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Routes to Regioselective Deuteriation of Heteroaromatic Compounds

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A systematic approach to the deuteriation of polypyridyl type ligands is reported. A range of isotopologues of heteroaromatic compounds containing pyrazyl, pyridyl, 1,2,4-triazole, thienyl, methyl, and phenyl moieties, have been prepared in a cost-effective manner, using a range of methods based on subcritical aqueous media. Selectively and fully deuteriated ligands are characterized by mass spectrometry and ^{1}H, ^{2}D, and ^{13}C NMR spectroscopy. The application of deuteriation to supramolecular chemistry is discussed.

Introduction

The application of transition metal complexes incorporating polypyridyl type ligands in inorganic photochemistry and supramolecular chemistry, in particular, has increased rapidly since the mid 1970s.[1] In particular, ruthenium(II) and osmium(II) based polypyridyl complexes have been utilized as building blocks for large multinuclear structures, mostly because of their synthetic versatility and suitable photophysical and electrochemical properties.[2] However, with the ever-increasing complexity of supramolecular systems, the ability to characterize these molecules fully by standard NMR techniques has become difficult.[3] An additional challenge often encountered is the identification of the nature of the emitting state, which, for heteroleptic compounds, may be located on different parts of the molecular assembly. Deuteriation of ligands has been proposed as a tool to help overcome these problems, at least in part.[4]

To date, however, the widespread use of deuteriation as a general spectroscopic aid has been limited, primarily because of the lack of generally applicable, high yield, and low cost H/D exchange procedures for polypyridyl type ligands. In this contribution, a general and systematic approach to the deuteriation of polypyridyl type heteroaromatic compounds is reported. This approach is based on the use of subcritical D_2O. The methods reported in this contribution are a significant improvement on traditional routes reported for the deuteriation of 2,2′-bipyridyl, which require several synthetic steps or the use of the environmentally unfriendly material asbestos.[5,6] Both methods yield only fully deuteriated compounds, in low to moderate yields. With the systematic approach reported in this contribution, more than 30 partially and fully deuteriated compounds (Figure 1) are obtained in high yields (~90%). The procedures used are relatively low cost and straightforward and can be carried out on at least gram scale. The approach reported is of a general nature and can be applied to a wide range of compounds, and as a result, the widespread use of partial deuteriation to elucidate the properties of supramolecular structures is now possible.

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Table 1. Conditions, Yields, and Extent of Isotope Exchange Reactions

	compound	overall % H−D exchange (site)[a]	method[b]	% yield[c]	reaction time (days)
1b	$[D_8]$-2,2′-bipyridine	>98	A	80	2 × 3 days
		>98	C	90	6
2b	$[D_4]$-4,4′-bipyridine	>98 (C2/C6); <15 (C3/C5)	B	95	3
2c	$[D_8]$-4,4′-bipyridine	>98	A	80	4
		>98	C	90	6
3b	$[D_{12}]$-4,4′-dimethyl-2,2′-bipyridine	>98 (50% exchange at C3)	A	70	4
		>98	C	95	6
4b	$[D_8]$-1,10-phenanthroline	>98	A	70	4
		>98	C	95	6
5b	$[D_6]$-4,7-diphenyl-1,10-phenanthroline	>98 phenanthroline protons (<5% for phenyl rings, C5/C6 show incomplete exchange)	C	95	6
5c	$[D_{10}]$-4,7-diphenyl-1,10-phenanthroline	~95% for phenyl rings	D (from **5d**)	95	6
5d	$[D_{14}]$-4,7-diphenyl-1,10-phenanthroline	>98 (<5 at C5/C6)	A	60	6
5e	$[D_{16}]$-4,7-diphenyl-1,10-phenanthroline	>98	A then C	80	2 × 3 days
6b	$[D_{12}]$-2,2′-biquinoline	>98	A	80	3
6c	$[D_4]$-2,2′-biquinoline	>98 C2/C3/C4 (<10 at remaining positions)	C	60	4
7b	$[D_{10}]$-2,3-di-(pyrid-2yl)-pyrazine	> 98	C	90	6
8b	$[D_2]$-2-(thien-2′-yl)-pyridine	>98 (py-H6/th-H5′)	B	85	6
8c	$[D_7]$-2-(thien-2′-yl)-pyridine	>98	C	95	6

[a] In the case of partially deuteriated compounds, exchange at individual positions is given in parentheses. [b] **A** 0.1 g of 10% Pd/C in 20 mL of D_2O at 200 °C; **B** in 20 mL of D_2O at 200 °C; **C** in 20 mL of 1 M NaOD/D_2O at 200 °C; **D** in 20 mL of 1 M NaOH/H_2O at 200 °C. [c] Based on recovered yield.

