Synthesis and photophysical properties of 7-deaza-2′-deoxyadenosines bearing bipyridine ligands and their Ru(II)-complexes in position 7†

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The synthesis of the title 7-deazaadenine 2′-deoxyribonucleosides bearing bipyridine, phenanthroline or terpyridine ligands linked to position 7 *via* an acetylene or phenylene spacer is reported based on aqueous cross-coupling reactions of unprotected 7-iodo-7-deaza-2′-deoxyadenosine with ligand-functionalized acetylenes or boronic acids. The aqueous cross-coupling with acetylene or boronate building blocks containing the $Ru(bpy)_3$-type of complex gave the corresponding Ru-containing nucleosides. Photophysical and electrochemical properties were studied and the most efficient type of complex was selected for future luminescent and redox labelling of DNA. The title nucleosides also showed some cytostatic and anti-HCV activities.

Introduction

Complexes of bipyridine and phenanthroline ligands with transition metals possess[1] unique electrochemical and photophysical properties and thus could be used for electrochemical or luminescent labeling of biomolecules. Some of the phenanthroline complexes, which are efficient DNA intercalators, have been extensively used as luminescent and electroactive DNA labels.[2] Attachment of probes based on metal complexes directly to the nucleobase *via* conjugate linkers should increase efficiency of the charge transfer and thus enhance sensitivity. Covalently bound conjugates of pyrimidine nucleotides and phenanthroline complexes of Ru and Os have been studied as luminescence probes for DNA hybridization and charge transfer through DNA.[3] The corresponding labeling of purine bases has not been studied until recently, when we have reported[4] on the synthesis and electrochemistry of model 9-benzyladenine derivatives bearing oligopyridine ligands or their Ru or Os complexes linked to position 8 *via* conjugate phenylene or acetylene tethers that are designed to transmit electronic changes on the nucleobase to the electroactive label. Later on, we reported[5] the synthesis of a 2′-deoxyadenosine nucleoside bearing bipyridine ligands and the corresponding Ru complexes in position 8. However, our follow-up study on chemical incorporation of the corresponding protected 8-substituted 2′-deoxyadenosine phosphoramidites on solid support was unsuccessful due to very low coupling yields.[6]

An alternative method for the construction of functionalized nucleic acids is based on polymerase incorporations of base-modified nucleoside triphosphates (dNTPs).[7] It can be even combined with cross-coupling reactions of dNTPs, and we have recently used this novel approach[8] for the synthesis of DNA bearing amino acids,[9] ferrocenes[10] and amino- and nitrophenyl groups.[11] However, we[9] and others[7c] have shown that 8-substituted purine dNTPs are poor substrates for DNA polymerases (presumably due to their preference for *syn*-conformation and steric hindrance between the substituent and DNA backbone) and should be replaced by 7-substituted 7-deazapurine dNTPs.

In order to be able to proceed to polymerase incorporation of purines bearing bipyridine ligands and their Ru complexes, we had to first develop the synthetic methodology for the introduction of the bipyridine and phenanthroline ligands linked *via* acetylene or phenylene, as well as the corresponding Ru(II)-complexes, to position 7 of 7-deaza-2′-deoxyadenosine and study the electrochemical and photophysical properties of the resulting labeled nucleosides and this is the topic of the present paper.

Results and discussion

Synthesis of 7-deaza-2′-deoxyadenosine conjugates

In order to attach bipyridine-type ligands linked *via* an acetylene or phenylene linker to position 7 of 7-deaza-2′-deoxyadenosine,[12] we have followed our previous study[5] on 8-substituted-2′-deoxyadenosines and utilized aqueous-phase cross-coupling reactions.[13] The Sonogashira cross-coupling reactions of ethynyl oligopyridines **2a** and **2b** with 7-iodo-7-deaza 2′-deoxyadenosine (**1**) were performed in DMF (rather than in H_2O–CH_3CN which caused problems in the 8-substituted adenosine series[5]) in the presence of $Pd(OAc)_2$, water soluble ligand $P(PhSO_3Na)_3$ (TPPTS), CuI and Et_3N to afford the desired ethynyl conjugates **4a**,**b** in excellent yields of 91 and 82% respectively (Scheme 1, Table 1). The aqueous-phase Suzuki–Miyaura cross-coupling reaction of boronates **3a**,**c**,**d** with **1** also proceeded well. Using a mixture of H_2O–CH_3CN (2 : 1) as solvent, in the presence of $Pd(OAc)_2$, TPPTS and Cs_2CO_3 as a base, the phenylene-bridged conjugates **5a**,**c**,**d** were prepared in excellent yields (Scheme 1,

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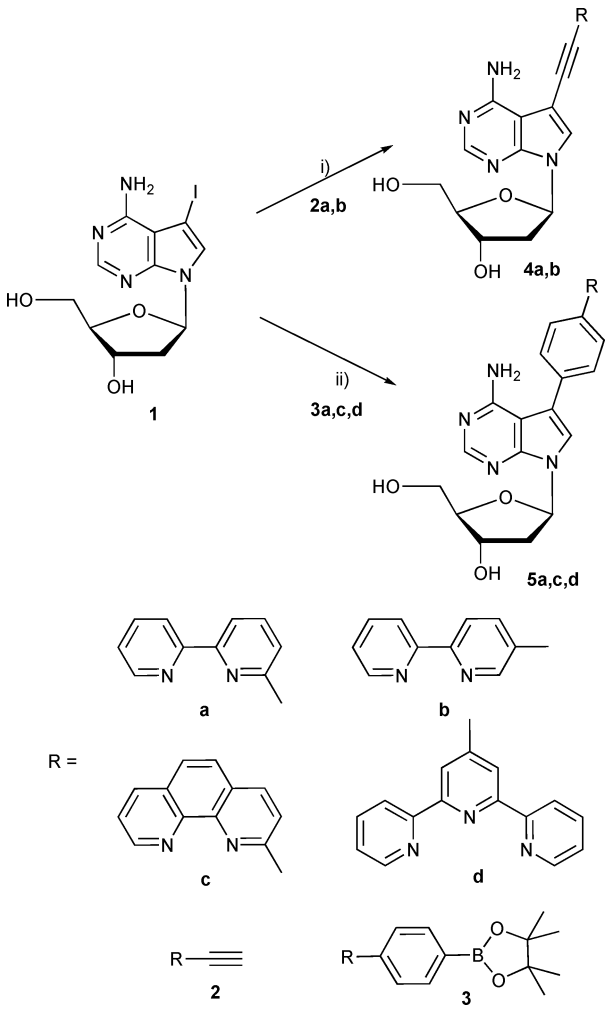


Scheme 1 Synthesis of 7-deaza 2′-deoxyadenosine conjugates. *Reagents and conditions*: i) $Pd(OAc)_2$ (5 mol%), TPPTS (2.5 equiv. to Pd), Et_3N (10 equiv.), CuI (10 mol%), DMF; ii) $Pd(OAc)_2$ (5 ;mol%), TPPTS (2.5 equiv. to Pd), Cs_2CO_3 (3 equiv.), H_2O–CH_3CN = 2 : 1.

