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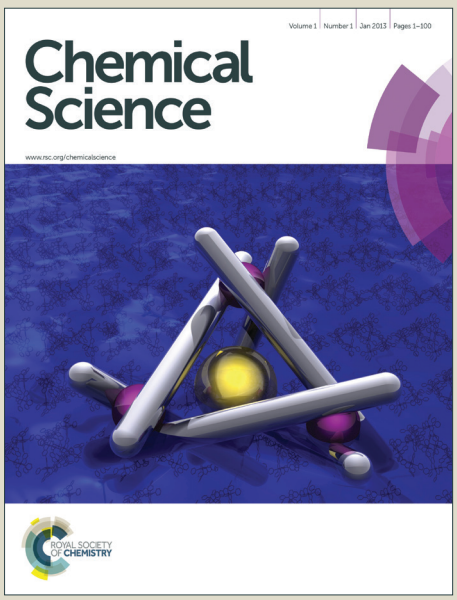

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ARTICLE TYPE

Novel *ortho*-OPE Metallofoldamers: Binding-Induced Folding Promoted by Nucleating Ag(I)-Alkyne Interactions

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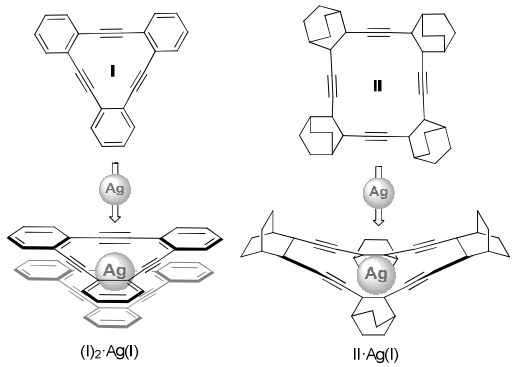
We have developed a new family of *ortho*-oligophenylenethynylenes (*o*-OPE) metallofoldamers, whose folding of these helicates is induced by a nucleating carbon-metal interaction between Ag(I) cations and the alkynes of the inner core of the *o*-OPEs. These *o*-OPEs form metal-organic assemblies where at least three alkynes moieties are held in close proximity to originate novel Ag(I)-complexes with the metal ion lodged into the helical cavity. NMR titration experiments and photokinetic studies have provided quantitative data about the thermodynamic and kinetic features of such binding/folding phenomena. X-ray diffraction and DFT studies have been performed to extract structural information on how the Ag(I) cation is accommodate into the cavity. The great simplicity and versatility of these new metallofoldamers open the possibility to develop novel structures with applications in material science and/or in asymmetric catalysis.

Introduction

Generating synthetic macromolecules with spatial control is of great interest in view of their prospective applications in catalysis, chemical sensing and material science.[1,2] One of the most successful progress has been provided by the foldamer concept. In supramolecular chemistry, a foldamer is defined as a synthetic chain molecule that adopts a conformationally ordered state in solution by a collection of non-covalent interactions between non-adjacent monomer units. Because coordination bonds are relatively strong among the non-covalent interactions, metallohelicates[3] based on oligopyridines and metallofoldamers[4] based on salen-type multidentated ligands have been extensively investigated. In most of such cases, the metal coordination sphere is inherently helical (templated approach). Examples in which the metal coordination sphere is not inherently helical, but instead causes a series of cooperative, non-covalent interactions that ultimately result in a folded structure (nucleated approach) are much less common.[4] Moreover, the possibility to induce the folding process using the coordination capabilities of carbon-based π-donor ligands such alkynes to carbophillic metals has not been described to date.

Herein, we demonstrate the utility of Ag(I)-alkyne bonds to prepare new metal–organic folded assemblies. Inspiration for the work developed here comes from an original idea of Nelson and Moore,[5] who proposed that the inner void of folded OPEs should be potentially able to coordinate metals.[6] Coinage metals-alkyne interactions are believed to efficiently initiate and mediate several catalytic reactions.[7] In contrast to the well-documented chemistry of Ag(I) interacting with heteroatoms, literature involving structurally characterized η^2-alkyne-Ag(I) complexes is rather limited,[8] specially in the case of monomeric complexes with more than one alkyne moiety bounded to the same Ag(I) metal center.[9] Young[9] and Komatsu[9] *et al.* reported respectively the syntheses of $(\mathbf{I})_2\cdot$Ag(I) and $\mathbf{II}\cdot$Ag(I) (Scheme 1), which represent the first structurally characterized complexes involving more than one triple bond interacting with Ag(I). Tetrabenzo[16]dehydroannulene **II** was found to have a cavity size suitable for the incorporation of one Ag(I) cation, while tribenzo[12]dehydroannulene ligand **I** is too small thus forming a sandwich-type complex $(\mathbf{I})_2\cdot$Ag(I).

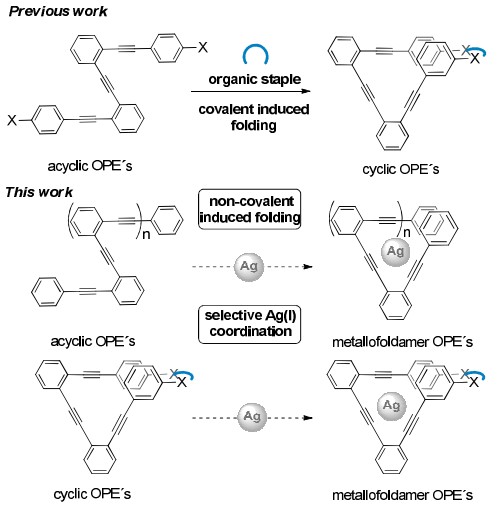


Scheme 1. Structure of the ligands and silver complexes reported by Young and Komatsu.