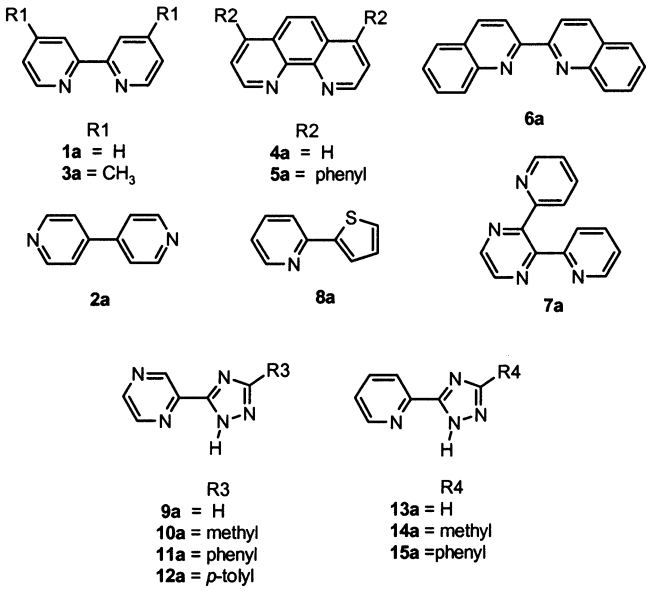

Figure 1. Structures of compounds examined.

Preliminary results on the deuteriation of 2,2′-bipyridyl using a Pd/C catalyst and D_2O as deuterium source were reported in an earlier communication.[7] Subsequently, this approach was applied to the full deuteriation of 1,10-phenanthroline,[7,8] pyridyl- and pyrazyl-1,2,4-triazole,[9] imidazole,[10] and 2-(thien-2′-yl)-pyridine.[11]

Results

As outlined in the Experimental Section, several H/D exchange procedures, methods A, B, and C, have been developed. In method A, Pd/C is used as a catalyst in the presence of D_2O, and in method B, only D_2O is used, while method C is based on the use of basic D_2O (pD = 10/11). In addition, "reverse" D/H exchange has been used to achieve further regioselectivity. The approaches taken are basic H_2O, method D, neutral H_2O, method E, and neutral H_2O in the presence of Pd/C, method F. In all methods, the reaction is carried out in a sealed steel container with a Teflon liner at 200 °C. The products obtained, together with yields, the degree of deuteriation, and experimental conditions are given in Tables 1 and 2. Spectroscopic characterization of the products has been carried out using mass spectrometry and ^1H, ^2D, and ^{13}C NMR spectroscopy. Data are given as Supporting Information. The degree of deuteriation was determined using both ^1H NMR spectroscopy and mass spectrometry. In Tables 1 and 2 (and for convenience throughout this paper), the exchange of the N−H proton of 1,2,4-triazole rings is not considered because exchange at this position is fast and occurs under ambient conditions in protic solvents.

Discussion

General. The application of high temperature and supercritical aqueous media in organic reactions has attracted significant interest in recent years.[12] Much less attention has been focused on medium temperature (150−250 °C) aqueous media despite it being the more accessible temperature range. H/D exchange of pyridine under acidic, neutral, and basic conditions was investigated in some detail in the medium (150−250 °C) and low (<150 °C) temperature range.[13−15] The usefulness of transition metal catalysts was examined,

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Table 2. Conditions, Yields, and Extent of Hydrogen/Deuterium Exchange Reactions

	compound	overall % H−D exchange (site)[a]	method[b]	% yield[c]	reaction time (days)
9b	[D_4]-Hpztr	>98%	B	95	3
10b	[D_6]-Hmepztr	>98%	B	95	3
11b	[D_3]-Hphpztr	>98% (pz)	B	95	3
11c	[D_5]-Hphpztr	>98% (ph)	E (#)	95	3
11d	[D_8]-Hphpztr	>98%	A	80	2 × 3 days
12b	[D_3]-Htolpztr	>98% (pz)	B	95	3
12c	[D_3]-Htolpztr	>98% (Me)	E (prepared from **12e**)	95	2
12d	[D_4]-Htolpztr	>80% (tolyl, see Scheme 2)	F (#)	95	6
12e	[D_6]-Htolpztr	>98% (pz and Me)	A	95	6
12f	[D_7]-Htolpztr	>98% (tolyl)	E (#)	95	3(§)
12g	[D_{10}]-Htolpztr	>98%	C	95	2 × 10 days
13b	[D_5]-Hpytr	>98%	C	80	3
14b	[D_7]-Hmepytr	>98%	C	80	3
15b	[D_1]-Hphpytr	>95% (py H6)	B	95	30
15c	[D_4]-Hphpytr	>95% (py), <15% (ph)	C	90	3
15d	[D_5]-Hphpytr	>95% (ph), <15% (py)	E (#)	90	3
15e	[D_9]-Hphpytr	>98%	A	80	6
	[Ru(bpy)$_2$(**11a**)](PF_6)	>98% pz C3/5, <20% at pz C6	B	70	3
	[Ru(bpy)$_3$](PF_6)	no exchange obsd	B	90	3
		no exchange obsd	B	90	3