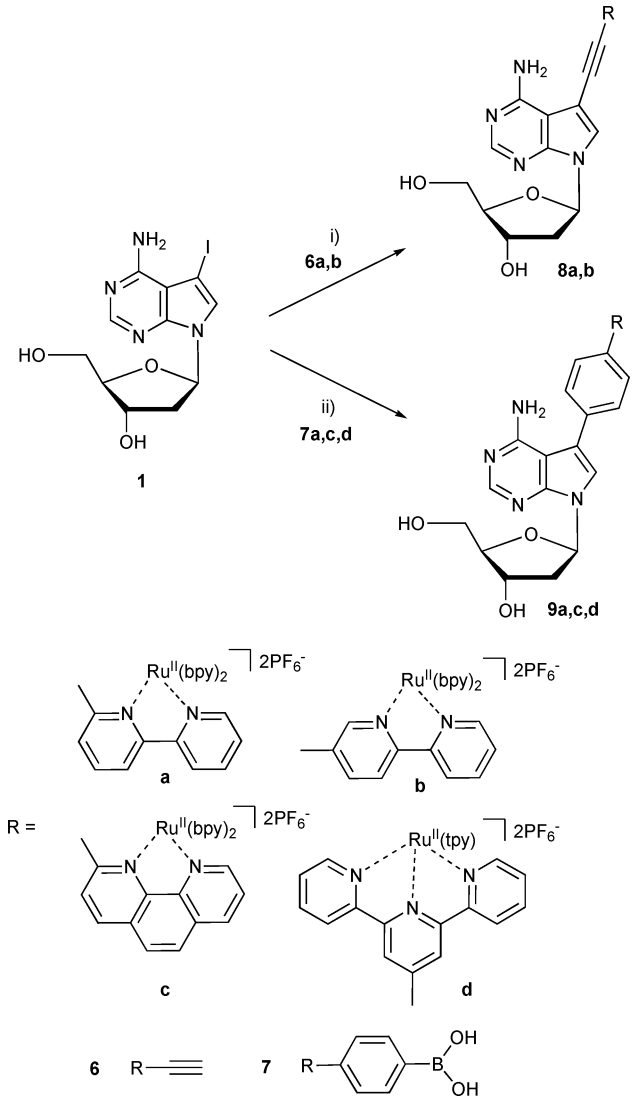
Table 1 Synthesis of 7-deaza 2′-deoxyadenosine conjugates

Entry	Reagent	Product	Yield (%)
1	**2a**	**4a**	91
2	**2b**	**4b**	82
3	**3a**	**5a**	95
4	**3c**	**5c**	96
5	**3d**	**5d**	78

Table 1). The yields of all these reactions were substantially better than in the case of 8-substituted adenosines.[5] We have shown that a catalytic system consisting of $Pd(OAc)_2$ and TPPTS is applicable for efficient protection-free attachment of oligopyridine type ligands to position 7 of 7-deaza-2′-deoxyadenosine.

Synthesis of 7-deazaadenine nucleosides bearing Ru(II) complexes

The next goal of our study was to prepare the corresponding Ru(II) complexes of the 7-deazapurine nucleosides. In analogy to our previous results, we have applied the direct aqueous-phase cross-coupling reactions of Ru-containing acetylene **6** and boronate **7** building blocks[4] with 7-iodo-7-deaza-2′-deoxyadenosine (**1**). All the cross-coupling reactions of Ru-containing acetylenes and boronates were performed in a mixture of H_2O–CH_3CN in order to be further applicable for labeling of nucleoside triphosphates (dNTPs). The Sonogashira reaction of Ru(II)-containing acetylenes **6a**,**b** with the nucleoside **1**, using $Pd(OAc)_2$–TPPTS, CuI and Et_3N, gave the corresponding nucleoside Ru-complexes **8a**,**b** in moderate yields of 47 and 59% respectively (Scheme 2, Table 2).



Scheme 2 Synthesis of 7-deazaadenine nucleosides bearing Ru(II) complexes. *Reagents and conditions*: i) $Pd(OAc)_2$ (5 mol%), TPPTS (2.5 equiv. to Pd), Et_3N (10 equiv.), CuI (10 mol%), H_2O–CH_3CN = 2 : 1; ii) $Pd(OAc)_2$ (5 mol%), TPPTS (2.5 equiv. to Pd), Cs_2CO_3 (3 equiv.), H_2O–CH_3CN = 2 : 1.

Table 2 Synthesis of 7-deazaadenine nucleosides bearing Ru(II) complexes

Entry	Reagent	Product	Yield (%)
1	**6a**	**8a**	47
2	**6b**	**8b**	59
3	**7a**	**9a**	95
4	**7c**	**9c**	73
5	**7d**	**9d**	76

In both cases some byproducts were formed, probably due to the decomposition of the starting materials. However, the reactions still proceeded much better when compared to 8-substituted-2′-deoxyadenosine analogs (16% for **6a** and 0% for **6b**). On the other hand, the aqueous-phase Suzuki–Miyaura cross-coupling reaction of Ru-containing boronic acids proceeded relatively cleanly in accord with our previous results.[5]

Reactions of the boronates **7a**,**c**,**d** with 7-iodo-7-deaza-2′-deoxyadenosine (**1**) in the presence of $Pd(OAc)_2$–TPPTS and Cs_2CO_3, gave the corresponding complexes **9a**,**c**,**d** in good yields (Scheme 2, Table 2). The Ru(II)-containing complexes were isolated by column chromatography using a mixture of H_2O–CH_3CN–sat. KNO_3 as eluent. The only exception was the isolation of complex **9c** where even repeated column chromatography did not give pure compound and, therefore, it had to be isolated by preparative loose layer TLC using the same eluent. Final re-precipitation by saturated aqueous solution of NH_4PF_6 gave the desired Ru(II) complexes as PF_6^- salts. Due to the chirality of the Ru-complexes, the nucleosides **8** and **9** were isolated as inseparable (chromatographically homogeneous) mixtures of diastereoisomers (1 : 1).

Photophysical and redox properties of the 7-substituted 7-deazaadenine nucleosides

In order to characterize the new modified 7-deazaadenine nucleosides and to explore their potential applications in DNA labeling, we have examined their photophysical and redox properties. First we measured UV-Vis spectra. As shown in Fig. 1 the bipyridine

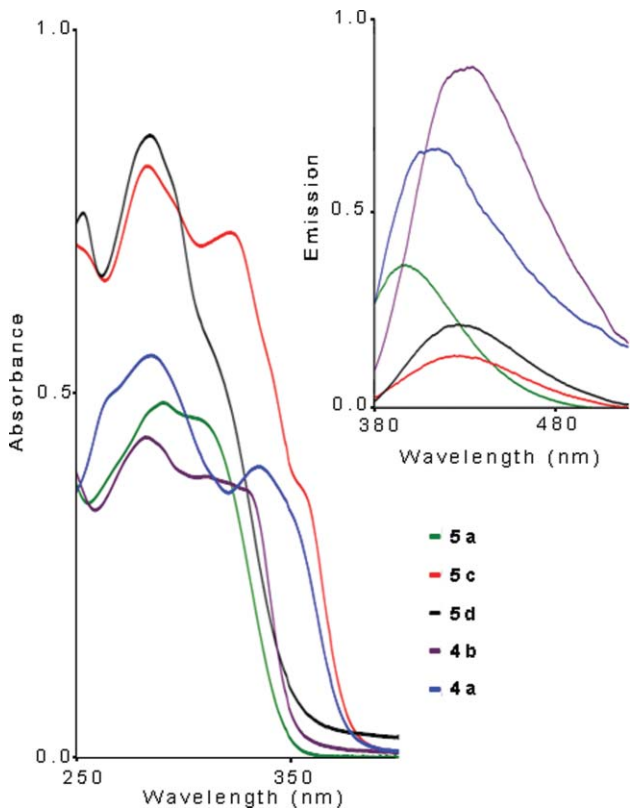


Fig. 1 UV/Vis and emission spectra of 7-deazaadenine nucleoside conjugates.