In this context, we recently reported a new strategy to covalently lock flexible *o*-OPEs[10] into well-defined single loops (**III**, Scheme 2), even in a chiral way, by means of an organic staple.[11,12] Due to the structural similarity between such stapled π-

conjugated systems and benzocyclynes **I** and **II**, we envisioned that such family of *o*-OPE macrocycles could be used to allocate a carbophylic metal such as Ag(I) into the helical cavity (metallocavitands).[13] Even more, the Ag(I)-alkyne interaction could induce the helical folding of all-carbon polymers such as acyclic *o*-OPEs resulting in a new class of metallofoldamers.[4]

Continuing our recent interest in all conjugated carbon-based materials,[11,14] here we report an in-depth experimental and theoretical study on the ability of Ag(I) cations to form complexes with cyclic and acyclic *ortho*-oligophenylenethynylenes (*o*-OPEs), resulting in a new class of metallofoldamers. We have found that this weak interaction efficiently acts as a nucleating event according to the helix-coil model[15] in acyclic *ortho*-OPEs with more than three triple bonds.



Scheme 2. Schematic chemical structure of the *o*-OPE-based ligands and Ag(I) complexes synthetized.

Results and discussion

A set of acyclic and cyclic *o*-OPEs (**1-16**, Chart 1) was synthesized using Sonogashira cross-coupling protocols[16] and the macrocyclic compounds were obtained following the *stapling* methodology developed in our lab.[11] Cyclic *o*-OPE **1** and acyclic **6** were selected as models for the coordination experiments with metal salts (Na(I), Li(I), Zn(II) and Ag(I)) bearing the weakly coordinating tetrafluoroborate counterion.

Initial ^{1}H NMR samples (CD_2Cl_2) were treated with an excess of metal salts under air and at room temperature. Analysis of ^{1}H NMR spectra before and after metal addition revealed that Na(I), Li(I) and Zn(II) salts did not induce any appreciable change in the proton spectra, whereas the samples treated with Ag(I) exhibited significant changes in the aromatic region, which evidenced the formation of new organometallic species (Figure 1). Interestingly, the addition of Ag(I) led to an almost identical spectra for complex formed with acyclic ligand **6** and cyclic *o*-OPE **1**, which unequivocally presents a folded arrangement in solution. Moreover, the upfield shift of the terminal aromatic hydrogens in **6** (Figure 1d, grey-labeled protons) pointed to the stacking of both rings consistent with a metallo-induced folding phenomenon in solution.

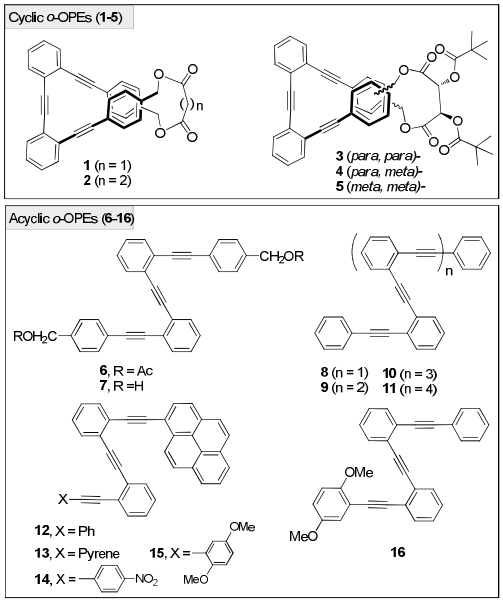


Chart 1. Chemical structure of *o*-OPEs **1-16**.

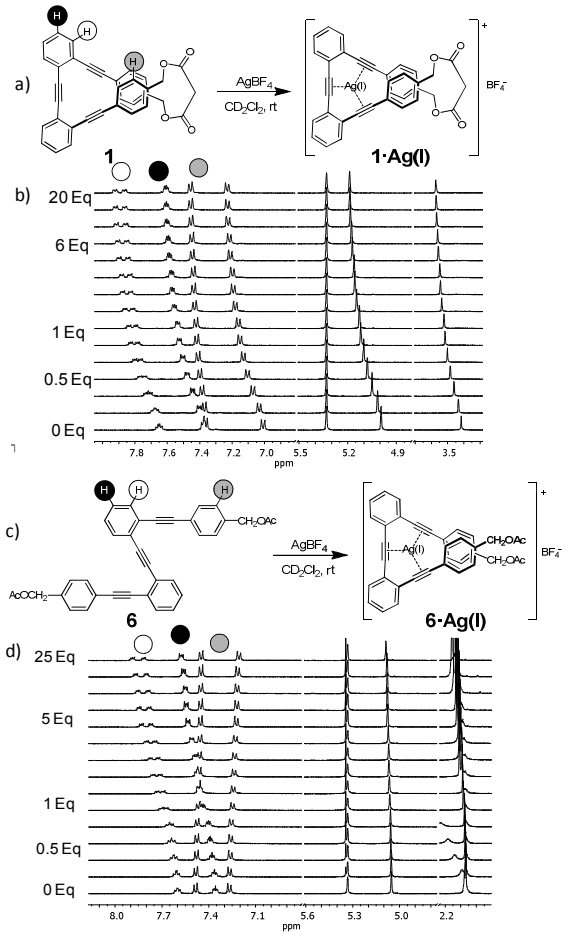


Figure 1. a) and c) Schematic representations of the coordination reaction, b) and d) ^{1}H NMR titration of the ligand with $AgBF_4$ indicating the diagnostic shifts of proton signals (CD_2Cl_2, 500 MHz, 298 K). Only the representative parts of the spectra are shown.

Since Ag(I) ions can coordinate π-donors such as arenes and alkynes, two kinds of folded structures could be formed by

coordination involving the aromatic superimposed aromatic rings[9c,17] or the triple bonds. In order to clarify the type of coordination governing our complexes, a careful analysis of ^{1}H and ^{13}C NMR spectra of *o*-OPE **1**·Ag(I) and **6**·Ag(I) was accomplished. The deshielding of the two non-equivalent *ortho*-H of inner phenyl groups (Figure 1b and 1d, white-labeled hydrogens) indicates a loss of electron density of the triple bonds. These data together with the significant changes (2-5 ppm) observed in the ^{13}C chemical shifts of the alkynes (Figure S1) strongly suggested the Ag(I)-alkyne coordination.[18] These evidences led us to conclude that Ag(I) was able to bind the three alkynes of the *o*-OPEs. Under the light of these results, we decided to study the stability of the Ag(I)-alkyne interaction and its relationship with the nature of the *o*-OPEs.