[a] In the case of partially deuteriated compounds, exchange at individual positions is given in parentheses. [b] **E** in 20 mL of H_2O at 200 °C; **F** 0.1 g of 10% Pd/C in 20 mL of H_2O at 200 °C; # indicates preparation from perdeuteriated reagents (see Experimental Section). For other reaction conditions, see Table 1. [c] On the basis of recovered yield, § indicates that when species reacted for 30 days, no further exchange was observed. For **12b**−**g**, see Scheme 2 for further information.

with Pt and Pd receiving the most attention.[15] However, to the authors' knowledge, no detailed study on the general application of such methods has been reported. The motivation behind the interest in the deuteriation of polypyridyl ligands is their potential applicability in the study of supramolecular systems. One approach taken has been the direct deuteriation of the metal complexes.[16−18] For example, deuteriation of $[Ru(bpy)_3]^{2+}$ in 0.1 M $NaOCD_3/(CD_3)_2SO/CD_3OD$ at 35 °C was found to occur rapidly at the 3,3′-positions and more slowly at the 5,5′-positions. In the present study, $[Ru(bpy)_3]^{2+}$ is found to be inert to H/D exchange in both neutral and basic D_2O (Table 2). When using method B, [Ru(bpy)$_2$(**11a**)]$^+$ shows a very slow exchange at the H6 position of the pyrazyl ring (adjacent to the coordinating nitrogen), whereas the H3 and H5 positions of the pyrazine ring undergo complete exchange. Overall deuteriation of metal complexes is slow and has severe limitations, especially in the case of heteroleptic complexes; for this reason, a general strategy for the H/D exchange of ligands is needed.

With the strategy reported in this contribution, deuteriation has been achieved on the gram scale, with high yields (typically >80% after purification) and to high degrees of isotopic purity (typically >98%). No impurities were observed for any of the reactions listed in Tables 1 and 2. The yields reported are recovered yields, and the less than quantitative values obtained for method A reflect the difficulty of removing the substrates from the Pd/C catalyst. It is also important to realize that there is a theoretical limit to the extent of deuteriation. This limit is dependent on the molar ratio between the substrate and the solvent D_2O. For example, 3 g of 2,2′-bipyridine contains 0.1538 mol equiv of protons, and 20 mL of D_2O contains 2.214 mol equiv of deuterons; for this reaction mixture, the maximum theoretical deuteriation is 93.5%. When 1 g of bpy is employed, the maximum theoretical limit is raised to 98%. When large amounts are deuteriated (>1 g) by any of the procedures, the sample is subjected to two cycles rather than one, and after the second cycle, the equilibrium limit rises to greater than 99.5%. This is indicated in the tables. We thank one of the reviewers for highlighting this issue. By careful manipulation of the conditions employed and by the combination of different methods, regioselective deuteriation is achieved. The behavior of the compounds studied is discussed in more detail in the next sections.

Deuteriation of Heterocyclic Groups. Compounds **1a**−**8a** (Figure 1) are among the most commonly employed bidentate ligands in the preparation of inorganic polypyridyl complexes.[1] Table 1 shows that Pd/C is not needed to achieve full deuteriation. Neutral and basic D_2O solutions also yield high deuteriation ratios and high yields. The absence of a catalyst has the advantage that the workup of the reaction mixture is easier, and hence, yields improve (See Table 1).