Table 3 Photophysical properties of the 7-bipyridine-derivatives of 7-deazaadenine nucleosides

Entry	Compd	UV-Vis, λ/nm, (ε)[a]	Excitation/nm[b]	Emission/nm[b]
1	**4a**	282 (2.8), 321 (2.4)	351	406
2	**4b**	285 (3.5), 336 (2.5)	368	427
3	**5a**	291 (3.1), 325 (3.0)	340	395
4	**5c**	283 (5.1), 322 (4.5)	330	424
5	**5d**	253 (4.7), 284 (5.4)	343	425

[a] In $CHCl_3$, 1.6×10^{-5} M solutions, extinction coefficients $\varepsilon \times 10^4$ in $M^{-1}.cm^{-1}$; [b] 1.6×10^{-4} M solutions in $CHCl_3$.

7-deazaadenosine conjugates **4** and **5** exhibit intense overlapping π–π* transitions of the aromatic diimine ligands[14] at 280 nm. The excitation of a chloroform solution of this nucleoside conjugates at absorption maxima exhibited intensive emissions centered at 415 nm (Fig. 1, Table 3).

The emission spectra of the Ru complexes (both nucleosides **8** and **9** and parent starting acetylenes **6** and boronates **7**) are summarized in Table 4 and one example is given in Fig. 2. The intense 288 nm band indicates a π→π* (LC) transition in the bipyridine ligands, and the 450 nm band corresponds to a d→π* (^{1}MLCT) transition in analogy with $Ru(bpy)_3^{2+}$.[15] On the other hand, the Ru(II) complexes of nucleosides **8** and **9** showed unexpectedly weak red luminescence. Creation of the ^{1}MLCT state is followed immediately, in <100 fs, by intersystem crossing to the lowest ^{3}MLCT state with near-unit quantum yield.[16] The lowest triplet is responsible for the weak emission around 650 nm and photochemical redox reactions; it has an oxidized Ru(III) core while the corresponding electron is localized on one of the ligands.[17] Fluorescence is expected before electron localisation, but this period is still under hot debate.[18]

Emission quantum yields Φ_{em} in acetonitrile are summarized in Table 4 where the Ru(II) complexes of acetylenes and phenylboronates, are compared to the corresponding Ru-complexes of 7-deazaadenosine. Standard errors refer to absolute yields (note that a comparison between a complex and its conjugate is significantly more accurate than the cited errors imply). Three kinds of behavior are observed. (1) **6b** and **8b** have a quantum yield between 2–3%, comparable to $Ru(bpy)_3^{2+}$.[15] Therefore, nucleoside **8b** may be in principle used for optical labeling of DNA strands. (2) Coupling of the Ru complex **6a** to form **8a** leads to a significant decrease of Φ_{em} from 18.8 to 2. 1 $\times 10^{-4}$. (3) For the remaining pairs, Φ_{em} is very low in the pure Ru(II) complex but increases slightly upon coupling to 7-deazaadenine. Thus, the emission enhancement which is observed upon intercalation into duplex DNA[19] is already incipient when the nucleoside is attached. Therefore it can be concluded that only the complex **8b** (where $Ru(bpy)_3$ is linked through the 3-position of bipyridine *via* acetylene to position 7 of 7-deazaadenine) is promising for luminescent labelling of DNA, while the other types of linkages (attachment of acetylene or phenylene to the 2-position of bipyridine or phenanthroline or to 4″-position of terpyridine) are not efficient.

Table 4 Photophysical and redox properties of the Ru-complexes and Ru-containing 7-deazaadenine nucleosides

Entry	Compd	UV-VIS, λ/nm, (ε)[a]	Emission/nm[b]	$\Phi_{em}/10^{-4}$[c]	E^{ox} (V)[d]
1	**6a**	243 (3.5), 287 (8.2), 448 (1.8)	637	18.8 ± 1.3	—
2	**6b**	246 (3.9), 287 (9.8), 451 (1.8)	664	228 ± 15	1.175[e]
3	**7c**	268 (9.6), 287 (10.8), 448 (2.7)	654	3.5 ± 0.3	1.165[e]
4	**7d**	272 (9.0), 307 (10.9), 481 (3.3)	~ 715	0.9 ± 0.3	—
5	**8a**	288 (8.2), 448 (1.4)	639	2.1 ± 0.3	1.205
6	**8b**	254 (3.6), 287 (9.8), 384 (2.6)	665	289 ± 20	1.200
7	**9a**	245 (3.3), 289 (7.3), 450 (1.2)	667	1.9 ± 0.3	1.200
8	**9c**	287 (7.1), 448 (1.0)	648	4.3 ± 0.4	1.210
9	**9d**	273 (5.1), 308 (6.4), 485 (2.3)	633	2.4 ± 0.4	1.200

[a] Compounds **4** and **5** in $CHCl_3$, **8** and **9** in acetonitrile, all 1.6×10^{-5} M solutions, extinction coefficients $\varepsilon \times 10^4$ in M^{-1} cm^{-1}. [b] From a lognormal fit to the emission band. [c] With standard errors. [d] Oxidation potentials of Ru(II)/Ru(III) on PGE. [e] taken from ref. 4

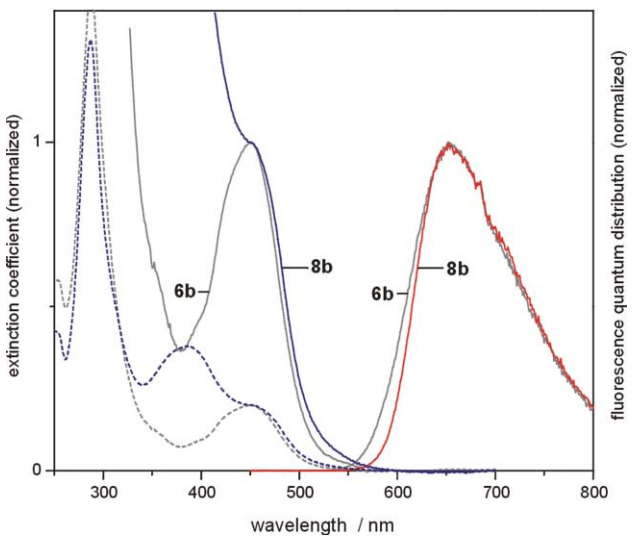


Fig. 2 Absorption and emission spectra of the labelled deaza--deoxyadenosine **8b** (blue and red lines). The absorption of the Ru(II) complex **6b** is shown for comparison (gray). Dashed lines repeat the absorption spectra, but scaled by 0.2. The solvent was acetonitrile throughout.