Binding affinity of the Ag(I) cation to *o*-OPEs

Quantitative binding affinities and stoichiometries were calculated for **1-16** (CD_2Cl_2:acetone-d_6 = 9:1)[19] by ^{1}H NMR titration experiments (Figures 2, 3 and supporting information) using Dynafit code (Table 1).[20] Characteristic deshielding of the *ortho*-H of inner phenyl groups and ^{13}C NMR chemical shifts of the alkynes attributed to the Ag(I)-alkyne interaction could be unambiguously identified in all the cases.[21] Only one set of signals was observed along the titration experiments suggesting stable complexation under fast exchange conditions.[22] All compounds, containing up to six alkynes, presented 1:1 ligand:Ag(I) stoichiometries.[23]

From the ^{1}H NMR data, a higher binding constant was obtained for the cyclic *o*-OPE **1** (K_a= 1001 ± 180 M^{-1}, Figure 2a) in comparison to bis(acetylated) acyclic **6**, (K_a= 63 ± 6 M^{-1}). This observation is consistent with the existence of a binding site of suitable size that requires a less unfavorable entropic coordination (macrocyclic effect).[25] An unexpectedly high binding constant was also obtained for the di-hydroxylated acyclic *o*-OPE **7** (K_a= 739 ± 140 M^{-1}, Figure 2c) in comparison to the unsubstitued acyclic **8** analog (K_a= 49 ± 2 M^{-1}, Figure 2d). Previous DFT calculations revealed that in compound **7** an intramolecular hydrogen bond formed between the two benzyl alcohol groups further stabilizes the folded conformation.[11] Hence, the significantly higher value obtained for **7** could reasonably stem from a synergetic effect played by the intramolecular hydrogen bond and the Ag(I) ion acting simultaneously as driving forces in the folding event.[26]

Table 1. Association Constants (K_a) measured by ^{1}H NMR spectroscopy.[a,24]

o-OPEs	K_a (M^{-1})	*o*-OPEs	K_a (M^{-1})
1	1001 ± 180	**9**	667 ± 50
2	852 ± 260	**10**	680 ± 24
3	86 ± 7	**11**	559 ± 16
4	53 ± 2	**12**	22 ± 5
5	318 ± 25	**13**	71 ± 17
6	63 ± 6	**14**	7.3 ± 0.3
7	739 ± 140	**15**	187 ± 84
8	49 ± 2	**16**	> 10^5

[a] Measured in CD_2Cl_2:d_6-acetone =9:1 mixtures at 298 K.

Succinoyl macrocycle **2** gave a slightly smaller binding constant (K_a= 852 ± 260 M^{-1}) than macrocycle **1**. Surprisingly, the *para,para*- (Figure 2b) and *para,meta*-substituted chiral tartrate derivates **3** and **4** presented binding constants one order of magnitude smaller (K_a = 86 ± 7 M^{-1} and K_a = 53 ± 2 M^{-1}, respectively) than those obtained for ligands **1** and **2**. This lower binding affinity could be related to the major rigidity imposed by the chiral tartrate staple[11] and, hence, altering the optimal conformation of the alkynes for the coordination (and the corresponding mismatch of the cavity size). Consistent with this hypothesis was the higher value (K_{as}= 318 ± 25 M^{-1}) measured for the less rigid *meta,meta*-substituted chiral tartrate derivate **5**.

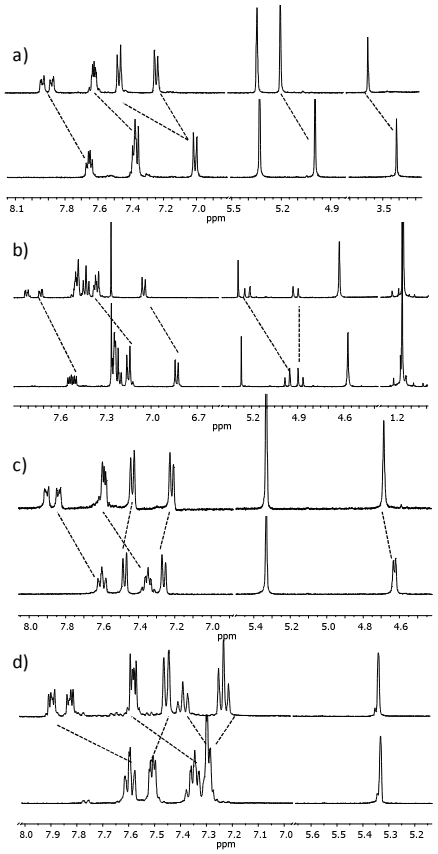


Figure 2. ^{1}H NMR spectra of the ligand a) **1** (6 mM), b) **3** (17 mM), c) **7** (8 mM), and d) **8** (14 mM) with an excess of $AgBF_4$ (CD_2Cl_2-acetone-d_6 = 9:1 mixtures, 500 MHz, 298 K). Only the representative parts of the spectra are shown.

In order to explore if the binding/folding phenomenon could be extended to *o*-OPEs with more than three alkyne units, we titrated *o*-OPEs **9** (n = 2, four alkynes), **10** (n = 2, five alkynes) and **11** (n = 3, six alkynes) (Figure 4).[27] Again, a 1:1 stoichiometry was observed for all cases in spite of the increased number of alkyne potential ligands. The ^{1}H NMR spectra recorded during the tritation of *o*-OPE **9** (n = 2) (Figure 4a) showed analogous changes than the tritation experiment of *o*-OPE **8** (n = 1) (Figure 2d). Thus, the two *ortho*-H of outer phenyl group appear upfield and the two *ortho*-H of the inner phenyl group are deshielded (Figure 4). These common features strongly suggest the presence of folded structures. Moreover, the comparison of the binding constant values obtained for 1:1 complexes of *o*-OPE **8**·Ag(I) (K_a = 49 ± 2 M^{-1}) and *o*-OPE **9**·Ag(I) (K_a = 667 ± 50 M^{-1}) revealed that the ability of the alkynes to roll-around the metal is

modest in terms of free energy (-2.3 kcal/mol and -3.8 kcal/mol respectively) but increases significantly with the presence of a new alkyne.