The effect of the reaction conditions used (e.g., time, pH/pD and catalyst) is found to be dependent on the type of proton to be exchanged. For example, as shown in Figure 2,

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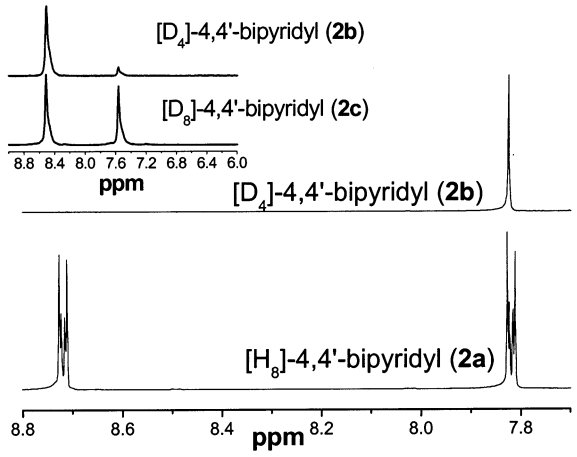


Figure 2. ^{1}H NMR spectra of [H_8]-4,4′-bipyridine (**2a**) (lower spectrum) and [D_4]-4,4′-bipyridine (**2b**) (upper spectrum) in [D_6]-acetone. Inset: ^{2}D NMR spectra of [D_8]-4,4′-bipyridine (**2c**) (lower spectrum) and [D_4]-4,4′-bipyridine (**2b**) (upper spectrum) in [D_6]-acetone).

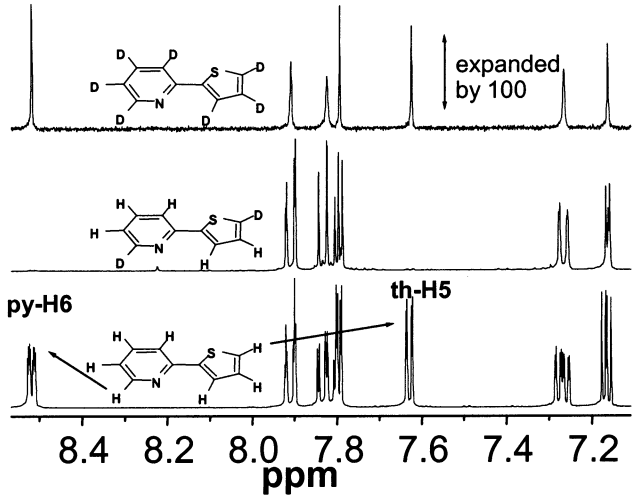


Figure 3. ^{1}H NMR spectra of [H_7]-2-(thien-2′-yl)-pyridine (**8a**) (lower spectrum), [D_2]-2-(thien-2′-yl)-pyridine (**8b**) (middle spectrum), and [D_7]-2-(thien-2′-yl)-pyridine (**8c**) (upper spectrum) in [D_6]-DMSO (all spectra were obtained at equal concentrations).

by using method B, little exchange is observed for the H3/H5 position of 4,4′-bipyridine (**2a**). Another example is illustrated in Figure 3 for compounds **8a**−**c**. This figure shows that after use of method B only the pyridine H6 and the thienyl H5 are exchanged, while full exchange is obtained with method C. In general, with method B, only exchange at the positions adjacent to heteroatoms (e.g., N and S) takes place even with extended reaction times (see Tables 1 and 2). Pyrazyl groups (compounds **9a**−**12a**) readily undergo complete exchange. This is not unexpected because every position can be considered as analogous to the H2/H6 position of pyridine.

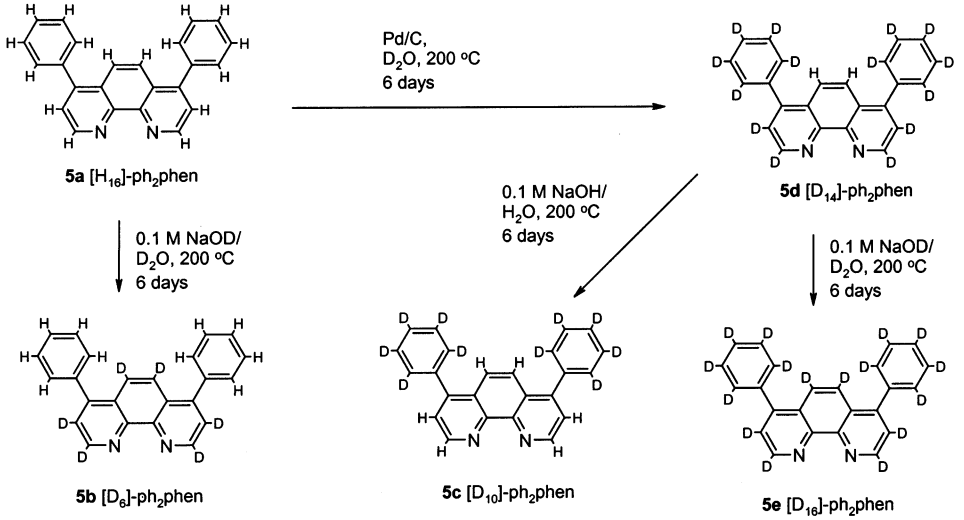
Under basic conditions, much less variation is observed in exchange rates at different positions, with thienyl, pyridyl, and pyrazyl groups showing complete H/D exchange. However, with this method, a significant level of control over the deuteriation of the aryl and pyridyl moieties in **5a** and **6a** can be achieved. It should be noted that with method C the regioselectively observed for **5a** is different than that observed with method B. This is discussed later in more detail.