Transient absorption spectra are shown in Fig. 3 for **9d** (the other investigated conjugates are in the ESI†). Excitation was performed with 40 fs pump pulses at 403 nm on the blue side of the ^{1}MLCT band. Ground-state bleaching and excited-state absorption (ESA) is observed immediately. Stimulated emission $S_1 \rightarrow S_0$ is not resolved, indicating that the triplet manifold is reached on a timescale < 20 fs, in agreement with recent fluorescence-upconversion results.[18] Transient spectra for the $Ru(tpy)_2$-7-deazaadenosine **9d** may be compared with those for **7d** alone, which has a lifetime of 120 ps in acetonitrile.[20] In the present case, phenyl extension of a *tpy* ligand leads to an increase of ESA in the range $\lambda \geq 530$ nm, and the lifetime is increased to 720 ps. A characteristic feature of **9d** is a rise of ESA on a 10 ps time scale, an effect which has been attributed to structural relaxation of the extended ligand until the reduced-ligand delocalization is complete.[21] With the phenyl-linked complexes **9a** and **9c** a picosecond ESA rise is not observed. Small changes with a 5 ps time constant are found for all compounds studied across the entire spectral range; they are attributed to vibrational relaxation of the ^{3}MLCT state.

The oxidation of the Ru(II) complexes **8** and **9** on PGE (pyrolitic graphite electrode) showed the peak at around +1.2 V against Ag/AgCl/3 M KCl electrode, due to oxidation of the Ru atom in the complexes (Table 4). Compared to unsubstituted $[Ru(bpy)_3]^{2+}$ (1.095 V) and acetylene **6b** or boronate **7c** (1.075 and 1.065, respectively), the apparent redox potentials of the Ru(II) nucleosides were significantly more positive as a result of electron-withdrawing effect of the deazaadenine moiety, in agreement with our previous results with 9-Bn-adenine model compounds.[4] The different oligopyridine ligands (bpy, phen or tpy) in these complexes do not show any significant influence on the redox potential values.

Biological activity

Although the main goal was to develop electrochemical and luminescent DNA labelling, any novel nucleosides can also possess biological effects and there were previous precedents[22] of interesting biological activities of some Ru complexes. Therefore, all the compounds prepared within this study were also subjected to biological activity screening (Table 5). The cytostatic activity *in vitro* (inhibition of cell growth) was studied on the following cell cultures: (i) mouse leukemia L1210 cells (ATCC CCL 219); (ii) human promyelocytic leukemia HL60 cells (ATCC CCL 240); (iii) human cervix carcinoma HeLaS3 cells (ATCC CCL 2.2) and (iv) human T lymphoblastoid CCRF-CEM cell line (ATCC CCL 119).[23] Terpyridine nucleoside **5d** showed the most significant cytostatic effect in all the cell-lines studied, while bipyridine nucleosides **4b** and **5c** were less effective. All the other compounds, including the Ru complexes were entirely inactive. This is in accord with our previous report[5] on 8-substituted 2′-deoxyadenosine, where the terpyridine derivative was the most active.

The title modified nucleosides were also tested up to 100 μM for antiviral activity in the HCV genotype 1b replicon.[24,25] Again, the terpyridine nucleoside **5d** showed a very strong effect but, unfortunately, the compound is toxic at the same concentration. Most of the other bipyridine nucleosides showed activities at low μM concentrations but, again, accompanied by toxicity in Huh-7 and/or MT-4 cells. The Ru complexes were much less effective.

Conclusions

The synthesis of 7-deazaadenine 2′-deoxyribonucleosides bearing bipyridine-type ligands in position 7 by direct cross-coupling

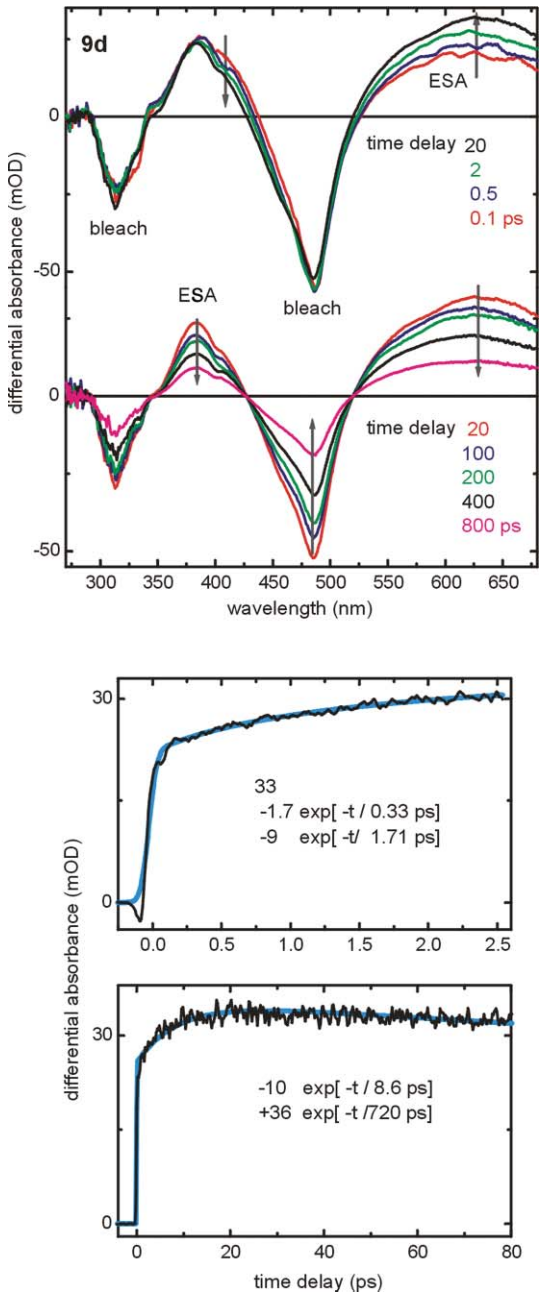


Fig. 3 Transient absorption spectra (top) and kinetics (below) of **9d** in acetonitrile upon 403 nm excitation. Only the bleached absorption band and ESA are seen. Stimulated emission $S_1 \rightarrow S_0$ is not resolved, indicating that the triplet manifold is reached on a timescale < 20 fs. Vertical arrows show signal evolution. The band integral 550–684 nm (right) rises before 20 ps, followed by uniform decay with a 720 ps time constant.

reactions of bipiridine-linked boronic acids and acetylenes with unprotected 7-iodo-7-deaza-2′-deoxyadenosine in the presence of the $Pd(OAc)_2$–TPPTS catalytic system, in H_2O–acetonitrile or in DMF was developed. Analogous aqueous-phase cross-coupling reactions were also used for the attachment of the corresponding Ru-complexes of bipyridine ligands through cross-coupling reactions of the unprotected nucleoside with boronic acid or acetylene derivatives of Ru-complexes. In general, the reactions proceeded much better than in the previously reported 8-substituted adenosine series. The title nucleosides are promising building blocks for the labelling of DNA and, therefore, their photophysical and redox properties have been studied. All the bipyridine-ligand containing 7-deaza-2′-deoxyadenosine nucleosides show strong blue fluorescence. On the other hand, the Ru-complexes show only very weak red luminescence with very low quantum yields. The only exception is compound **8b** (where $Ru(bpy)_3$ is linked through the 3-position of bipyridine *via* acetylene to position 7 of 7-deazaadenine) which gives a moderate (but still useful) quantum yield of 0.03 and, therefore, it is promising for luminescent labelling of DNA. All the Ru complexes gave electrochemical oxidation at *ca.* 1.2 V and thus could be used for electrochemical DNA labelling. The follow-up studies on the preparation of modified dNTPs bearing Ru and Os complexes of 7-[(bipyridin-3-yl)ethynyl]-2′-deoxyadenosine triphosphates and other related modified dNTPs, their incorporation to DNA and applications in bioanalysis are under way and will be published separately.

