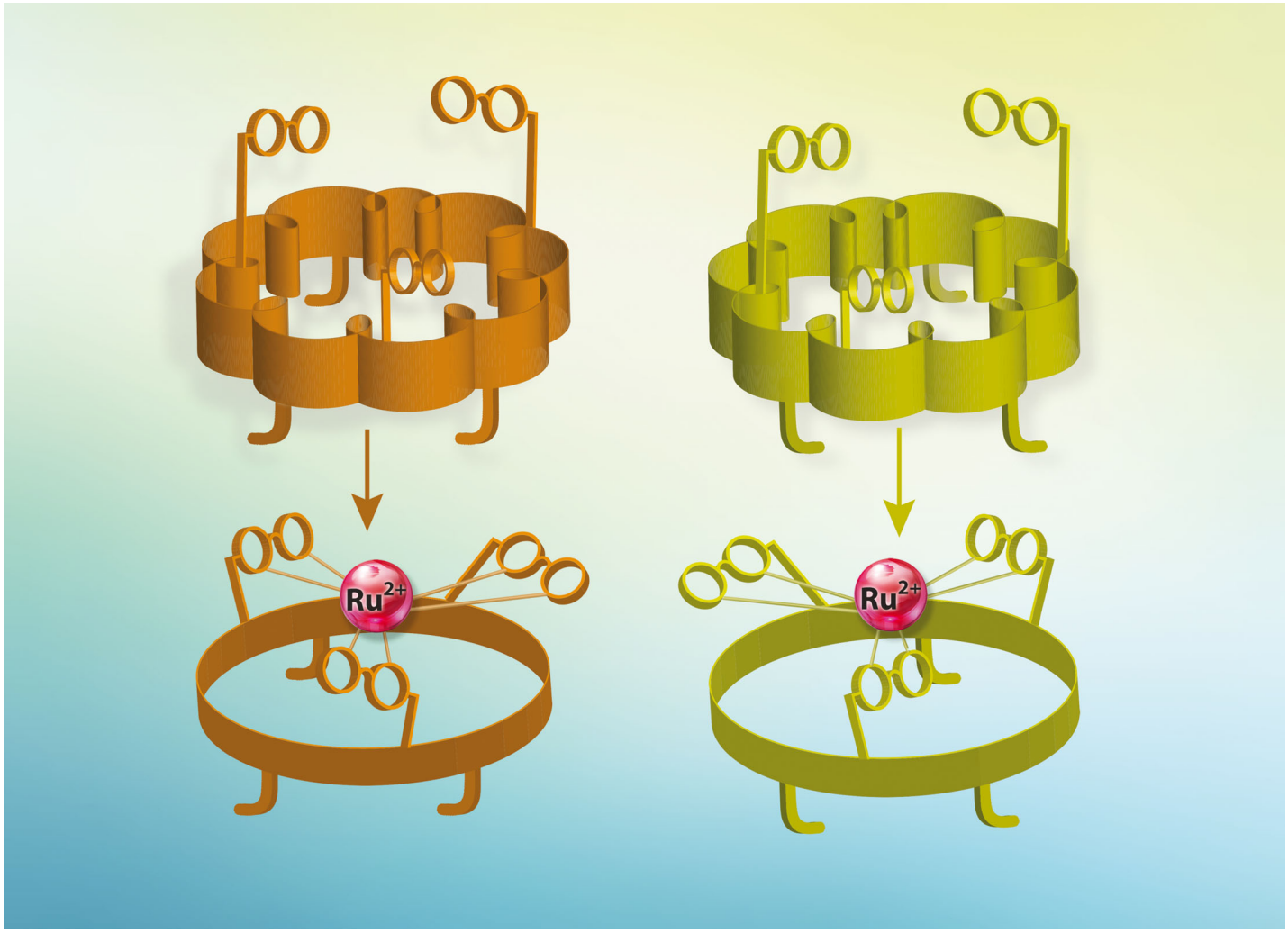

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Versatile ruthenium complexes based on 2,2′-bipyridine modified peptoids

The dual effect of ruthenium binding to *N*-substituted glycine oligomers – peptoids – is demonstrated: achiral 2,2′-bipyridine ligands form Δ or Λ chiral Ru(II) complexes when they are incorporated within left or right chiral helical peptoids, respectively, while Ru(II) binding to these peptoids causes modifications to the helical character of their backbone. Specifically, a dramatic change in the CD spectra of a cyclic peptoid upon Ru(II) binding indicates a significant alternation in its conformational order.