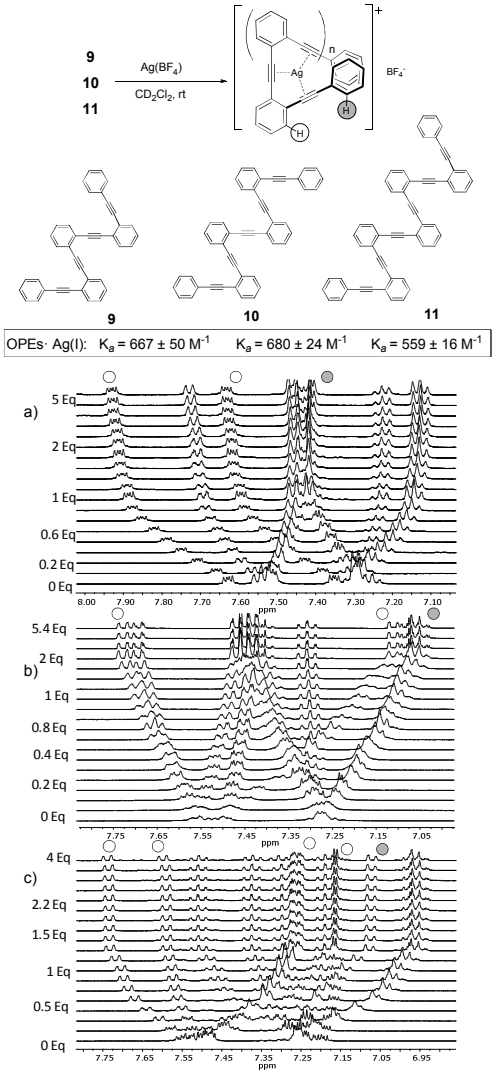


Figure 3. a) ^{1}H-NMR titrations of the ligand **9** (10 mM), b) **10** (20 mM) and c) **11** (10 mM) with $AgBF_4$ (CD_2Cl_2-acetone-d_6 = 9:1 mixtures, 500 MHz, 298 K).

The affinity constant obtained for the next ligands of the series containing five and six alkynes revealed similar binding constant than *o*-OPEs **9** (compound **10** (n = 2), K_a = 680 ± 24 M^{-1}, compound **11** (n = 3), K_a = 559 ± 16 M^{-1}, Figure 4b and 4c). Every additional alkyne should increase the ligand affinity toward Ag(I), however the similar value measured for ligand **9-11** suggests that the Ag(I) can coordinate efficiently to only four alkyne groups.

X-Ray crystallographic data and theoretical calculations.

We also investigated the structure and the coordination features of the Ag(I)-*o*-OPE complexes in solid state. We were able to obtain suitable crystals to determine the X-ray structures of the Ag(I) complexes of **1** and **8** (Figure 4).

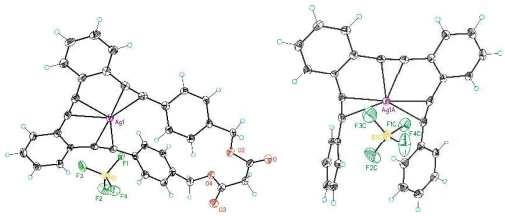


Figure 4. X-ray structures of **1·Ag(I)** and **8·Ag(I).**

In agreement with the NMR evidences in solution, in both complexes one silver ion was located into the cavity of the *o*-OPE backbone and simultaneously coordinated to the three alkynes in the solid-state (mean distance Ag(I)-alkyne 2.3 Å).[28] In both adducts, the *o*-OPE moiety was not arranged into a helical geometry around the metals but into a slightly distorted trigonal-bipyramidal geometry (torsion angles 8.8º for complex **8·Ag(I)** and 6.4º for complex **1·Ag(I)**). In the crystal structure of **1·Ag(I)** (Figure 4), the two apical positions of the distorted trigonal-bipyramidal geometry were occupied by an oxygen atom from the malonyl group of a neighboring complex (*ca.* 2.57 Å) and a BF_4^- anion (*ca.* 2.61 Å). In **8·Ag(I),** the silver atom instead of binding an oxygen atom, lied at an average distance of 2.99 Å from one of the benzene rings of the neighboring complex. DFT calculations using the M06 functional with the 6–31G* basis set for the ligands and the LANL2DZ relativistic effective core potential basis set for the Ag(I) ion[21] of the expected cationic structure **8·Ag(I)** (Figure 5a) showed the same slightly distorted trigonal geometry (but with a larger torsion angle of 14.6º), which is presumably the one adopted in solution.

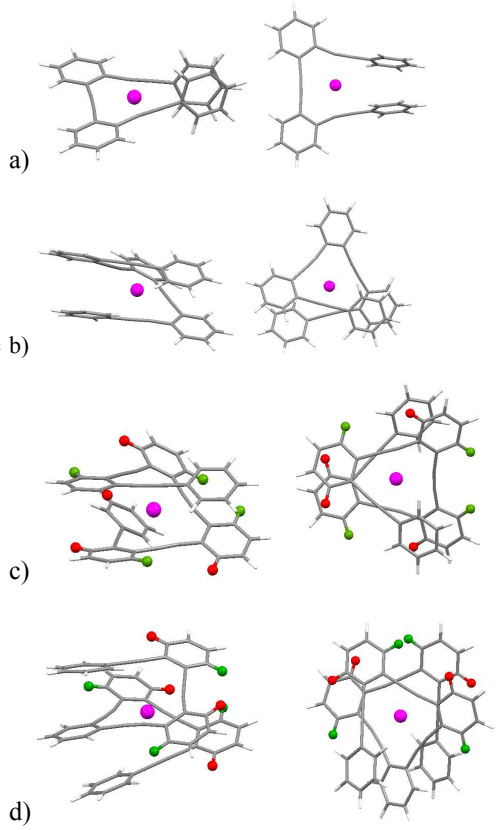


Figure 5. DFT calculated structure for **8·Ag(I)**, **9·Ag(I)**, **10·Ag(I)**, and **11·Ag(I)** side views (left) and top views (right).