Experimental section

All cross-coupling reactions were performed under argon atmosphere. Et_3N was degassed *in vacuo* and stored over molecular sieves under argon. Compounds **1**,[9] **2a**,**b**, **3a**,**c**,**d**, **6a**,**b**, **7a**,**c**,**d**,[4] were prepared according to the literature procedures. Other chemicals were purchased from commercial suppliers and used as received. Typical experimental procedures and representative examples of characterization of compounds are given below. The complete detailed experimental section including characterization data for all compounds is in the Electronic Supplementary Information (ESI)†.

General procedure for Sonogashira cross-coupling reaction of 7-iodo-7-deaza-2′-deoxyadenosine (1) with ligands 2a,b

DMF (2.5 ml) and Et_3N (0.35 ml, 2.5 mmol, 10 equiv.) were added to an argon-purged flask containing nucleoside **1** (94 mg, 0.25 mmol), an alkyne **2a**,**b** (0.375 mmol, 1.5 equiv.) and CuI (4.8 mg, 0.025 mmol, 10 mol%). In a separate flask, $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol, 5 mol%), $P(Ph\text{-}SO_3Na)_3$ (18 mg, 0.0313 mmol, 2.5 equiv. to Pd) were combined, evacuated and purged with argon followed by addition of DMF (0.5 ml). This solution of catalyst was added through a syringe to the reaction mixture which was then stirred at 75 °C until complete consumption of the starting material. The solvent was evaporated *in vacuo*. The products were purified by silica gel column chromatography using $CHCl_3$ and MeOH (1% to 10%) as eluent.

7-Deaza-7-[(2″,2‴-bipyridin-6″-yl)ethynyl]-2′-deoxyadenosine (4a)

The product was isolated as white powder 97 mg (91%). Mp 115–120 °C. ^{1}H NMR (600 MHz, DMSO-d_6): 2.24 (ddd, 1H, J_{gem} = 13.2, $J_{2'b,1'}$ = 6.0, $J_{2'b,3'}$ = 2.8, H-2′b); 2.53 (ddd, 1H, J_{gem} = 13.2, $J_{2'a,1'}$ = 8.0, $J_{2'a,3'}$ = 5.8, H-2′a); 3.55 (ddd, 1H, J_{gem} = 11.7, $J_{5'b,OH}$ = 5.9, $J_{5'b,4'}$ = 4.4, H-5′b); 3.61 (ddd, 1H, J_{gem} = 11.7, $J_{5'a,OH}$ = 5.2, $J_{5'a,4'}$ = 4.6, H-5′a); 3.86 (ddd, 1H, $J_{4',5'}$ = 4.6, 4.4, $J_{4',3'}$ = 2.5, H-4′); 4.39 (m, 1H, $J_{3',2'}$ = 5.8, 2.8, $J_{3',OH}$ = 4.1, $J_{3',4'}$ = 2.5, H-3′); 5.12 (dd, 1H, $J_{OH,5'}$ = 5.9, 5.2, OH-5′); 5.32 (d, 1H, $J_{OH,3'}$ = 4.1, OH-3′); 6.54 (dd, 1H, $J_{1',2'}$ = 8.0, 6.0, H-1′); 6.93 (bs, 2H, NH_2); 7.50 (ddd,

Table 5 Cytostatic and antiviral activity of nucleosides

Compd	Cytostatic activity IC_{50}/μM[a]			HCV antiviral activity/μM	
	HeLa S3	HL60	CCRF-CEM	EC_{50} replicon[b]	CC_{50} Huh7[c] (MT-4)[d]
4a	n.a.	n.a.	n.a.	13	>100 (7)
4b	13.18 ± 0.81	n.a.	4.15 ± 0.06	1	2
5a	n.a.	n.a.	n.a.	16	>100 (1)
5c	6.77 ± 0.37	8.98 ± 1.30	1.77 ± 0.05	1	1
5d	3.29 ± 0.22	2.54 ± 0.51	0.57 ± 0.07	0.15	0.66
8a	n.a.	n.a.	n.a.	32	>100
8b	n.a.	n.a.	n.a.	> 100	>100
9a	n.a.	n.a.	n.a.	23	>100
9c	n.a.	n.a.	n.a.	12	>100 (19)
9d	n.a.	n.a.	n.a.	23	>100

[a] Concentration of a compound needed to reduce population growth by 50% *in vitro* (XTT test). [b] Antiviral activity in HCV-Con1 replicon ($N = 2$). [c] MTT measurement of cellular toxicity in Huh-7 cells harboring con-1 replicon ($N = 2$). [d] Cellular toxicity in MT-4 cells ($N = 2$).

1H, $J_{5''',4'''} = 7.4$, $J_{5''',6'''} = 4.7$, $J_{5''',3'''} = 1.2$, H-5‴); 7.75 (dd, 1H, $J_{5'',4''} = 7.7$, $J_{5'',3''} = 1.1$, H-5″); 7.98 (ddd, 1H, $J_{4''',3'''} = 8.0$, $J_{4''',5'''} = 7.4$, $J_{4''',6'''} = 1.8$, H-4‴); 8.01 (dd, 1H, $J_{4'',3''} = 8.0$, $J_{4'',5''} = 7.7$, H-4″); 8.04 (s, 1H, H-6); 8.19 (s, 1H, H-2); 8.378 (dd, 1H, $J_{3'',4''} = 8.0$, $J_{3'',5''} = 1.1$, H-3″); 8.383 (ddd, 1H, $J_{3''',4'''} = 8.0$, $J_{3''',5'''} = 1.2$, $J_{3''',6'''} = 0.9$, H-3‴); 8.71 (ddd, 1H, $J_{6''',5'''} = 4.7$, $J_{6''',4'''} = 1.8$, $J_{6''',3'''} = 0.9$, H-6‴).^{13}C NMR (151 MHz, DMSO-d_6): 40.16 (CH_2–2′); 62.07 (CH_2-5′); 71.16 (CH-3′); 83.11 (bpy-C≡**C**); 83.59 (CH-1′); 87.88 (CH-4′); 91.76 (bpy-**C**≡C); 93.97 (C-5); 102.51 (C-4a); 120.06 (CH-3″); 120.89 (CH-3‴); 124.84 (CH-5‴); 126.97 (CH-5″); 127.94 (CH-6); 137.78 (CH-4‴); 138.24 (CH-4″); 142.38 (C-6″); 149.62 (CH-6‴); 149.80 (C-7a); 153.25 (CH-2); 154.66 (C-2‴); 155.92 (C-2″); 157.86 (C-4). ESI MS: *m/z* (%) 451.1 (100) [M^+ + Na], 429.1 (93) [M^+ +H], 313.3 (70) [M^+ − dRf]. $C_{23}H_{20}N_6O_3{\cdot}2H_2O$ (428.44) calcd. C 59.48, H 5.21, N 18.09; found C 59.73, H 4.57, N 17.94%. IR (KBr): 3437, 2211, 1631, 1569, 1427, 1094 cm^{-1}. UV/Vis (CH_2Cl_2) λ_{max} (ε) 282 (27724). Fluorescence (CH_2Cl_2): excitation at 351 nm gave emission at 406 nm.