Deuteriation of Aromatic and Aliphatic Groups. H/D exchange of methyl groups depends on the nature of the moiety to which they are attached. When bound directly to pyridyl (**3a**) or 1,2,4-triazole (**10a**, **14a**) groups, complete exchange occurs under all conditions examined (Tables 1 and 2). In contrast, methyl groups attached to phenyl rings (**12a**) show no exchange using method B but deuteriate completely in basic media and with method A. Phenyl (**5a**, **11a**, and **15a**) and tolyl groups (**12a**) are the least reactive moieties. No exchange of aromatic protons was observed using method B, but phenyl groups do exchange in the presence of Pd/C catalyst (method A). Using method C, complete exchange of both phenyl and methyl protons is observed, albeit at a much slower rate than for heteroaromatic groups.

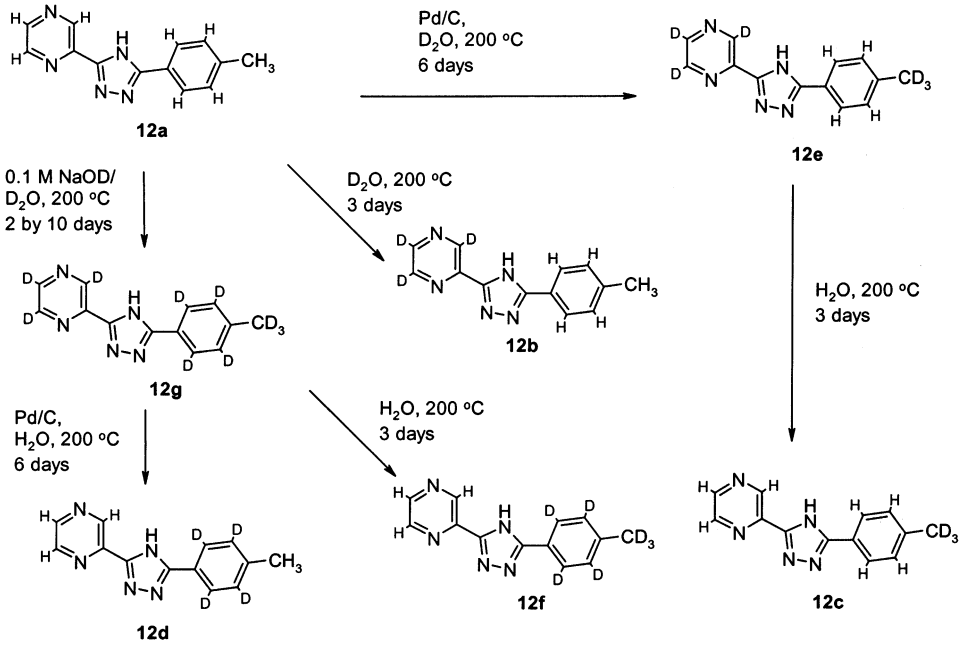
Regioselective Deuteriation. The differences in the reactivities of the various moieties allow for the development of strategies for the regioselective isotope exchange. Two examples of how different methods can be combined to achieve particular selectively deuteriated compounds are shown in Schemes 1 and 2. Scheme 1 (and Table 1) illustrates the routes taken in the preparation of four isotopologues of 4,7-diphenyl-1,10-phenanthroline (ph_2phen), namely [D_6]-ph_2phen, [D_{10}]-ph_2phen, [D_{14}]-ph_2phen, and [D_{16}]-ph_2phen. H/D exchange of the phenyl groups is achieved in the presence of the Pd/C catalyst in neutral D_2O but occurs only very slowly in basic D_2O. Consequently, using method A, the D_{14}- isotopologue (**5d**) is obtained in good yield with excellent regioselectivity. Interestingly, it is the phenanthroline H5 and H6 positions, which do not exchange under these conditions. However, deuteriation of the complete phenanthroline moiety takes place using method C. The fact that these reactions are high yield and can be carried out on a gram scale opens the possibility to use the products obtained as materials for further reaction. Therefore, a reverse D/H exchange as shown in Scheme 1 becomes a viable option. With this approach, compounds such as **5c** can be prepared from **5d**. In this process, the moiety that is most easily exchanged, namely the phenanthroline grouping, is regenerated in the perprotio form.