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Versatile ruthenium complexes based on 2,2′-bipyridine modified peptoids†

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Helical peptoids bearing 2,2′-bipyridine form ruthenium complexes *via* intermolecular binding to linear peptoid strands or intramolecular binding to a cyclic scaffold. Ru(ii) binding promoted changes in the conformational order of the peptoids, and chiral induction from the peptoids to their metal center was observed.

One of the most extensively used ligands in coordination chemistry is 2,2′-bipyridine (bipy),[1] a bidentate chelator capable of forming complexes with various metal ions including Ru^{2+}.[2] In the last two decades, bipy derivatives were also incorporated within peptides[3] and peptide mimics,[4,5] and their metal-binding properties were described. The combination between bipy and peptidomimetic scaffolds allowed coordination of versatile metal cations to peptides[3b] and high binding affinities for metal ions[6] targeting various biological and chemical applications.[6–10] Thus, the introduction of bipy to peptidomimetics holds promise as a platform for the construction of unique metallofoldamers.[11] Peptoids,[12] *N*-substituted glycine oligomers, are a class of foldamers[13] that can adopt helical secondary structures with a helical pitch of three residues per turn *via* the incorporation of bulky chiral side chains within the oligomer sequence.[14] Peptoids can be efficiently synthesized from primary amines on a solid support *via* the two-step "submonomer" approach,[15] resulting in highly versatile scaffolds. This synthesis should enable not only the facile incorporation of metal-binding ligands but also a simple tuning of the ligand(s) position, quantity and identity, towards the creation of various metallopeptoids.[16] Herein we explore the incorporation of bipy within the peptoid sequence and study three bipy modified helical peptoids – a linear pentamer bearing one bipy ligand (**L1B**), a linear hexamer with two bipy ligands (**L2B**) and a cyclic hexamer having three bipy ligands (**C3B**) – for the creation of versatile peptoid–ruthenium architectures as the intermolecular complexes $(\mathbf{L1B})_3Ru$ and $(\mathbf{L2B})_3Ru_2$, and the intramolecular complex (**C3B**)Ru (Fig. 1).

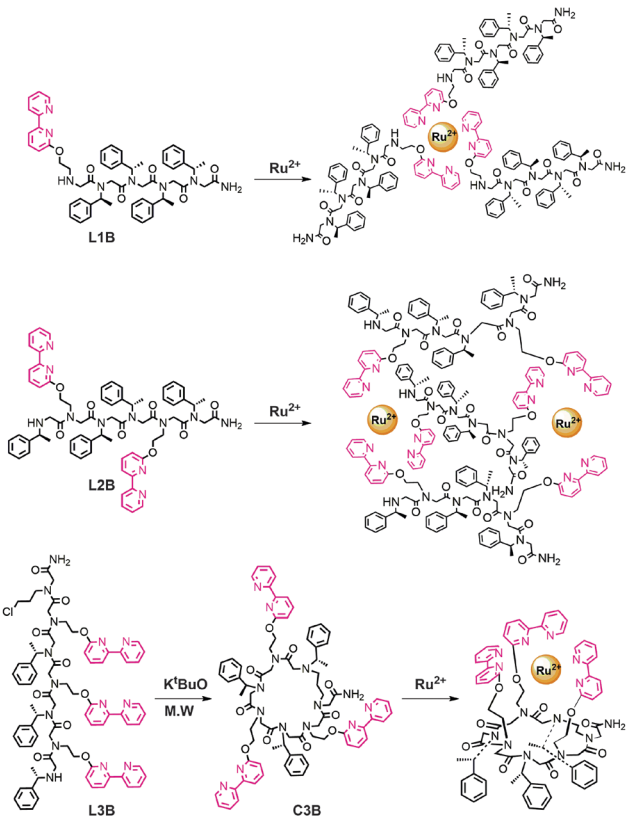

Fig. 1 Chemical structures of peptoid oligomers bearing 2,2′-bipyridine units and their anticipated ruthenium complexes.