Although for higher oligomers we were not able to obtain crystal structures, the agreement between experimental and calculated structures of **8·Ag(I)** encouraged us to explore the soft accommodating nature of the Ag(I) ion[29,30] into *o*-OPEs **9**, **10** and **11** by theoretical calculations (Figure 5b-5d). In the case of **9·Ag(I)**, **10·Ag(I)**, and **11·Ag(I)** a pseudo-tetrahedral coordination was obtained with the silver cation simultaneously coordinated to the four alkynes. In complexes **10·Ag(I)** and **11·Ag(I)** the additional alkynes were loosely bound, although a completely folded conformation can be inferred from the NMR data. Both structures are symmetric and, remarkably, the terminal benzene rings are significantly shielded owing to the presence of a superposed aromatic ring. Moreover, the *ortho*-H of inner phenyl groups are non-equivalent, being one of them shielded (red hydrogen atoms, Figure 5c-d) and the other deshielded (green hydrogen atoms, Figure 5c-d). This spectroscopic behavior can only be explained taking into account the predicted folded structure (Figures 5c-d) in which one of such protons is placed over a phenyl ring and the other outside of the anisotropy cone. Interestingly, all these complexes with four to six alkynes have an helical arrangement, thus inducing chirality around the metal center.[31] These results also point toward the potential formation of larger *o*-OPE metallofoldamers (each *o*-OPE comprising 4n alkynes chelating n Ag(I) atoms) with two potentially conductive substructures: the metallic core and the all-conjugated carbon backbone.

Photo kinetical studies of *o*-OPEs 12-15.

NMR data and DFT-based theoretical calculations described above provided thermodynamic and structural data, as well as multiple evidences about the formation of folded structures in solution owing to Ag(I)-coordination features. Nevertheless, an unequivocal demonstration of their existence can only emerge from responses that could only exist in the folded state of the *o*-OPE. Furthermore, the structural effects of the Ag(I) coordination on the electronic energy levels of the ligands, as well as the kinetics of the random-coil to helix transition are interesting issues to elucidate. For this purpose, we prepared four fluorescent *o*-OPEs **12-15** bearing one terminal pyrene group and four different rings in the opposite end (Chart 1). Compound **13** was chosen to study the rate constant of pyrenyl-excimer formation.

Excimers are short-lived dimeric species formed in the electronic excited state by some compounds. The study is based on the effect of dynamic phenomena, such as quenching or excimer formation, on the fluorescence emission spectra and fluorescence lifetime of pyrene derivatives. In systems with conformational flexibility, metal-ion-mediated conformational changes have been frequently tested by using excimer formation kinetic data.[32] *o*-OPE **12** was prepared as a model compound, and *o*-OPEs **14** and **15** to evaluate the effect of tuning the electronic properties with electron-poor and electron-rich groups.

Despite the wide π-surface of the pyrene moiety, which could potentially interfere with the Ag(I)-alkyne coordination in compounds **12-15**, ^{1}H NMR titrations and ^{13}C NMR data evidenced the folding by coordination with the alkynes (Figure 6 and ESI). Moreover, the binding constant values calculated had the same order of magnitude than *o*-OPE **8** (K_a = 22 ± 5 M^{-1} for **12** and K_a = 71 ± 17 M^{-1} for **13**). Then, we investigated the spectroscopic features of both compounds (Figure S4) and the metal binding effect in solution by UV-vis and fluorescence spectroscopy (Figure 7 and Figures S5-S6). The most interesting results were obtained from the fluorescence measurements.

The emission spectra of **12** and **13** showed significantly different spectral shapes (Figure 7 and figure S4). Emission maxima of **12** occurred at shorter wavelengths (λ_{em} from 410 to 450 nm) in comparison to the broad, multi-band emission of **13** (λ_{em} from 420 to 520 nm). The formation of intermolecular excimers was ruled out in the working concentration conditions and the long-wavelength band registered for **13** was attributed to the emission of an intramolecularly formed excimer.[33] When Ag(I)-titrations of compounds **12** and **13** were recorded, fluorescence quenching was detected in both cases. Nevertheless, only along the titration of **13** a significant ratiometric change was observed (Figure 7 and S6).

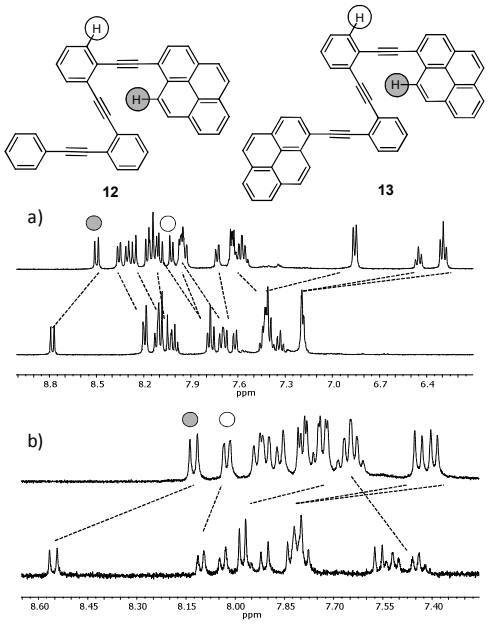


Figure 6. ^{1}H NMR spectra of the ligands a) **12** (7 mM) and b) **13** (40 mM) with an excess of $AgBF_4$ (CD_2Cl_2-acetone-d_6 = 9:1 mixtures, 500 MHz, 298 K). Only the representative parts of the spectra are shown.

