BIPYRIDINE BUILDING BLOCKS FOR SELF-ORGANIZATION SYSTEMS: FIRST COMPLETE NMR-SPECTROSCOPIC INVESTIGATION OF 6,6'-DISUBSTITUTED 2,2'-BIPYRIDINES OBTAINED *VIA N*-OXIDATION ROUTE AND RELATED REACTIONS

Ulrich S. Schubert,*[a] George R. Newkome,*[b] Andreas Göldel,[c] Alexander Pemp,[d] Jörg L. Kersten,[e] and Claus D. Eisenbach*[e]

[a] Lehrstuhl für Makromolekulare Stoffe, Technische Universität München, Lichtenbergstr. 4, 85747 Garching, Germany. [b] Center for Molecular Design and Recognition, Department of Chemistry, University of South Florida, Tampa 33600, FL, USA. [c] Lehrstuhl für Makromolekulare Chemie II and Bayreuther Institut für Makromolekülforschung (BIMF), Germany. [d] Lehrstuhl für Organische Chemie I/2, Universität Bayreuth, Universitätsstr. 30, 95440 Bayreuth, Germany. [e] Institut für Technische Chemie II, Universität Stuttgart, Pfaffenwaldring 55, 70569 Stuttgart, Germany

Abstract — One- and two-dimensional NMR-spectroscopic data of eight 6,6'-disubstituted 2,2'-bipyridines, prepared by the *N*-oxidation route, were used to confirm their structures. These key compounds in supramolecular construction lead to the characterization of larger *oligo*(bipyridine) building blocks. Furthermore some related reactions are described which lead to unsymmetrically functionalized bipyridines or can be used for the purification of *bis*hydroxy compounds.

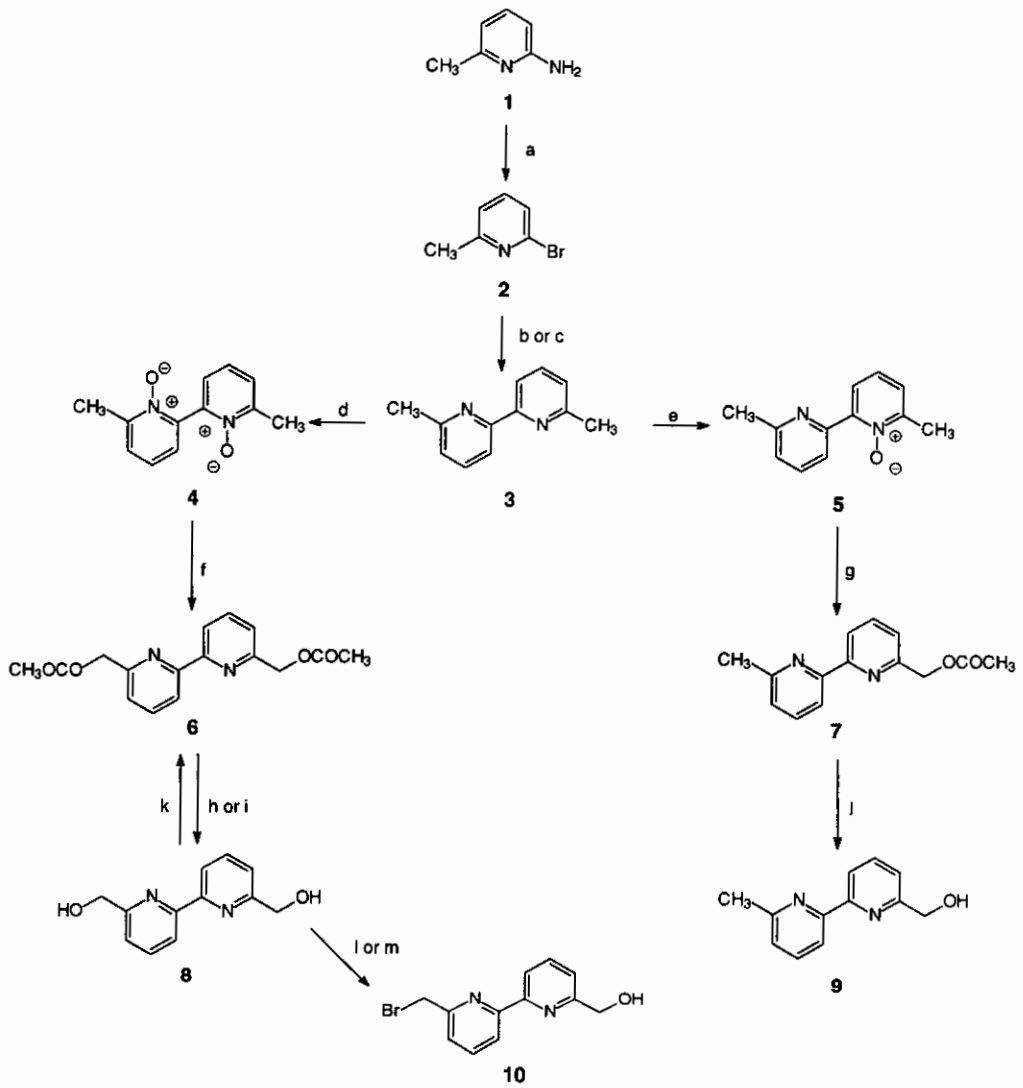
The design of organic or inorganic molecular compounds with the ability to form well-defined supramolecular architectures is one major goal in modern synthetic chemistry.[1] Such systems often show recognition-directed, self-assembly features.[2,3] One of the most famous self-organization systems is the *oligo*(bipyridine) metal complexes[4-8] which spontaneously form helical architectures in the presence of Ag^{I} or Cu^{I} cations, whereby two *oligo*(bipyridine) strands wrap around the metal cations to form structures, similar to the Watson and Crick double-helix in nucleic acids.[9]