Initial attempts to incorporate 6-methylamine-2,2′-bipyridine[17] within several peptoid sequences were not successful, probably due to extensive side reactions on the nitrogen atoms.[18] We therefore decided to synthesize the bipy amine derivative 2-(2,2′-bipyridin-6-yloxy) ethylamine according to a previously published procedure for the synthesis of 2-(2,2′:6′,2″-terpyridin-4′-yloxy) ethylamine.[19] The compatibility of this bipy derivative (*N*bp) with the "submonomer"

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method was tested by its incorporation at the third position of a peptoid tetramer containing methyl benzyl synthons at the other positions. HPLC analysis at 214 nm of the crude peptoid after each step – *N*bp displacement, subsequent acylation and the successive methyl benzylamine displacement (Fig. S16, ESI†), as well as ESI-MS analysis of the crude peptoid tetramer, confirmed the successful incorporation of this bipy derivative within the sequence.

Peptoid oligomers **L1B** and **L2B** were designed such that each contains four bulky chiral side chains, which are sufficient for attaining helicity in oligomers of this length.[14d] In **L2B**, the ligands were placed at positions i and $i + 3$, which match the pitch of the helix, in order to orient these groups in proximity on the same face of the backbone and facilitated the creation of the intermolecular complex depicted in Fig. 1.[20] Peptoid **C3B** was designed as a hexamer with three bipy ligands in alternating positions on the sequence such that they will all face the same side of the macrocycle plain and facilitate an intramolecular binding.[21] The linear peptoids **L1B**, **L2B** and **L3B**, as well as the dimer **Di-L1B** (see the ESI†), incorporating *N*bp, (*S*)-(−)-1-phenylethylamine (*N*spe) and chloropropylamine (*N*pl, only **L3B**) as synthons were synthesized on the solid support employing the "submonomer" protocol. The peptoid **C3B** was prepared by a microwave-assisted cyclization of peptoid **L3B** following a method that we have recently published.[22] All the peptoids were analysed and purified by HPLC, and their sequences were confirmed by ESI-MS. The Ru^{2+} complexes (**L1B**)$_3$Ru, (**L2B**)$_3$Ru$_2$, (**C3B**)Ru and (**Di-L1B**)$_3$Ru were synthesized using a modification of a previously reported protocol,[23] by adding 1 equiv. of $RuCl_3$ hydrate to 3 equiv. of **L1B** or **Di-L1B**, 1.5 equiv. of **L2B** and 1 equiv. of **C3B**, respectively in ethanol under reflux conditions. After a few hours of stirring, the pale yellow colour of the peptoid solution turned blue in the case of **L1B** and **Di-L1B**, and red-brown in the case of **L2B** and **C3B**. The final colour of all the complexes was red-orange. These complexes were purified and analysed by HPLC, and their identity was confirmed by detailed mass spectrometry studies including computed and experimental isotopic envelope analysis (see the ESI†). These studies show that all the Cl^- ligands were replaced by the bipy-peptoids, supporting the suggested binding mode of the complexes presented in Fig. 1.

Metal free peptoids **L1B**, **L2B** and **C3B** exhibit absorption bands near λ = 302, 299 and 298 nm, respectively, in acetonitrile, corresponding to the π–π^* transition of bipy. The complexes (**L1B**)$_3$Ru, (**L2B**)$_3$Ru$_2$ and (**C3B**)Ru reveal shifts in these absorption bands with values of λ = 303, 305 and 305 nm, respectively, and additional bands near λ = 463, 461 and 464 nm, respectively, which correspond to the metal-to-ligand charge transfer (MLCT) bands of the ruthenium polypyridine complexes (Fig. 2A, D and G).