General procedure for Suzuki–Miyaura cross-coupling reactions of 7-deaza-7-iodo-2′-deoxyadenosine (1) with ligands 3a,c,d

A mixture of H_2O–CH_3CN = 2 : 1 (2.5 ml) was added to an argon-purged flask containing nucleoside **1** (94 mg, 0.25 mmol), a boronate **3a**,**c**,**d** (0.3 mmol, 1.2 equiv.) and Cs_2CO_3 (247 mg, 0.75 mmol, 3 equiv.). In a separate flask, $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol, 5 mol%) and $P(Ph\text{-}SO_3Na)_3$ (18 mg, 0.0313 mmol, 2.5 equiv. to Pd) were combined, evacuated and purged with argon followed by addition of H_2O–CH_3CN = 2 : 1 (0.5 ml). The catalyst mixture was then injected to the reaction mixture and the reaction mixture was stirred at 80 °C until complete consumption of the starting material. The solvent was evaporated *in vacuo*. Products were purified by silica gel column chromatography using $CHCl_3$ and MeOH (1% to 10%) as eluent.

7-Deaza-7-[(2″,2‴-bipyridin-6″-yl)phenyl]-2′-deoxyadenosine (5a)

The product was isolated as a white powder 114 mg (95%). Mp 135–137 °C. ^{1}H NMR (600 MHz, DMSO-d_6): 2.23 (ddd, 1H, $J_{gem} = 13.2$, $J_{2'b,1'} = 6.1$, $J_{2'b,3'} = 2.7$, H-2′b); 2.60 (ddd, 1H, $J_{gem} = 13.2$, $J_{2'a,1'} = 8.2$, $J_{2'a,3'} = 5.9$, H-2′a); 3.53 (dd, 1H, $J_{gem} = 11.7$, $J_{5'b,4'} = 4.3$, H-5′b); 3.60 (dd, 1H, $J_{gem} = 11.7$, $J_{5'a,4'} = 4.5$, H-5′a); 3.86 (ddd, 1H, $J_{4',5'} = 4.5$, 4.3, $J_{4',3'} = 2.5$, H-4′); 4.39 (bm, 1H, H-3′); 5.10 (bs, 1H, OH-5′); 5.31 (bs, 1H, OH-3′); 6.35 (bs, 2H, NH_2); 6.62 (dd, 1H, $J_{1',2'} = 8.2$, 6.1, H-1′); 7.50 (ddd, 1H, $J_{5''',4'''} = 7.4$, $J_{5''',6'''} = 4.7$, $J_{5''',3'''} = 1.1$, H-5‴); 7.65 (m, 2H, H-*o*-phenylene); 7.67 (s, 1H, H-6); 8.02 (ddd, 1H, $J_{4''',3'''} = 8.0$, $J_{4''',5'''} = 7.4$, $J_{4''',6'''} = 1.8$, H-4‴); 8.06 (dd, 1H, $J_{4'',5''} = 7.9$, $J_{4'',3''} = 7.7$, H-4″); 8.11 (dd, 1H, $J_{5'',4''} = 7.9$, $J_{5'',3''} = 1.0$, H-5″); 8.19 (s, 1H, H-2); 8.36 (dd, 1H, $J_{3'',4''} = 7.7$, $J_{3'',5''} = 1.0$, H-3″); 8.37 (m, 2H, H-*m*-phenylene); 8.63 (ddd, 1H, $J_{3''',4'''} = 8.0$, $J_{3''',5'''} = 1.1$, $J_{3''',6'''} = 0.9$, H-3‴); 8.72 (ddd, 1H, $J_{6''',5'''} = 4.7$, $J_{6''',4'''} = 1.8$, $J_{6''',3'''} = 0.9$, H-6‴). ^{13}C NMR (151 MHz, DMSO-d_6): 39.84 (CH_2–2′); 62.19 (CH_2-5′); 71.29 (CH-3′); 83.27 (CH-1′); 87.66 (CH-4′); 100.45 (C-4a); 116.39 (C-5); 119.32 (CH-3″); 120.59 (CH-5″); 120.94 (CH-3‴); 121.44 (CH-6); 124.59 (CH-5‴); 127.45 (CH-*m*-phenylene); 129.02 (CH-*o*-phenylene); 135.55 (C-*i*-phenylene); 136.97 (C-*p*-phenylene); 137.69 (CH-4‴); 138.75 (CH-4″); 149.55 (CH-6‴); 150.75 (C-7a); 151.62 (CH-2); 155.24 (C-2″); 155.33 (C-6″); 155.52 (C-2‴); 157.31 (C-4). ESI MS: *m/z* (%) 365.4 (100) [M^+ − dRf], 481.2 (70) [M^+], 503.2 (40) [M^+ + Na]; $C_{27}H_{24}N_6O_3{\cdot}H_2O$ (480.2) calcd. C 65.05, H 5.26, N 16.86; found C 64.95, H 5.12, N 16.77. IR (KBr): 3470, 3393, 1616, 1582, 1430, 1098 cm^{-1}. UV/Vis (CH_2Cl_2) λ_{max} (ε) 291 (30685). Fluorescence (CH_2Cl_2): excitation at 340 nm gave emission at 395 nm.

General procedure for Sonogashira cross-coupling reactions of Ru(II) building blocks 6a,b

A mixture of H_2O–CH_3CN = 2 : 1 (1 ml) was added to an argon-purged flask containing nucleoside **1** (47 mg, 0.125 mmol), an alkyne **6a**,**b** (0.188 mmol, 1.5 equiv.), CuI (2.4 mg, 0.0125 mmol, 10 mol%) and Et_3N (0.175 ml, 1.25 mmol, 10 equiv.). In a separate flask, $Pd(OAc)_2$ (1.4 mg, 0.00625 mmol, 5 mol%) and $P(Ph\text{-}SO_3Na)_3$ (9 mg, 0.0156 mmol, 2.5 equiv. to Pd) were combined, evacuated and purged with argon followed by an addition of H_2O–CH_3CN = 2 : 1 (0.5 ml). This catalyst solution was then injected to the reaction mixture which was further stirred at 75 °C until complete consumption of the starting material. The solvent was evaporated *in vacuo*. The products were purified by silica gel column chromatography using a mixture of CH_3CN–H_2O–sat. KNO_3 = 10 : 1 : 0.1 as eluent. The products were isolated as PF_6^-

salts by precipitation from a water solution by addition of sat. NH_4PF_6.

