(CH_3)_2$ substituents by ^{13}C and ^{1}H NMR spectroscopy, derivatives of **4** showed only one resonance for the same group, indicating free rotation of the N-C bond at room temperature. This indicates that the exocyclic amino group exerts a stronger π-donating effect in the oxidized species **6** than in neutral **4**, suggesting the importance of the quinoid-type form **6'**, despite the fact that this would decrease the aromatic character of the ring.[24] It is worth noting that calculations on the twice-oxidized form of **4c**,[22] and X-ray data for the dication of **4a**,[7] also support the idea of more localized π-bonding and the importance of structures of type **6'** in describing these dications.

Another noticeable difference between the ^{1}H NMR spectra for derivatives of **4** and **6** is found for the N-CH_2-R groups. For **6**, these four protons are observed as two multiplets integrating for two protons each, between 3.6 and 4.2 ppm. This indicates that the two protons of each methylene group are rendered diastereotopic through atropisomers caused by hindered rotation of the C-C bond between the two pyridinium rings. In the case of **4**, the minor isomer shows a multiplet in the range of

3.2 to 3.3 ppm, indicating no diastereotopicity of the CH_2 group, as expected for the assigned *E* arrangement, while the major isomer shows a broad resonance around 2.9 ppm at room temperature, which becomes resolved around 60 °C (see Figure 1, for **4d**). This latter observation is consistent with a *Z* conformation and is interpreted in terms of steric induced anti-pyramidalization of the two pyridyl nitrogens,[22] causing diastereotopic protons for the N-CH_2-R group. At room temperature, these undergo intermediate chemical exchange via inversion of the nitrogen atoms, but coalesce at higher temperature as the exchange rate increases relative to the frequency difference between the two proton environments.

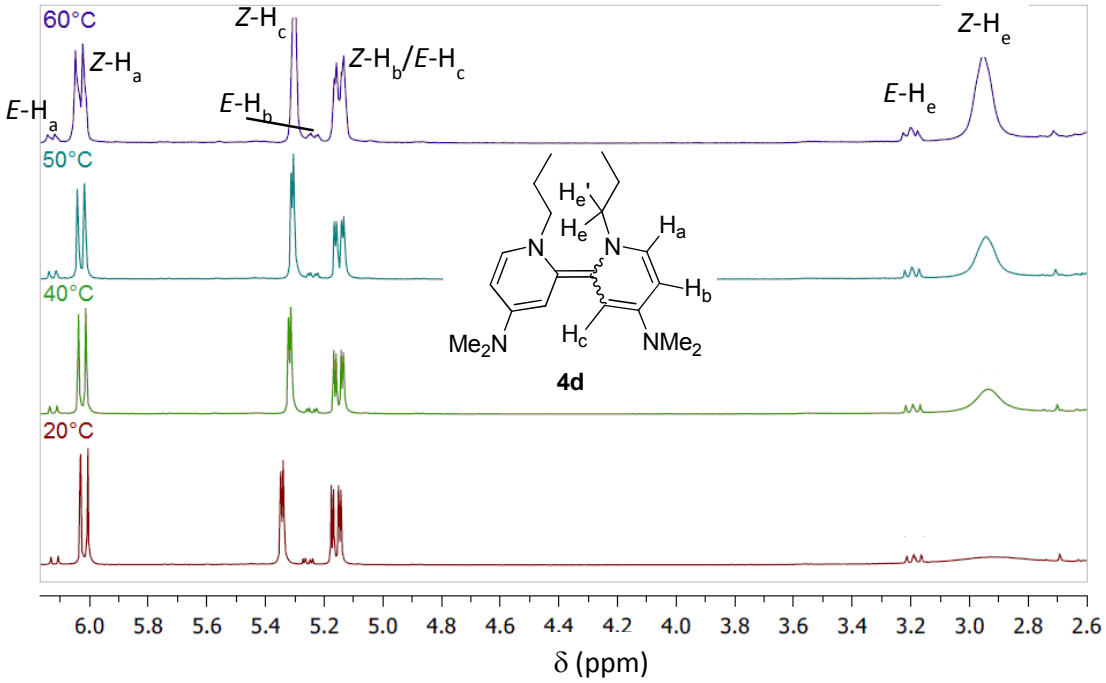
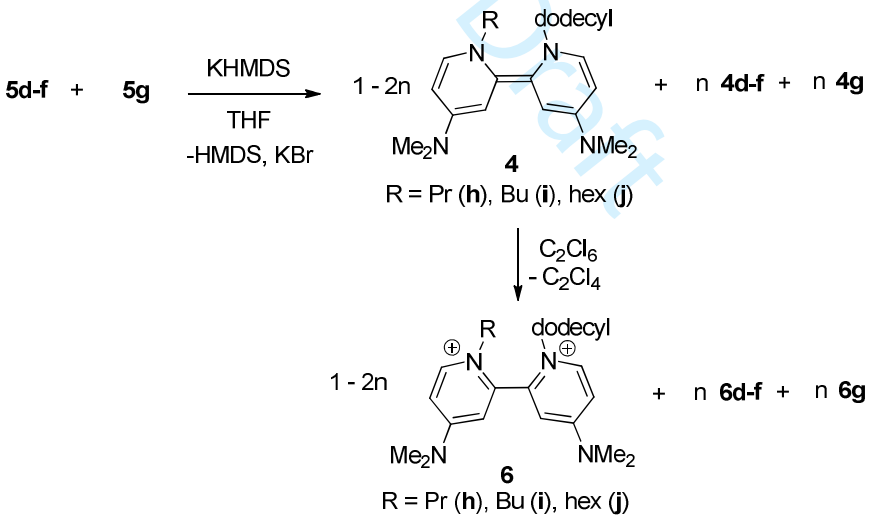