Circular dichroism (CD) measurements revealed some changes upon the formation of the complexes (**L1B**)$_3$Ru and (**L2B**)$_3$Ru$_2$, and significant changes upon (**C3B**)Ru formation. Solutions of all three complexes showed an increase, relative to the metal-free peptoids, in the ellipticity near 200 nm while only the complex (**C3B**)Ru exhibited a major decrease, relative to the metal-free peptoid, in the magnitude of the CD signal near 218 nm (Fig. 2B, E and H, black and red lines).

It has been previously demonstrated that *N*spe peptoids adopt right-handed helices,[14b] that have characteristic CD spectra with

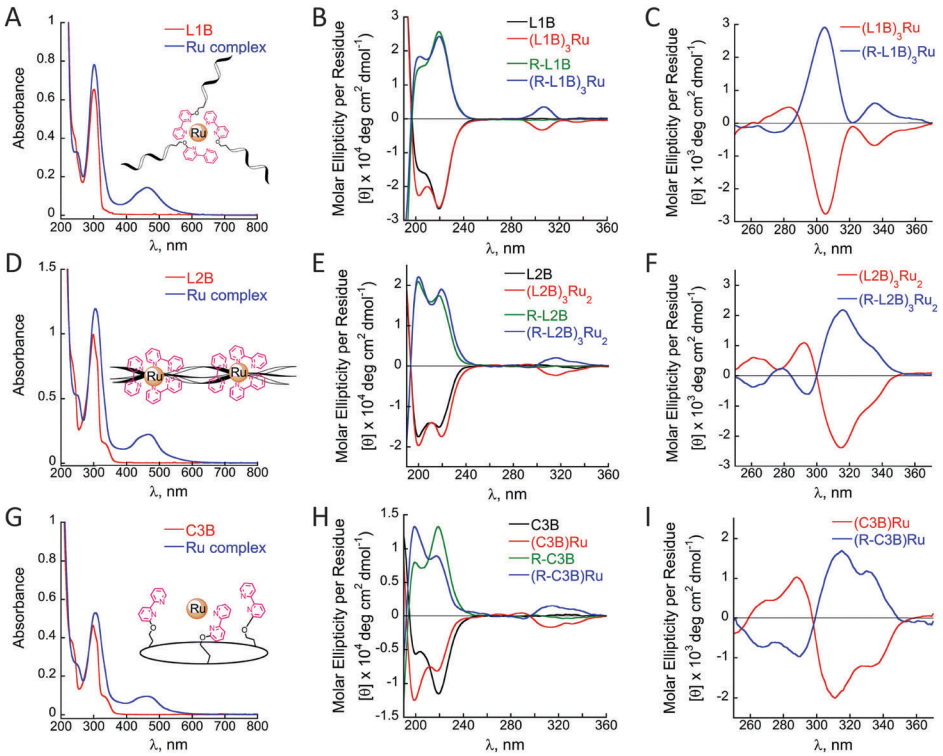


Fig. 2 UV-Vis and CD spectra measured at rt. in acetonitrile: (A, D and G) UV-Vis spectra of **L1B** (50 μM), **L2B** (50 μM), **C3B** (17 μM) and their Ru^{2+} complexes (17 μM each) respectively. (B, E and H) CD spectra of **L1B**, **L2B**, **C3B** (100 μM each) and their Ru^{2+} complexes (30 or 100 μM each), respectively. (C, F and I) CD spectra of (**L1B**)$_3$Ru and (**L2B**)$_3$Ru$_2$, and (**C3B**)Ru (200 μM each), respectively.