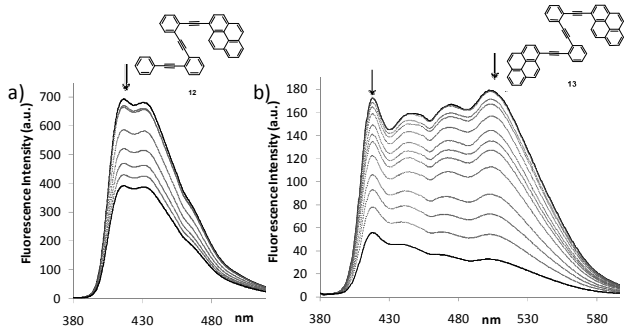


Figure 7. a) Emission changes observed upon stepwise addition of $AgBF_4$ to a solution of **12** ($2.7\cdot10^{-5}$M; up to 500 eq.) and b) **13** ($4.4\cdot10^{-5}$M; up to 1500 eq.) using λ_{exc}= 375 nm in CH_2Cl_2-acetone = 9:1 mixtures at 298 K.

Time-resolved fluorescence measurements can provide information on the kinetics of excimer formation, and thus on the

dynamics of the formation of folded structures. Fluorescence decay traces of **13** at the pyrene monomer emission wavelengths (420 nm, Figure S7) and excimer emission wavelengths (560 nm, Figure S8) were recorded,[21] and global deconvolution analysis was used to extract the fluorescence decay times (Figure 8). Global analyses of fluorescence decay traces of **13** in solution showed three different decay times, the shortest (τ_3) of 0.713±0.01 ns and two long components of τ_2 = 6.37±0.14 and τ_1 = 12.36±0.05 ns (Figure 8a). Importantly, the fluorescence decays traces at the monomer emission wavelengths (420 nm) were effectively mono-exponential with the single τ_3 decay time, whereas at the characteristic wavelength of the excimer emission (560 nm) the shortest component is a rise time (it has a negative amplitude), hence indicating the excited-state built up of excimer species. Nevertheless, the sum of all the amplitudes for the excimer trace is not equal to zero, thus indicating the presence of dimers formed in the ground state.[34] Analysis of the absolute amplitudes (Figure 8b) at 560 nm revealed that the amplitude associated to τ_2 was almost equal in absolute value than the amplitude associated to τ_3. This suggests that the component τ_2 corresponds to the emission of the folded species formed dynamically during the excited state, and that τ_3 is associated to the kinetics of the excimer formation reaction. On the other hand, prefolded species before excitation were associated to τ_1. This is supported by the changes observed in the decay times and amplitudes when Ag(I) is added: the rise-time, τ_3, becomes faster (Figure 8), which involves an Ag(I)-facilitated excimer formation; and the contribution of the ground-state dimer is enhanced, as supported by the growth in τ_1 amplitude. Under the light of these results, we proposed the following kinetic model which relates the ground state equilibrium in which compound **13** is involved with the excited-state data (Figure 9). Unfortunately, this dynamic situation avoids a direct evaluation of the relative ratio between folded and unfolded species.

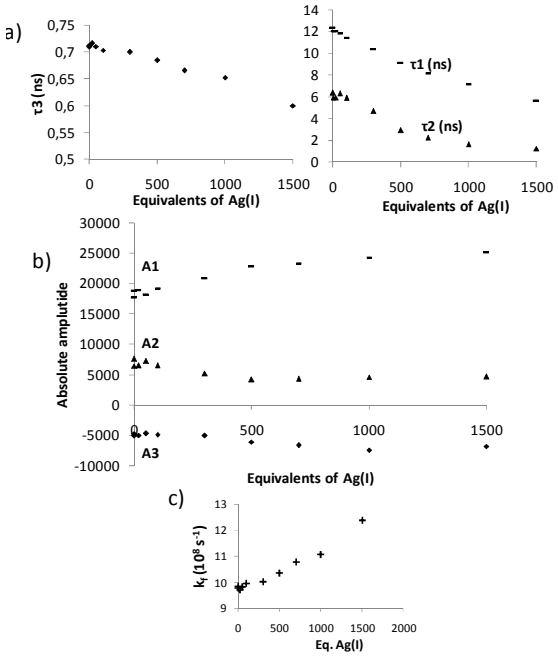


Figure 8. a) Plots of the global lifetime components τ_i and b) absolute amplitudes (at λ_{em} = 560 nm) obtained from the fluorescence decays of **13** registered upon stepwise addition of $AgBF_4$ in CD_2Cl_2- acetone-d_6 =9:1 mixtures at 298 K. c) Evolution of the excimer formation rate constant k_f due to the Ag(I) coordination.

Interestingly, compound **12** also presents a rich photochemistry. From the global deconvolution analysis two lifetimes could be extracted, τ_1 = 2.93±0.03 and τ_2 = 1.42±0.06 ns, which were related with two different species in solution. Previously described alkynyl pyrenes only present one lifetime and, therefore, rotations of the pyrene moiety can be ruled out as the origin of those lifetimes.[35] We assigned those lifetimes to the folded and unfolded conformers of compound **12** and, for consistency with compound **13**, we assigned the longest one to the folded species. The absence of excimer formation in this case favored the quantification of the two conformers in solution. We performed time-resolved emission spectroscopy (TRES) to obtain the emission spectra associated to each species (Figure S9), and quantified a conformational population consisting in a 70:30 folded:unfolded approximate relationship.[21]

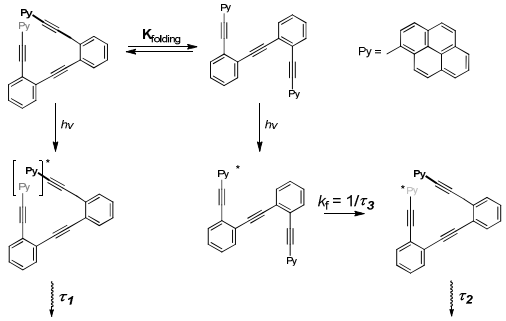


Figure 9. Schematic model which relates the ground state equilibrium of **13** ($K_{folding}$) and the kinetics of the excited-state folding reaction.