Our research interest is to build these special building blocks into synthetic macromolecules or dendrimers in order to obtain new ordered systems with specific structural and functional properties.[10,13] We recently published optimized routes to functionalized 6,6'-disubstituted 2,2'-bipyridines in a multigram scale using *N*-oxidation procedures to hydroxymethyl terminated bipyridines[14] and a general new synthetic approach towards unsymmetrically functionalized bipyridine and *oligo*(bipyridine) building

blocks, based on 6,6'-*bis*(hydroxymethyl)-2,2'-bipyridine.[15] Although bipyridine molecules have been known more than 100 years[16] there are limited data based on NMR analysis (the last pure NMR literature dates back to 1967[17,18]), which is the appreciate analytical tool to characterize these bipyridines. Comparing our own spectroscopic data with literature data[4,5,19-23] showed, in part, significant differences. Furthermore, we could not find a fundamental proof for the peak attachments.[19-23] Therefore we used one- and two-dimensional homo- and heteronuclear coupled NMR techniques to collect a set of data from the intermediates to key molecules for functionalized bipyridine building blocks (Scheme 1; most synthetic procedures are published elsewhere, see also experimental section). This represents the first step to be able to predict the NMR shifts of new compounds in this family and to compare their data with complex supramolecular and macromolecular systems containing bipyridine segments.

6,6'-Dimethyl-2,2'-bipyridine (**3**) was the key precursor in most of the recent applications of 2,2'-bipyridines in synthetic chemistry.[4-8,10-15,19-23] Functionalization using the *N*-oxidation strategy *via* the 6,6'-dimethyl-2,2'-bipyridine mono-*N*-oxide (**5**) or the *bis*-*N*-oxide (**4**) resulted in the corresponding 6-hydroxymethyl-6'-methyl- (**9**) and the 6,6'-*bis*(hydroxymethyl)-2,2'-bipyridine (**8**) after the Boekelheide rearrangement. The intermediates were the 6-acetoxymethyl-6'-methyl- (**7**) and the 6,6'-*bis*(acetoxymethyl)-2,2'-bipyridine (**6**). The *N*-oxidation could be controlled by using either 3-chloroperbenzoic acid or hydrogen peroxide in acetic acid. All the reactions were conducted in 100 g quantities and purification was only required for the final products (**8** and **9**). However, for the recently described general new synthetic approach towards unsymmetrically functionalized bipyridine and *oligo*(bipyridine) building blocks, very pure 6,6'-*bis*(hydroxymethyl)-2,2'-bipyridine (**8**) is required (as well as for polymerization reactions). For large quantities, the purification of the *bis*hydroxymethyl functionalized bipyridine is the difficulty in this synthetic strategy. Furthermore, the *bis*hydroxymethyl material, recycled in the approach towards unsymmetrically functionalized bipyridines,[15] could not be sufficiently purified using normal chromatography techniques or crystallization. To circumvent this difficulty, we developed a simple two step purification procedure: The acetoxy compound (**6**) could be prepared by reaction of partly contaminated hydroxymethyl compounds with acetic anhydride in high yields. After purification by crystallization, transesterification using the K_2CO_3 method, described earlier,[12,19] was utilized. This affords a simple way, after recrystallization, to extremely pure products.