Complex 8a

The product was isolated as red powder 66 mg (47%). Mp > 300 °C. 1 : 1 mixture of diastereoisomers ^{1}H NMR (500 MHz, acetone-d_6): 2.46 (ddd, 2H, $J_{gem} = 13.3$, $J_{2'b,1'} = 6.0$, $J_{2'b,3'} = 2.8$, H-2′b); 2.61 and 2.62 (2 × ddd, 2 × 1H, $J_{gem} = 13.3$, $J_{2'a,1'} = 7.9$, $J_{2'a,3'} = 5.6$, H-2′a); 3.77, 3.81, 3.84 and 3.89 (4 × dd, 4 × 1H, $J_{gem} = 12.0$, $J_{5',4'} = 3.2$, H-5′); 4.07 and 4.10 (2 × td, 2 × 1H, $J_{4',5'} = 3.2$, $J_{4',3'} = 2.5$, H-4′); 4.61 (ddd, 2H, $J_{3',2'} = 5.6, 2.8$, $J_{3',2'a} = 2.5$, H-3′); 6.59 and 6.62 (2 × dd, 2 × 1H, $J_{1',2'} = 7.9, 6.0$, H-1′); 6.87 and 6.93 (2 × ddd, 2 × 1H, $J_{5,4} = 7.5$, $J_{5,6} = 5.7$, $J_{5,3} = 1.4$, H-5-bpy); 7.328 and 7.333 (2 × ddd, 2 × 1H, $J_{4,3} = 8.2$, $J_{4,5} = 7.5$, $J_{4,6} = 1.5$, H-4-bpy); 7.48 (ddd, 2H, $J_{5,4} = 7.5$, $J_{5,6} = 5.7$, $J_{5,3} = 1.4$, H-5-bpy); 7.53 (ddd, 2H, $J_{5''',4'''} = 7.5$, $J_{5''',6'''} = 5.7$, $J_{5''',3'''} = 1.4$, H-5‴); 7.555, 7.560, 7.67 and 7.68 (4 × ddd, 4 × 1H, $J_{5,4} = 7.6$, $J_{5,6} = 5.6$, $J_{5,3} = 1.3$, H-5-bpy); 7.728 and 7.731 (2 × s, 2 × 1H, H-6); 7.81 and 7.82 (2 × ddd, 2 × 1H, $J_{6,5} = 5.7$, $J_{6,4} = 1.5$, $J_{6,3} = 0.7$, H-6-bpy); 7.89 (ddd, 2H, $J_{6''',5'''} = 5.7$, $J_{6''',4'''} = 1.5$, $J_{6''',3'''} = 0.7$, H-6‴); 7.91 (dd, 1H, $J_{5'',4''} = 7.8$, $J_{5'',3''} = 1.4$, H-5″); 7.92, 7.93, 7.95 and 7.96 (4 × ddd, 4 × 1H, $J_{6,5} = 5.7$, $J_{6,4} = 1.5$, $J_{6,3} = 0.7$, H-6-bpy); 8.15 (ddd, 2H, $J_{4,3} = 8.2$, $J_{4,5} = 7.5$, $J_{4,6} = 1.5$, H-4-bpy); 8.20 (ddd, 2H, $J_{4''',3'''} = 8.2$, $J_{4''',5'''} = 7.5$, $J_{4''',6'''} = 1.5$, H-4‴); 8.22–8.27 (m, 4H, H-4-bpy); 8.29 (dd, 2H, $J_{4'',3''} = 8.3$, $J_{4'',5''} = 7.8$, H-4″); 8.39 (bs, 2H, H-2); 8.40 (ddd, 2H, $J_{6,5} = 5.7$, $J_{6,4} = 1.5$, $J_{6,3} = 0.7$, H-6-bpy); 8.45, 8.47, 8.73, 8.74, 8.79 and 8.80 (6 × ddd, 6 × 1 H, $J_{3,4} = 8.2$, $J_{3,5} = 1.4$, $J_{3,6} = 0.7$, H-3-bpy); 8.86 (ddd, 2H, $J_{3''',4'''} = 8.2$, $J_{3''',5'''} = 1.4$, $J_{3''',6'''} = 0.7$, H-3‴); 8.87 (dd, 2H, $J_{3'',4''} = 8.3$, $J_{3'',5''} = 1.4$, H-3″); 8.94 and 8.95 (2 × bddd, 2 × 1H, $J_{3,4} = 8.2$, $J_{3,5} = 1.4$, $J_{3,6} = 0.7$, H-3-bpy). ^{13}C NMR (125.7 MHz, acetone-d_6): 41.90 and 41.98 (CH_2–2′); 63.08 and 63.13 (CH_2-5′); 72.53 (CH-3′); 85.96 and 86.30 (CH-1′); 89.48 (CH-4′); 89.86 (bpy-*C*≡C-); 90.11 and 90.24 (bpy-C≡*C*-); 95.80 and 85.88 (C-5); 102.98 and 103.11 (C-4a); 124.54 and 124.72 (CH-3-bpy), 124.87 (CH-3″); 125.33, 125.43 and 125.72 (CH-3-bpy); 125.97 (CH-3‴); 127.62, 127.91, 128.30, 128.57, 128.89 and 129.03 (CH-5‴, CH-5-bpy); 131.03 and 131.11 (CH-6); 135.47 and 135.50 (CH-5″); 136.51 and 136.57 (CH-4-bpy); 138.88, 138.98, 139.12 and 139.24 (CH-4″,4‴, CH-4-bpy); 147.91 (CH-2); 148.50 and 148.61 (C-7a); 149.26 and 149.30 (C-6″); 152.07, 152.14, 152.31, 152.35, 152.57, 153.73 and 153.76 (CH-6‴ and CH-6-bpy); 154.11 (C-4); 157.81, 157.99, 158.01, 158.27, 158.74 and 158.80 (C-2‴, C-2-bpy); 158.98 (C-2″). ESI MS: *m*/*z* (%) 987.1 (100) [$M^+ - PF_6^-$], HR MS (TOF ES MS+) calc. 987.1657 found. 987.1691. UV/Vis (CH_3CN) λ_{max} (ε) = 288 (81880), λ (ε) = 448 (14150).

General procedure for Suzuki–Miyaura cross-coupling reactions of Ru(II) building blocks 7a,c,d

A mixture of H_2O–CH_3CN = 2 : 1 (1 ml) was added to an argon-purged flask containing nucleoside **1** (47 mg, 0.125 mmol), a boronate **7a**,**c**,**d** (0.15 mmol, 1.2 equiv.) and Cs_2CO_3 (122 mg, 0.375 mmol, 3 equiv.). In a separate flask, $Pd(OAc)_2$ (1.4 mg, 0.00625 mmol, 5 mol%) and $P(Ph\text{-}SO_3Na)_3$ (9 mg, 0.0156 mmol, 2.5 equiv. to Pd) were combined evacuated and purged with argon followed by an addition of H_2O–CH_3CN = 2 : 1 (0.5 ml). The solution of this catalyst was injected to the reaction mixture which was then stirred at 80 °C until complete consumption of the starting material. The solvent was evaporated *in vacuo*. The products **9a**,**c**,**d** were purified by silica gel column chromatography using a mixture of CH_3CN–H_2O–sat. KNO_3 = 10 : 1 : 0.1 as eluent. The products were isolated as PF_6^- salt by precipitation from water solution by addition of sat. NH_4PF_6.