Remarkably, the kinetics of the excited-state folding reaction (k_f in figure 8c) can be also accessible through the fluorescence decay times. Using compound **12** as reference, we could determine the excited-state folding kinetic constant in the absence of Ag(I) (k_f) of (9.8±0.3)×10^8 s^{-1}.[21,36] This value represents one of the few examples of experimentally determined kinetic folding constant in OPE-based foldamers.[37] As expected, the presence of Ag(I) favors the excited-state folding process, and the k_f value increases (Figure 8c). Although the increase may seem modest taking into account the number of equivalents of Ag(I) added, it is consistent with the diluted conditions used (10^{-6} M) and the low binding constant determined for **13** in the ^{1}H NMR experiments.

The effect of tuning the chemical structure of two additional *o*-OPEs with electron-rich and electron-poor terminal aryl groups (compounds **14** and **15**) was subsequently investigated (Figure 10). A careful examination of the ^{1}H NMR titration spectra revealed that side-chain variation with a nitro group (compound **14**) resulted in weaker coordination (K_a = 7.3 ± 0.3 M^{-1}). The strong quenching of the fluorescence due to the electronic communication along the carbon backbone was evidenced by the low fluorescence quantum yield, which characterized this compound in comparison to other pyrene derivatives (ϕ=0.009±0.005 for **14**, 0.59±0.07 for **15** and 0.26±0.03 for **13**).[21]

Influence of a new coordination group.

Although compound **15,** bearing two methoxy groups on the benzene ring, did not show relevant photophysical information, it displayed a completely new phenomenon, evidenced in the ^{1}H-NMR titration owing to methoxy groups are taking part in the complexation (Figure 10b).

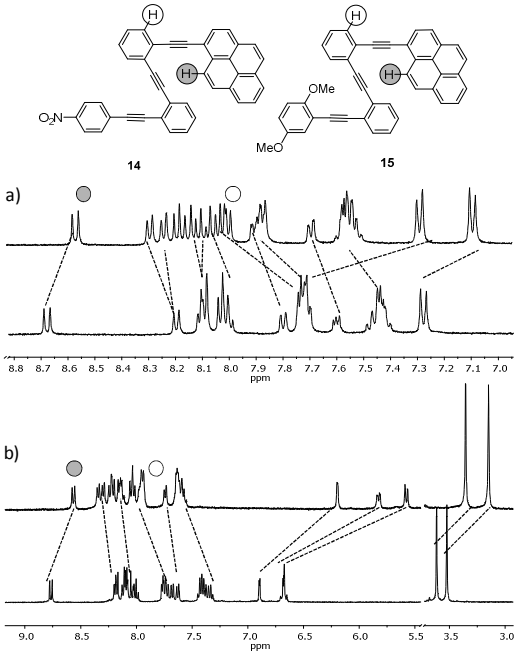


Figure 10. a) ^{1}H NMR titrations of the ligands **14** and b) **15** with $AgBF_4$ (CD_2Cl_2: d_6-acetone =9:1 mixtures, 500 MHz, 298 K).

At the beginning of the titration of **15** with up to 0.5 equiv of Ag(I) the more affected signals were those corresponding to the dimethoxybenzene ring closely followed by the aromatic hydrogens of the inner benzenes. The broadening of the proton signals corresponding to the phenyl ring between 0.16 and 1.2 equiv revealed that a slow exchange process was taking place for such titration range. Moreover, in this range, the protons of the inner aryls experienced more accused shifts from $\Delta\delta \approx 0.11$ to 0.23 ppm consistent with a cooperative change. Above 1.2 equiv, any change was subsequently observed suggesting that the saturation plateau have been reached. A stronger interaction for compound **15** with the silver was also evidenced by the increase of the binding constant (K_a = 187 ± 84 M^{-1}). The coordination of the silver into the foldamer void with a helical conformation was evidenced by the ^{13}C shift of the alkynes signals and by several strong 2D-NOESY cross peacks.[21] Complementary cross-peaks between the methoxy group located at the *ortho* position (δ = 3.36 ppm) and the more deshielded H-10 proton of the pyrene ring together with some crosspeaks between the *m*-MeO group (δ=3.14 ppm) and other pyrene protons were consistent with a stable helical conformation in which the *o*-MeO group was located onto the cavity of the helix probably coordinating the silver ion (Figure S10). Hence, compound **15** appeared to be a quite promising ligand to obtain the discrete and stable 1:1 Ag(I)-helix. In order to check if the presence of the pyrene has a crucial role in such behavior, we decided to study its phenyl analog **16**. For compound **16**, again fast exchange was observed during the ^{1}H NMR titration (Figure 11). Noteworthy, when the binding constant was calculated from the NMR data, values higher than 10^5 M^{-1} were obtained with good fitting parameters for a 1:1 stoichiometry. NOESY cross-peaks were again observed confirming the helical conformation of **16** in solution (Figure S11). It is remarkable the extraordinary cooperative effect of alkyne-based coordination and oxygen coordination taking into account the low values of the binding constant for each independent binding site.

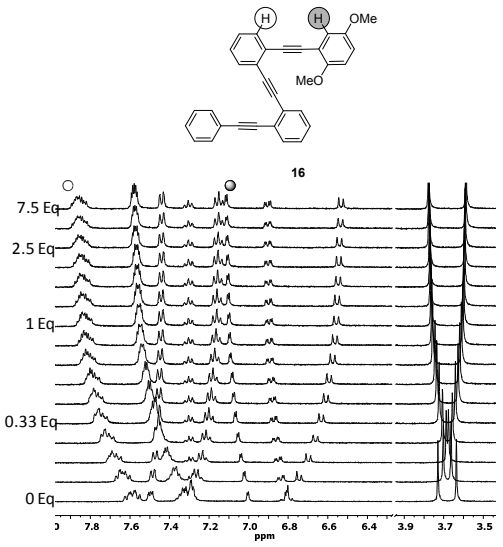


Figure 11. ^{1}H NMR titration of **16** with $AgBF_4$ (CD_2Cl_2: d_6-acetone =9:1 mixtures, 500 MHz, 298 K).