Furthermore we investigated different methods towards unsymmetrically functionalized bipyridines and *oligo*(bipyridine) building blocks. The treatment of the *bis*hydroxymethyl compound with CBr_4 and PPh_3 or HBr resulted in the unsymmetrically functionalized 6-bromomethyl-6'-hydroxymethyl-2,2'-bipyridine (**10**),[25] however, the yields are rather low compared to our previously published procedure.[15]

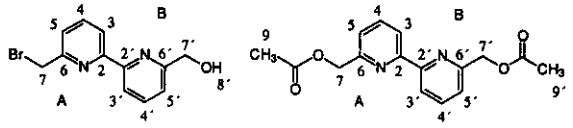


Scheme 1: Synthetic routes to hydroxy terminated bipyridine building blocks.

a) 1. HBr, Br_2, -35°C; 2. $NaNO_2$; 3. NaOH (90%); Lit.[12,14,19]
b) Pd/C, HCOONa, $BzEt_3NCl$, NaOH, H_2O, reflux, 48 h (69%); Lit.[12,14,19]
c) 1. Ni(0), toluene, reflux, 2. H_2O (58%); Lit.[24,26]
d) H_2O_2, AcOH, reflux, 16 h (82%); Lit.[12,19]
e) mCPBA, $CHCl_3$ (76%); Lit.[14,19]
f) Ac_2O, reflux, 20 min (68%); Lit.[12,19]
g) Ac_2O, reflux, 20 min (95%); Lit.[14,19]
h) K_2CO_3, EtOH, 2 h (94%); Lit.[12,19]
i) 6 N HCl, reflux, 12 h (92%); Lit.[14,19]
j) 6 N HCl, reflux, 14 h (96%); Lit.[14,19]
k) Ac_2O, pyridine (94%)
l) 48% HBr, reflux, 2 h (18%)
m) PPh_3, CBr_4, CH_2Cl_2, 0°C, 20 min (13%).

In Table 1 the complete set of ^1H-^1H COSY NMR data of the eight described 6,6'-substituted 2,2'-bipyridine compounds is collected.

Table 1: ^1H NMR (300 MHz) chemical shift data.