Figure 1: Variable temperature ^{1}H NMR spectra of **4d** in C_6D_6 at temperatures of 60, 50, 40, and 20°C (top to bottom).

Derivatives of **6** were found to be highly hygroscopic owing to the chloride ions, so they were converted to the corresponding bis-hexafluorposphate salts **7d**-**g** by metathesis with potassium hexafluorophosphate in water (Scheme 1). In order to assess the electrochemical properties of the new bis-pyirdinylidenes **4**, cyclic voltammetric analysis (see Supporting Information) was carried out on these air-stable hexafluorophosphate salts (**7d**-**g**). Each compound displayed a single, two-electron process at -1.26 to -1.27 V vs SCE, which is in line with the reported potential for the methyl derivative **4c**.[12] Therefore, the length of the alkyl chain has no effect on the redox properties of the compound, but the unbridged compounds **4c**-**g** are stronger electron donors than **4a** and related compounds featuring ethylene and butylene bridges between pyridinic rings.[7] The voltammograms show nearly reversible behaviour, with the difference between anodic and cathodic peaks being in the range of 30-50 mV (ideal value of 29 mV for a two-electron process)[23] and the ratio of peaks (anodic/cathodic) being approximately 0.8, rather than the ideal value of one. This latter difference is ascribed to the difference in diffusion coefficients between the neutral and dicationic redox partners.

In an effort to see if it would be possible to form asymmetrical electron donor derivatives, with alkyl chains of differing lengths on opposing pyridyl nitrogen atoms, equimolar mixtures of **5g** and **5d** were reacted with KHMDS in THF to afford red oils in excellent yields (Scheme 2). Analysis of the isolated products by NMR spectroscopy and cyclic voltammetry did not allow for the conclusive distinction between the formation of **4h**, mixtures of **4d** and **4g,** or mixtures of all three compounds. Thus, in order to determine some information as to the composition of the products, the product mixture was oxidized with hexachloroethane to the

corresponding bipyridinium ions **6**, which were then analysed by electrospray ionization mass spectrometry. This analysis (Figure 2) revealed that the mixtures contained the assymetrically substituted dication **6h** (m/z = 234.2) as well as the corresponding symmetrical compounds **6d** (m/z = 178.1) and **6g** (m/z = 290.3), implying that a mixture of all possible electron donors is formed in the initial deprotonation reaction (Scheme 2). Similar results were obtained when **5g** was reacted analogously with **5e** or **5f** (see Supporting Information). The bipyridinium ions mixtures **6h-j** were converted to the corresponding hexafluorophosphate salts **7h-j**. Cylcic voltammetry of these mixtures was indistinguishable from derivatives **7d-g** (see Supporting Information).