In Scheme 2, the different reactivities of pyrazine, aromatic, and methyl groupings are illustrated. On the basis of the behavior observed in Scheme 1, it is surprising that the tolyl aromatic protons do not exchange in any significant manner using method A, and this suggests that the methyl group deactivates the tolyl ring toward H/D exchange. Exchange of these protons is more efficient in the presence of base, albeit at a slower rate than for methyl or pyrazinyl protons. In contrast to the results obtained for **3a** and **10a**, the protons of the methyl group in **12a** can be exchanged using method A, but not by the use of method B. Again, the reverse D/H exchange can be used to yield isotopologues, such as **12c**, **12d**, and **12f**, which contain deuterium atoms in positions, which undergo H/D exchange with most difficulty.

Scheme 1. Routes Examined in the Deuteration of **5a**



Scheme 2. Routes Examined for the Deuteration of **12a**



Application of Deuteriation in Supramolecular Systems. The effect of deuteriation on ^{1}H and ^{13}C NMR spectroscopy is already well-known.[3,4] Deuteriation results not only in a loss in intensity but also in the splitting of ^{13}C signals into multiplets. An example of this is shown in Figure 4, which shows the ^{13}C spectra for **4a** and **4b**. In the spectrum of **4b**, only the signals that can be attributed to the quaternized carbon atoms remain as singlets; the others appear as triplets. Selective deuteriation is therefore useful in the assignment of ^{13}C resonances.[3c] In addition, ^{2}D NMR spectroscopy can be used to monitor specific sites in complexes, which have complicated ^{1}H NMR spectra (see Figure 2 and Supporting Information). Furthermore, for large molecules such as ruthenium(II) and osmium(II) polypyridyl complexes, deuteriation has been shown to be very useful in simplifying ^{1}H NMR spectra,[3] and an example of this can be seen in Figure 5 (and Supporting Information), where ^{1}H NMR resonances are eliminated by selective deuteriation. The spectra shown illustrate how well-defined NMR based information can be obtained for compounds, which contain a large number of hydrogen atoms. It is also important to point out that no evidence for H/D exchange was observed, under the reaction conditions employed to prepare ruthenium complexes from deuteriated ligands.[9] This is in agreement with the observed temperature dependence of the deuteriation methods discussed, which indicates that no measurable exchange occurs below 140 °C.[19]

The application of deuteriation is not limited to structural characterization. Isotope exchange has found application as a probe for studying excited-state processes in transition metal complexes in time-resolved resonance Raman spectroscopy.[18] In addition, deuteriation has received considerable attention, in the study of the excited-state properties of rare earth ions and ruthenium(II) polypyridyl complexes.[4] Selec-

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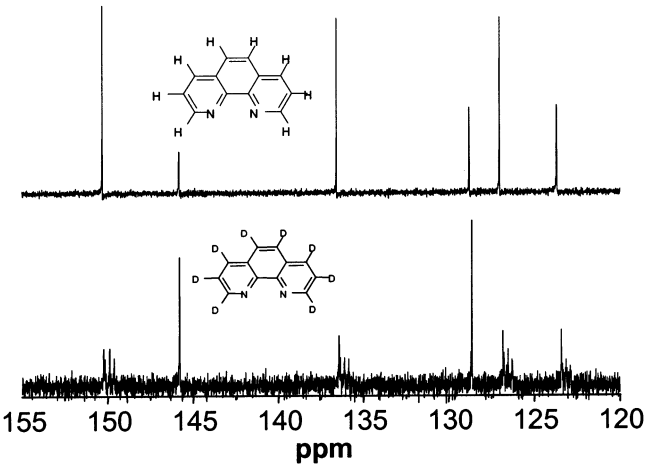

Figure 4. ^{13}C (proton decoupled) NMR spectra of $[H_8]$-1,10-phenanthroline (**4a**) (upper spectrum) and $[D_8]$-1,10-phenanthroline (**4b**) (lower spectrum) in $[D_6]$-DMSO.