Complex 9a

The product was isolated as red powder 140 mg (95%). Mp 244–249 °C. ^{1}H NMR (500 MHz, acetone-d_6): 2.534 and 2.536 (2 × ddd, 2 × 1H, $J_{gem} = 13.4$, $J_{2'b,1'} = 6.2$, $J_{2'b,3'} = 3.2$, H-2′b); 2.71 and 2.74 (2 × ddd, 2 × 1H, $J_{gem} = 13.4$, $J_{2'a,1'} = 7.5$, $J_{2'a,3'} = 5.7$, H-2′a); 3.88–3.98 (m, 4H, H-5′); 4.13 and 4.14 (2 × q, 2 × 1H, $J_{4',5'} = J_{4',3'} = 3.0$, H-4′); 4.73 (m, 2H, H-3′); 6.30 (bm, 2H, H-*m*-phenylene); 6.81 and 6.82 (2 × dd, 2 × 1H, $J_{1',2'} = 7.5, 6.2$, H-1′); 6.98 (ddd, 1H, $J_{5,4} = 7.6$, $J_{5,6} = 5.6$, $J_{5,3} = 1.3$, H-5-bpy); 7.02 (bm, 2H, H-*o*-phenylene); 7.09 (ddd, 1H, $J_{5,4} = 7.6$, $J_{5,6} = 5.6$, $J_{5,3} = 1.3$, H-5-bpy); 7.28 (bm, 2H, H-*o*-phenylene); 7.37 and 7.38 (2 × ddd, 2 × 1H, $J_{6,5} = 5.6$, $J_{6,4} = 1.5$, $J_{6,3} = 0.7$, H-6-bpy); 7.41 and 7.43 (2 × ddd, 2 × 1H, $J_{5,4} = 7.6$, $J_{5,6} = 5.6$, $J_{5,3} = 1.3$, H-5-bpy); 7.51 and 7.52 (2 × ddd, 2 × 1H, $J_{5''',4'''} = 7.6$, $J_{5''',6'''} = 5.6$, $J_{5''',3'''} = 1.3$, H-5‴); 7.53 (dd, 1H, $J_{5'',4''} = 7.7$, $J_{5'',3''} = 1.4$, H-5″); 7.615 and 7.616 (2 × ddd, 2 × 1H, $J_{5,4} = 7.6$, $J_{5,6} = 5.6$, $J_{5,3} = 1.3$, H-5-bpy); 7.67–7.72 (m, 4H, H-5,6-bpy); 7.78 (ddd, 2H, $J_{4,3} = 8.4$, $J_{4,5} = 7.6$, $J_{4,6} = 1.5$, H-4-bpy); 7.90 (s, 1H, H-6); 7.91 (m, 2H, H-6‴); 7.95 (s, 1H, H-6); 8.078 and 8.082 (2 × ddd, 2 × 1H, $J_{4,3} = 8.4$, $J_{4,5} = 7.6$, $J_{4,6} = 1.5$, H-4-bpy); 8.157 and 8.162 (2 × ddd, 2 × 1H, $J_{6,5} = 5.6$, $J_{6,4} = 1.5$, $J_{6,3} = 0.7$, H-6-bpy); 8.19–8.29 (m, 6H, H-4‴ and H-3,4-bpy); 8.33 and 8.34 (2 × ddd, 2 × 1H, $J_{6,5} = 5.6$, $J_{6,4} = 1.5$, $J_{6,3} = 0.7$, H-6-bpy); 8.343 and 8.345 (2 × dd, 2 × 1H, $J_{4'',3''} = 8.3$, $J_{4'',5''} = 7.7$, H-4″); 8.36 (ddd, 1H, $J_{3,4} = 8.4$, $J_{3,5} = 1.3$, $J_{3,6} = 0.7$, H-3-bpy); 8.501 and 8.503 (2 × s, 2 × 1H, H-2); 8.637, 8.642, 8.69, 8.716 and 8.722 (5 × ddd, 6H, $J_{3,4} = 8.4$, $J_{3,5} = 1.3$, $J_{3,6} = 0.7$, H-3-bpy); 8.90 (ddd, 2H, $J_{3''',4'''} = 8.4$, $J_{3''',5'''} = 1.3$, $J_{3''',6'''} = 0.7$, H-3‴); 8.94 (dd, 2H, $J_{3'',4''} = 8.3$, $J_{3'',5''} = 1.4$, H-3″). ^{13}C NMR (125.7 MHz, acetone-d_6): 42.24 and 42.38 (CH_2-2′); 62.96 and 63.07 (CH_2-5′); 72.35 and 72.44 (CH-3′); 85.50 and 85.52 (CH-1′); 89.25 and 89.37 (CH-4′); 100.29 and 100.33 (C-4a); 119.50 and 119.51 (C-5); 124.24 and 124.34 (CH-3-bpy), 124.62 (CH-3″); 124.87 and 124.95 (CH-6); 125.05, 125.14, 125.18, 125.48 and 125.51 (CH-3-bpy); 125.95 (CH-3‴); 127.37, 127.53, 128.16, 128.32 and 128.98 (CH-5‴, CH-5-bpy); 129.10, 129.24, 129.42 and 130.30 (CH-*o*,*m*-phenylene); 130.62 and 130.64 (CH-5″); 133.90 and 133.93 (C-*i*-phenylene); 136.99 (CH-4-bpy); 138.95, 139.08 and 139.27 (CH-4″,4‴, CH-4-bpy); 139.31 (C-*p*-phenylene); 143.44 (CH-2); 148.81 (C-7a); 151.90 (CH-6-bpy); 152.50 (C-4); 152.57, 152.84, 152.88, 152.91 and 153.64 (CH-6‴ and CH-6-bpy); 157.62, 157.64, 158.09, 158.22, 158.72, 158.74, 158.93 and 159.03 (C-2″, C-2‴ and C-2-bpy); 167.16 (C-6″).ESI MS: *m*/*z* (%) 1039.1 (100) [$M^+ - PF_6^-$], HR MS (TOF ES MS+) calc. 1039.1970 found. 1039.1986. UV/Vis (CH_3CN) λ_{max} (ε) = 289 (72812), λ (ε) = 450 (12178).

UV/Vis spectra

The UV-Vis spectra were measured on a Varian CARY 100 Bio Spectrophotometer at room temperature. Compounds **4** and **5**

were measured as 1.6×10^{-5} M solutions in $CHCl_3$. Compounds **8** and **9** were measured as 1.6×10^{-5} M solutions in CH_3CN.

Fluorescence measurements

The fluorescence measurements of compounds **4** and **5** were performed on an Aminco Bowman Series 2 Spectrofluorometer with 220–850 nm range, Xenon source, excitation and emission wavelength scans, spectral bandwidth 1–16 nm, PMT detector, scan rate 3–6000 nm min^{-1}, Saya-Namioka grating monochromator. Compounds **4** and **5** were measured as 1.6×10^{-4} M solutions in $CHCl_3$.

Stationary absorption and emission spectra of Ru-complexes in acetonitrile (Merck Uvasol) were obtained with a Cary 300 and Spex Fluorolog 212, respectively. For measurement of quantum yields, the emission was excited at 430 nm and compared to that from the dye DCM. The fluorescence band of DCM in acetonitrile ($\Phi_{em} = 0.60 \pm 0.04$)[26] is similar to the emission spectrum of the Ru(II) complexes studied here.

Transient absorption spectra were recorded upon excitation at 403 nm with 40 fs pump pulses. After a variable delay, the transmission of white-light, "supercontinuum" probe pulses was measured in a dual-beam arrangement.[27] The time resolution was 80 fs (fwhm of temporal apparatus function).

Electrochemistry

Voltammetric measurements were performed with an Autolab analyzer (Eco Chemie, The Netherlands) in connection with VA-Stand 663 (Metrohm, Switzerland). Pyrrolitic graphite electrode (PGE) was used as a working electrode (prepared and pretreated as described),[28] Then the electrode was rinsed with deionized water and was placed into the electrochemical cell. Electrochemical responses were measured in a conventional *in situ* mode (with the analyte dissolved in background electrolyte) initial potential −1.0 V, final potential +1.5 V, pulse amplitude 25 mV, frequency 200 Hz, potential step 5 mV. The measurements were performed at ambient temperature in 0.1M Tris, 0.2M NaCl, pH 7.3 by using an Autolab analyzer (EcoChemie, The Netherlands) in a three-electrode setup (with the PGE as working electrode, Ag/AgCl/3 M KCl as reference, and platinum wire as counter-electrode). The voltammograms were baseline corrected by means of a moving average algorithm (GPES 4 software, EcoChemie).

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