Nr.	ring A‡			ring B			substituents			
	3	*4*	*5*	*3´*	*4´*	*5´*	*7*	*7´*	*8* *8´*	*9* *9´*
3[a]	8.18 dd, 1 H *J* = 7.7, 7.7	7.66 t*, 1 H *J* = 7.7	7.12 dd, 1 H *J* = 7.7, 0.4	8.18 dd, 1 H *J* = 7.7, 7.7	7.66 t*, 1 H *J* = 7.7	7.12 dd, 1 H *J* = 7.7, 0.4	2.61 s, 3 H	2.61 s, 3 H	-	-
4[b]	7.44 dd, 1 H *J* = 7.7, 7.7	7.30 t*, 1 H *J* = 7.7	7.57 dd, 1 H *J* = 7.7, 0.6	7.44 dd, 1 H *J* = 7.7, 7.7	7.30 t*, 1 H *J* = 7.7	7.57 dd, 1 H *J* = 7.7, 0.6	2.37 s, 3 H	2.37 s, 3 H	-	-
5[b]	7.93 dd, 1 H *J* = 7.7, 7.7	7.35 t*, 1 H *J* = 7.7	7.53 dd, 1 H *J* = 7.7, 0.6	8.50 d, 1 H *J* = 7.8	7.80 t*, 1 H *J* = 7.8	7.05 d, 1 H *J* = 7.8	2.45 s, 3 H	2.55 s, 3 H	-	-
6[a]	8.32 dd, 1 H *J* = 7.8, 7.8	7.77 t*, 1 H *J* = 7.8	7.31 dd, 1 H *J* = 7.8, 0.5	8.32 dd, 1 H *J* = 7.8, 7.8	7.77 t*, 1 H *J* = 7.8	7.31 dd, 1 H *J* = 7.7, 0.5	5.26 s, 2 H	5.26 s, 2 H	-	2.14 s, 3 H
7[a]	8.26 d, 1 H *J* = 7.8	7.70 t*, 1 H *J* = 7.8	7.24 d, 1 H *J* = 7.8	8.12 d, 1 H *J* = 7.7	7.57 t*, 1 H *J* = 7.7	7.05 d, 1 H *J* = 7.7	5.22 s, 2 H	2.52 s, 3 H	-	2.09 s, 3 H
8[a]	8.31 dd,1 H *J* = 7.8, 7.8	7.81 t*, 1 H *J* = 7.8	7.24 dd, 1 H *J* = 7.8, 0.6	8.31 dd, 1 H *J* = 7.8, 7.8	7.81 t*, 1 H *J* = 7.8	7.24 dd, 1 H *J* = 7.7, 0.6	4.84 d, 2 H *J* = 4.7	4.84 d, 2 H *J* = 4.7	4.01 t, 2 H *J* = 4.7	-
9[a]	8.28 d, 1 H *J* = 7.8	7.74 t*, 1 H *J* = 7.8	7.19 d, 1 H *J* = 7.8	8.14 d, 1 H *J* = 7.8	7.65 t*, 1 H *J* = 7.8	7.13 d, 1 H *J* = 7.8	4.78 s, 2 H	2.59 s, 2 H	4.25 s, 1 H	-
10[a]	8.36 d, 1 H *J* = 7.7	7.81 t*, 1 H *J* = 7.7	7.46 d, 1 H *J* = 7.7	8.31 d, 1 H *J* = 7.7	7.81 t*, 1 H *J* = 7.7	7.24 d, 1 H *J* = 7.7	4.61 s, 2 H	4.81 s, 2 H	4.0 s, 1 H	-

*[a] recorded in $CDCl_3$, [b] DMSO-d_6, *no resolution to dd, ‡ring A = ring of higher priority*

Taking all the recorded cross-peaks, correlation peaks, and information of the 5-bromo-6,6'-dimethyl-2,2'-bipyridine[27] (Figure 1) allowed us to confirm every single resonance peak and coupling.

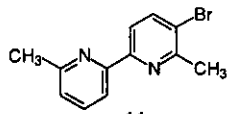


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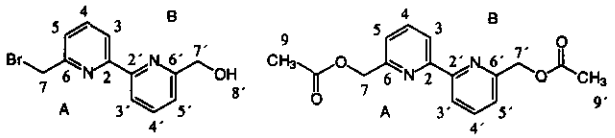
Figure 1: Schematic representation of 5-bromo-6,6'-dimethyl-2,2'-bipyridine[27] used for the assignement of the peaks and couplings.

The corresponding ^{13}C NMR data (Table 2) were also collected and assigned on the basis of spin echo fourier transformation (SEFT; in particular APT), ^{1}H-^{13}C COSY, and ^{1}H-^{13}C heteronuclear multiple bond correlated spectra (HMBC).

Table 2: ^{13}C NMR (75 MHz) chemical shift data.



	ring A					ring B					substituents			
Nr.	*2*	*3*	*4*	*5*	*6*	*2´*	*3´*	*4´*	*5´*	*6´*	*7*	*7´*	*8* *8´*	*9* *9´*
3[a]	155.9	118.2	137.0	123.0	157.8	155.9	118.2	137.0	123.0	157.8	24.6	24.6	- -	- -
4[b]	148.0	125.8	123.6	126.9	143.1	148.0	125.8	123.6	126.9	143.1	17.3	17.3	- -	- -
5[b]	149.4	125.2	123.9	126.0	146.4	149.4	121.9	136.2	123.4	157.4	17.9	24.1	- -	- -
6[a]	155.1	120.1	137.4	121.6	155.4	155.1	120.1	137.4	121.6	155.4	68.9	68.9	170.5 170.5	20.9 20.9
7[a]	155.2	120.0	137.4	121.2	157.8	155.2	118.0	136.9	123.3	156.0	66.9	24.5	170.5 -	20.8 -
8[a]	158.3	119.6	137.7	120.6	154.3	158.3	119.6	137.7	120.6	154.3	63.9	63.9	- -	- -
9[a]	155.0	119.6	137.4	120.1	158.2	154.9	118.0	137.0	123.3	157.9	63.9	24.5	- -	- -
10[a]	155.2	120.1	137.9	123.5	156.3	154.3	120.0	137.4	120.6	158.1	34.0	63.9	- -	- -