bands near 190 and 200 nm, the latter has been associated with the *trans*-amide bond conformation, and 218 nm, which is associated with the *cis*-amide bond conformation.[14] Both peptoids **L1B** and **C3B** exhibit CD spectra with an intense band at 218 nm (Fig. 2B and H, red lines), indicating that helices with only *cis*-amide bonds are the major population in solution. Upon formation of the complexes (**L1B**)$_3$Ru and (**C3B**)Ru an increase in the band near 200 nm was obtained (Fig. 2B and H, red lines), indicating that the helices with only *cis*-amide bonds are no longer the dominant population in solution. For (**L1B**)$_3$Ru, this increase implies a decrease in the overall conformational order of the peptoid upon ruthenium binding.[24] In the case of (**C3B**)Ru, there is also a decrease in the band near 218 nm, suggesting that the conformational order is almost diminished due to a significant alteration of the helical backbone after ruthenium complexation. The CD spectrum of **L2B** exhibits similar intensities of both bands near 200 and 218 nm (Fig. 2E, black line), reflecting the conformational heterogeneity of this peptoid. A solution of its ruthenium complex exhibited increases, relative to the metal-free peptoid, in the magnitude of both of these CD signals (Fig. 2E, red line), suggesting an increase in its overall conformational order as the magnitude of the signal in this case, reflecting the degree of helicity.[8d,e,16b]

Ruthenium binding to all three peptoids also produced new bands in the region between 260 and 360 nm corresponding to the π–π* transition of bipy. These bands, however, were very weak and did not show the expected Cotton effects. In order to probe this point we repeated the CD measurements using higher solution concentrations (200 μM instead of 30 or 100 μM) of (**L1B**)$_3$Ru, (**L2B**)$_3$Ru$_2$, and (**C3B**)Ru and indeed obtained stronger CD signals that showed clear Cotton effects with minima at λ_{max} = 305, 316 and 314 nm, respectively (Fig. 2C, F and I, red lines). These signals reflect the induction of chirality from the peptoid scaffold to the metal center,[16b] and imply at more preferable stereochemistry of the Δ isomer over the Λ isomer.[25] The bipy π–π* CD signal of (**C3B**)Ru exhibits an exciton couplet,[26] with a minimum at 314 nm and a maximum at 289 nm, crossing $\varepsilon = 0$ near 296 nm. In contrast, (**L2B**)$_3$Ru$_2$ exhibits a weaker exciton couplet, which is completely absent in the case of (**L1B**)$_3$Ru. This can be attributed to reduced conformational constraints in the intermolecular complexes, which can diminish the effect of the dipole–dipole interactions responsible for an exciton couplet. In order to further explore the preference of stereochemistry, we prepared three more peptoids using Nrpe monomers instead of Nspe monomers, namely **R-L1B**, **R-L2B** and **R-C3B**, and their corresponding Ru^{2+} complexes (**R-L1B**)$_3$Ru, (**R-L2B**)$_3$Ru$_2$ and (**R-C3B**)Ru. These complexes were purified and analysed by HPLC, characterized by UV and their identity was confirmed by detailed MS studies, exhibiting the same absorbance bands and masses as their corresponding Nspe containing Ru–peptoids (see the ESI†). CD measurements using 200 μM solutions of these complexes displayed the exact opposite spectra and Cotton effect relative to the Nspe containing peptoids–Ru complexes (Fig. 2C, F and I, blue lines). These results demonstrate that the stereochemistry of the Ru^{2+} center can indeed be controlled and dictated by the chirality of the peptoid scaffold.

The redox properties of the new ruthenium complexes were realized from cyclic voltammetry. (**L1B**)$_3$Ru, (**L2B**)$_3$Ru$_2$, (**C3B**)Ru

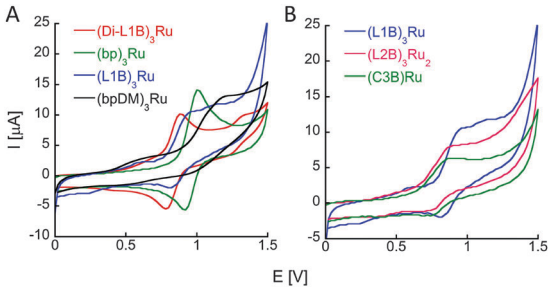
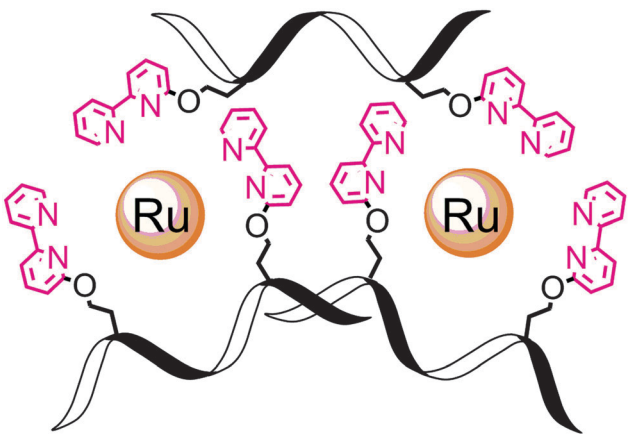