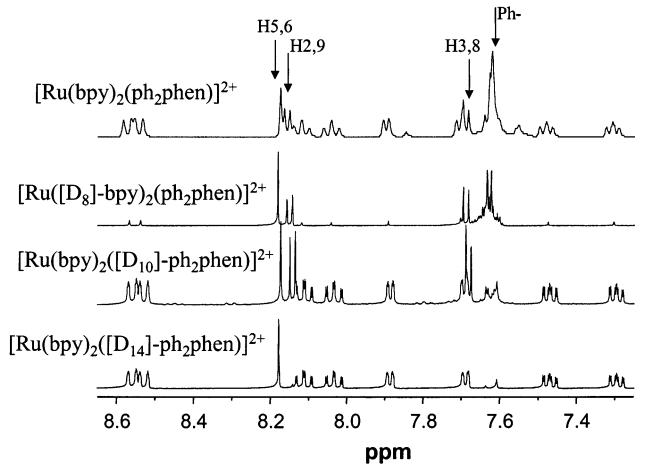

Figure 5. ^1H NMR spectra (400 MHz) of $[Ru([D_x]\text{-bpy})([D_y]\text{-ph}_2\text{phen})](PF_6)_2$ in $[D_3]$-acetonitrile. ($x = 0$ or 8, $y = 10$, 14, 16). Resonances due to ph_2phen ligand are indicated.

tive deuteriation of mixed ligand complexes was shown to yield important information about the location of the emitting state in mixed ligand complexes by its effect on emission lifetime.[7,8] For example, this approach can now be applied in the study of 2,3-bis(pyrid-2′-yl)-pyrazine (**7a**) based multinuclear ruthenium and osmium based bis(bipyridyl) complexes.[20] Deuteriation of either **7a** or **1a** would allow for the detailed study of the possible isomers present, and selective deuteriation could also be used to study the excited-state behavior of such compounds.

Limitations. During the course of this study, 1,2,4-triazines and compounds containing functional groups (e.g., carboxylic acids, esters, and carbonitriles) were found to decompose under the conditions employed. However, the deuteriation of relatively large amounts of material (up to 3 g in this study), coupled with high yields, allows for the preparation of a much larger range of deuteriated compounds through the deuteriation of precursors in synthetically useful amounts. Therefore, the preparation of perdeuteriated compounds containing thermally unstable functional groups such as carboxylic acids, carbonitriles, amides, and so forth may be achieved indirectly via perdeuteriated methyl precursors (e.g., $[D_6]$-4,4′-dicarboxy-2,2′-bipyridine can be prepared from **3b**).

Conclusions

In this contribution, a general approach to the deuteriation of heteroaromatic compounds is described. The potential for regioselective deuteriation is identified. The procedures employed allow for the reduction and often the complete elimination of the requirement for catalysts or derivatization (e.g., via *N*-oxide intermediates[5]) and much improved yields. The applicability of deuteriation in inorganic photophysics and supramolecular chemistry is already well-known.[4] However, its use has been severely limited by the cost and difficulty in preparing well-defined deuteriated materials. In this regard, the methods described here allow for the widespread application of deuteriation in such studies and provide an additional tool for the study of the spectroscopic and photophysical properties of supramolecular compounds.

Experimental Section

Materials. All reagents for synthesis were used as received without further purification. D_2O (99.9%) and 10% w/w Pd/C (Sigma-Aldrich) were used as received. NaOD/D_2O solution (1 M) was prepared in situ by addition of 460 mg of sodium metal to 20 mL of D_2O. 2,2′-Bipyridine (**1a**), 4,4′-bipyridine (**2a**), 4,4′-dimethyl-2,2′-bipyridine (**3a**), 1,10-phenanthroline (**4a**), 4,7-diphenyl-1,10-phenanthroline (ph_2phen) (**5a**), 2,2′-biquinoline (**6a**) (Sigma-Aldrich), and 2-(thien-2′-yl)-pyridine (2-thpy) (**8a**) (Lancaster) were obtained from commercial sources and used as received without further purification. The syntheses of 2,3-bis(pyrid-2′-yl)-pyrazine (**7a**),[21] 3-(pyrazin-2′-yl)-1,2,4-triazole (Hpztr) (**9a**), 3-methyl-5-(pyrazin-2′-yl)-1,2,4-triazole (Hmepztr) (**10a**), 3-(pyridin-2′-yl)-1,2,4-triazole (Hpytr) (**13a**), 3-methyl-5-(pyridin-2′-yl)-1,2,4-triazole (Hmepytr) (**14a**),[22] and 3-phenyl-5-(pyridin-2′-yl)-1,2,4-triazole (Hphpytr) (**15a**)[7] have been carried out using previously reported procedures. $[Ru(bpy)_3](PF_6)_2$,[23] $[Ru(d_x\text{-bpy})_2(d_y\text{-ph}_2\text{phen})](PF_6)_2$,[24] and $[Ru(bpy)_2(\mathbf{11a})](PF_6)_2$[25] (where bpy = **1a**, ph_2phen = **5a**, $x = 0$ or 8 and $y = 0$, 10, and 14) were prepared by literature procedures. The compounds 3-phenyl-5-(pyrazin-2′-yl)-1,2,4-triazole (Hphpztr) (**11a**) and 3-tolyl-5-(pyrazin-2′-yl)-1,2,4-triazole (Htolpztr) (**12a**) were carried out by previously reported procedures.[22]