[a] recorded in $CDCl_3$ and [b] DMSO-d_6 at 125 MHz

The NMR spectroscopic data reported here are the first examples of complete and consistent structural data of functionalized *oligo*(bipyridine) building blocks. This information will facilitate the interpretation of complex spectra of new bipyridine-based systems in organic, supramolecular and polymer chemistry and will allow researchers to predict chemical shifts of a wide range of new *N*-heterocyclic systems. Furthermore, we presented new reactions, related to the *N*-oxidation route, which are useful for the preparation of unsymmetrically functionalized bipyridines or the purification of the main important key molecule.

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EXPERIMENTAL

Bruker AMX 300 and DRX 500 spectrometers were used to record ^1H and ^{13}C NMR spectra in $CDCl_3$ (25°C). ^1H and ^{13}C chemical shifts are given in δ units relative to $CDCl_3$ as an external standard (compounds (**4**) and (**5**) in DMSO-d_6 relative to TMS).

6,6'-Bis(acetoxymethyl)-2,2'-bipyridine (**6**): A solution of 500 mg (2.3 mmol) of 6,6'-*bis*(hydroxymethyl)-2,2'-bipyridine (**8**) in 7.5 mL of dry pyridine and 10 mL (106 mmol) of freshly destilled Ac_2O was refluxed for 3 h. The mixture was concentrated *in vacuo* and the crude product crystallized ($CHCl_3$/cyclohexane 1:20) to yield 650 mg (94%) of a white solid with mp 102-104°C. – NMR data see Table 1 and Table 2. – MS (EI, 70 eV); m/z (%): 300 (18) [M^+].

6-Bromomethyl-6'-hydroxymethyl-2,2'-bipyridine (**10**):
via HBr-method: A solution of 1.0 g (4.7 mmol) of 6,6'-*bis*(hydroxymethyl)-2,2'-bipyridine (**9**) in 30 mL of HBr (48%) was refluxed for 2 h. After neutralization with 6 N NaOH, the precipitate was collected and dried *in vacuo*. The residue was solved in $CHCl_3$, washed with 1 M Na_2CO_3 solution (3 x 100 mL), dried with Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, $CHCl_3$) to yield 230 mg (18%, Lit. 8%[25]) of **10**, as white solid with mp 129–131°C. – NMR data see Table 1 and Table 2. – MS (EI, 70 eV); m/z (%): 280/278 (83/81) [M^+]. Also 640 mg (40%) of 6,6'-*bis*(bromomethyl)-2,2'-bipyridine (**12**) were isolated as white solid with mp 179–181°C. – ^1H-NMR: 4.63 (s, 6 H, 7,7'-H), 7.47 (d, J = 7.7, 2 H, 5,5'-H), 7.82 (t, J = 7.7, 2 H, 4,4'-H), 8.39 (d, J = 7.7, 2 H, 3,3'-H). – ^{13}C-NMR: 34.1 (7,7'-C), 120.5 (3,3'-C), 123.5 (5,5'-C), 137.9 (4,4'-C), 155.5 (6,6'-C), 156.2 (2,2'-C). – MS (EI, 70 eV); m/z (%): 342 (33) [M^+].

via PPh_3/CBr_4-method: To a solution of 1.0 g (4.6 mmol) of 6,6'-*bis*(hydroxymethyl)-2,2'-bipyridine (**9**) and 3.07 g (9.3 mmol) of CBr_4 in 200 mL of CH_2Cl_2 1.33 g (5.1 mmol) of triphenylphosphine was added at 0°C in several portions during 20 min. After 10 min stirring at 0°C, the solvent was evaporated *in vacuo* and the crude product was purified by column chromatography (SiO_2, CH_2Cl_2/MeOH 98:2) to yield 170 mg (13%) of **10** as white solid. – Characterization data see above.

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