Scheme 2: Reaction of pyridinium ions **5d, 5e** or **5f** with **5g,** and subsequent chemical oxidation of the product mixture.

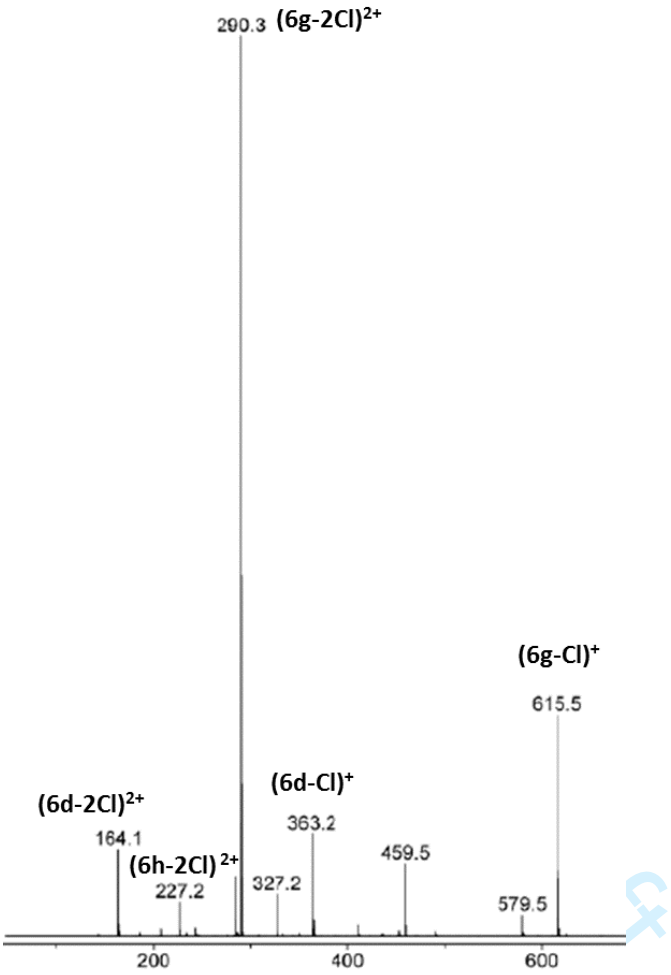


Figure 2: ESI-MS of the product mixture from the reaction of **5d** and **5g** with KHMDS, followed by subsequent oxidation with hexachloroethane (Scheme 2).

Conclusion

We have demonstrated that bispyridinylidenes **4d**-**g** featuring propyl, butyl, hexyl and dodecyl chains on the pyridyl nitrogen can be conveniently prepared and isolated as oils in excellent yields. These compounds, with two-electron redox potentials of -1.26 to -1.27 V vs SCE, can be stored indefinitely under inert atmosphere. The di-oxidized forms of these electron donors can be isolated as chloride salts by oxidation with hexachloroethane, or as more hydrophobic bis-hexafluorophosphate salts by

subsequent anion metathesis. The demonstration of isolable organic electron donors **4d-g** should further promote their utilization as homogeneous electron transfer agents, and should lead to exciting new applications of these compounds in the future.

Supporting data

Supplementary data are available with the article through the journal Web site at http://nrcresearchpress.com/doi/suppl/. Experimental procedures and characterization data, including NMR spectra, cyclic voltammograms and mass spectra are included.

Acknowledgements

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