Hydrogen−Deuterium Exchange Reactions. H−D exchange reactions were carried out using a Teflon cup contained in a general purpose dissolution Bomb P/N 4744 from Scientific Medical Products. Typical examples of each reaction type A−F are given in following paragraphs. Spectroscopic data for each partially and fully deuteriated compound are summarized as Supporting Information. In the case of method A, the solvent employed to remove deuteriated compound from the catalyst varied depending on the solubility of the compound. The extent of isotope exchange was determined from the isotopic pattern of the mass spectra of the compounds and by comparison of the ^1H NMR spectra of the

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deuteriated compound with its perprotio analogue at known concentrations using the residual solvent peak as an internal standard.

Method A. [D_8]-2,2′-Bipyridine (1b). 2,2′-Bipyridine (**1a**) (3 g) was reacted with 50 mg of 10% Pd/C in 20 mL of D_2O at 200 °C under pressure for 3 days. On cooling, the reaction mixture was filtered, and the catalyst was washed with 2 × 50 mL of diethyl ether to remove any 2,2′-bipyridine from the catalyst surface. The diethyl ether washings and the aqueous filtrate were evaporated to dryness to yield [D_8]-2,2′-bipyridine. It should be noted that with this method yields are sometimes lower than quantitative because of difficulty in removing the product from the catalyst.

Method B. [D_3]-Hphpztr (11b). A 1 g portion of 3-phenyl-5-(pyrazin-2-yl)-1,2,4-triazole (**11a**) was reacted at 200 °C in 20 mL of D_2O for 3 days. After cooling, the compound precipitated and was filtered and air-dried.

Method C. [D_4]-Hphpytr (15c). A 1.5 g portion of 3-phenyl-5-(pyridin-2-yl)-1,2,4-triazole (**15a**) was reacted at 200 °C in 20 mL of 1 M NaOD/D_2O for 3 days. On cooling, the reaction mixture was neutralized with concentrated HCl, and the white precipitate was filtered and air-dried.

Method D. [D_5]-Hphpytr (15d). A 0.5 g portion of [D_9]-3-phenyl-5-(pyridin-2-yl)-1,2,4-triazole (**15e**) was reacted at 200 °C in 20 mL of 1 M NaOH/H_2O for 3 days. On cooling, the reaction mixture was neutralized with concentrated HCl, and the white precipitate was filtered and air-dried.

Method E. [D_5]-Hphpztr (11c). A 0.5 g portion of [D_8]-3-phenyl-5-(pyrazin-2-yl)-1,2,4-triazole (**11d**) was reacted at 200 °C in 20 mL of H_2O for 3 days. On cooling the reaction mixture, the white precipitate was filtered and air-dried.

Method F. As for method A except H_2O was used in place of D_2O.

^{1}H,^{13}C, and ^{2}D NMR Spectroscopic and Mass Spectral Data. Assignments of ^{1}H and ^{2}D NMR resonances were made by comparison with assignments made for ^{1}H NMR spectra of their perprotio analogues and are available as Supporting Information. Assignments of ^{13}C spectra were made on the basis of comparison with assignments made for their perprotio analogues using HMQC and HMBC NMR experiments and on the basis of the loss of intensity and splitting upon deuteriation. ^{1}H, ^{2}D, ^{13}C and ^{1}H COSY, HMQC, and HMBC spectra were recorded on a Bruker Avance 400 (400 MHz) NMR spectrometer equipped with a QNP probe (a broad band probe was employed for ^{2}D NMR spectroscopy). All measurements were carried out in [D_6]-acetone or [D_6]-dimethyl sulfoxide. ^{2}D NMR spectra were acquired in [H_6]-acetone or [H_6]-dimethyl sulfoxide. Peak positions are relative to residual solvent peaks. Mass spectra were obtained using a Bruker-Esquire-LC_00050 electrospray ionization mass spectrometer at positive polarity with cap-exit voltage of 167 V. Spectra were recorded in the scan range of 50−2200 *m*/*z* with an acquisition time of between 300 and 900 μs and a potential between 30 and 70 V. Each spectrum was recorded by summation of 20 scans. The limited solubility of some compounds precluded the measurement of their ^{2}D and ^{13}C NMR spectra.

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Supporting Information Available: ^{1}H NMR spectra and characterization information. This material is available free of charge via the Internet at http://pubs.acs.org.

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