Fig. 3 Comparison between the cyclic voltammograms of (A) 0.5 mM intermolecular Ru complexes and (B) 0.5 mM (**L1B**)$_3$Ru and (**C3B**)Ru and 0.25 mM (**L2B**)$_3$Ru$_2$ that were recorded in acetonitrile at rt. using a glassy carbon working electrode, platinum counter electrode, and Ag/$AgNO_3$ reference electrode. Scan rate: 100 mV s^{-1}.

and (**Di-L1B**)$_3$Ru exhibit a reversible oxidation process of the metal centered $Ru^{2+/3+}$ couple at E_p^{ox} of 0.94 V, 0.88 V, 0.90 V and 0.88 V *vs.* Ag/$AgNO_3$ respectively. These oxidation potentials imply that all the bipy ligands from the peptoids are coordinating Ru^{2+} and there are no Cl^- ions bound as ligands.[27] These oxidation potentials are negatively shifted compared to that of (bp)$_3$Ru, which is centered around 1.02 V (Fig. 3A, green line), probably due to the electron withdrawing nature of the amides. To probe this point, we have synthesized 2-(2,2′-bipyridin-6-yloxy) ethyl(dimethyl)amine (**bp-DM**), which contains the methoxy group but lacks the amide. Its Ru^{2+} complex (**bp-DM**)$_3$Ru was prepared, purified and characterized by UV and MS spectroscopies, and its CV showed an oxidation potential at E_p^{ox} of 1.22 V, which expresses a positive shift compared to Ru(bipy)$_3$, probably due to the donating character of the methoxy group. Notably, similar intensities of the current flows are obtained in identical concentrations of the complexes (**L1B**)$_3$Ru and (**C3B**)Ru (0.5 mM) and in as twice as less concentrated solution of (**L2B**)$_3$Ru$_2$ (0.25 mM). We therefore propose that the two Ru centers in (**L2B**)$_3$Ru$_2$ are oxidized simultaneously, thus giving rise to only one oxidation peak.

Finally, we note that **L2B** can bind ruthenium in an intramolecular fashion leading to a different (**L2B**)$_3$Ru$_2$ complex in which two intramolecular (**L2B**)$_2$Ru complexes bind an additional **L2B** peptoid (Scheme 1). The weak exciton couplet exhibited



Scheme 1

by (**L2B**)$_3$Ru$_2$ and the similarity in the oxidation potentials of (**L2B**)$_3$Ru$_2$ and (**C3B**)Ru that demonstrate their similar central structure,[8c] support the existence of such a complex. We can therefore assume that both the intermolecular (**L2B**)$_3$Ru$_2$ and the intramolecular/intermolecular (**L2B**)$_3$Ru$_2$ are present in solution.

To conclude, this work describes the facile incorporation of bipy into the peptoid sequence for the design and synthesis of versatile bipy modified peptoid–ruthenium complexes. These include a helical triplex *via* intermolecular metal binding and a unique cyclometallopeptoid complex *via* intramolecular metal ligation of three pendant groups. Our results demonstrate that the dual effect of ruthenium binding; the chirality of the peptoid establishes an asymmetric environment about the metal center while metal complexation causes modifications in the conformational order of the peptoid backbone. Specifically, CD analysis indicates that the stereochemistry of the Ru^{2+} center is influenced by the chirality of the peptoid scaffold. We are currently studying other bipy-modified metallopeptoids and exploring the photophysical properties of peptoid–ruthenium complexes towards photocatalysis.

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