Conclusions

For the first time, Ag(I)-alkyne interaction has been shown to induce the folding of non-conformationally restricted *o*-OPE foldamers by simple C-C bond rotations yielding a new class of metallofoldamers. The diverse interactions of silver with the *o*-OPE defines the binding constant and three-dimensional structure of the foldamer. These interactions can be modulated as a function of size and/or the substituents in the organic structures, allowing foldamers of different structure and strength using Ag(I) as the only promoter. Additionally, synergic effects as hydrogen bonding, and preorganization of the ligands have been detected to increase the stability of the organometallic products facilitating the binding/folding event. Noteworthy, the unexpected but promising role displayed by the MeO group in compounds **15** and **16**, opens the opportunity to design a new generation of more robust helicates. The possibility to change the alkoxy chain for e.g. a chiral group would potentially be applicable to form a single *P* or *M* helicate and to transfer the chirality to the metal center.[38] Thus, the development of new chiral metal catalysts or chemoselective chemical sensors would start to become a realistic goal.

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1 D.-W. Zhang, X. Zhao, J.-L. Hou and Z.-T. Li, *Chem. Rev.* 2012, **112**, 5271; H. Juwarker, J.-M. Suk and K.-S. Jeong, *Chem. Soc. Rev.* 2009, **38**, 3316; *Foldamers: Structure, Properties and Applications*; S. Hecht, I. Huc, Eds.; Wiley-VCH: Weinheim, Germany, 2007; D. J. Hill, M. J. Mio, R. B. Prince, T. S. Hughes and J. S. Moore, *Chem. Rev.* 2001, **101**, 3893; S. H. Gellman, *Acc. Chem. Res.* 1998, **31**, 173.

2 T. Martinek and F. Fülöp, *Chem. Soc. Rev.* 2012, **41**, 687; Y.-B. Lim, K.-S. Moon and M. Lee, *Chem. Soc. Rev.* 2009, **38**, 925; M. C. Petty, *Molecular Electronics: From Principles to Practice;* Wiley-VCH: Weinheim, Germany, 2008; E. Yashima, K. Maeda and Y. Furusho, *Acc. Chem. Res.* 2008, **41**, 1166.

3 H. Miyake and H. Tsukube, *Chem. Soc. Rev.,* 2012, **41**, 6977; A. Petitjean, L. A. Cuccia, J.-M. Lehn, H. Nierengarten and M. Schmutz, *Angew. Chem., Int. Ed.* 2002, **41**, 1195; C. Piguet, G. Bernardinelli and G. Hopfgartner, *Chem. Rev.* 1997, **97**, 2005; J.-M. Lehn, *Supramolecular Chemistry, Concepts and Perspectives*; Wiley-VCH: Weinheim, 1995.

4 *Metallofoldamers. Supramolecular Architectures from Helicates to Biomimetics*; G. Maayan, M. Albrecht, Eds; Wiley-VCH: Weinheim, Germany, 2013; Z. Dong, J. N. Plampin III, G. P. A. Yap and J. M. Fox, *Org. Lett.* 2010, **12**, 4002; G. Maayan, *Eur. J. Org. Chem.* 2009, **33**, 5699; S. Akine, Y. Morita, F. Utsuno and T. Nabeshima, *Inorg. Chem.* 2009, **48**, 10670; Z. Dong, G. P. A. Yap and J. M. Fox, *J. Am. Chem. Soc.* 2007, **129**, 11850; Z. Dong, R. J. Karpowicz, S. Bai, G. P. A. Yap and J- M.; Fox, *J. Am. Chem. Soc.* 2006, **128**, 14242; F. Zhang, S. Bai, G. P. A. Yap, V. Tarwade and J. M. Fox, *J. Am. Chem. Soc.* 2005, **127**, 10590; R. B. Prince, T. Okada and J. S. Moore, *Angew. Chem., Int. Ed.* 1999, **38**, 233.

5 J. C. Nelson, J. G. Saven, J. S. Moore and P. G. Wolynes, *Science*, 1997, **277**, 1793.

6 For seminal works of *meta*-oligophenylenethynylene (OPEs): R. B. Prince, J. G. Saven, P. G.; Wolynes and J. S. Moore, *J. Am. Chem. Soc.* 1999, **121**, 3114. M. S. Gin, T. Yokozawa, R. B. Prince and J. S. Moore, *J. Am. Chem. Soc.* 1999, **121**, 2643. L. Brunsveld, E. W. Meijer, R. B. Prince and J. S. Moore, *J. Am. Chem. Soc.* 2001, **123**, 7978. S. Lahiri, J. L. Thompson and J. S. Moore, *J. Am. Chem. Soc.* 2000, **122**, 11315; A. Tanatani, M. J. Mio and J. S. Moore, *J. Am. Chem. Soc.* 2001, **123**, 1792; K. Matsuda, M. T. Stone and J. S. Moore, *J. Am. Chem. Soc.* 2002, **124**, 11836; A. Tanatani, T. S. Hughes and J. S. Moore, *Angew. Chem. Int. Ed.* 2002, **41**, 325; M. T. Stone, J. M. Fox and J. S. Moore, *Org. Let.,* 2004, **6**, 3317; R. F. Kelly, B. Rybtchinski, M. T. Stone, J. S. Moore and M. R. Wasielewski, *J. Am. Chem. Soc.* 2007, **129**, 4114; R. A. Smaldone and J. S. Moore, *J. Am. Chem. Soc.* 2007, **129**, 5444; R. A. Smaldone and J. S. Moore, *Chem. Eur. J.* 2008, **14**, 2650; S. Y.-L Leung, A. Y.-Y.Tam, C.-H. Tao, H. S. Chow and V. W.-W. Yam, *J. Am. Chem. Soc.* 2012, **134**, 1047.

7 *Modern Gold Catalyzed Synthesis*; A. S. K. Hashmi, F. D. Toste, Eds; Wiley-VCH: Weinheim, Germany, 2012; M. Bandini, *Chem. Soc. Rev.* 2011, **40**, 1358; L. Liang and D. Astruc, *Coord. Chem. Rev.* 2011, **255**, 2933; A. Corma, A Leyva-Perez and M. J. Sabater, *Chem. Rev.* 2011, **111**, 1657; S. Flügge, A. Anoop, R. Goddard, W. Thiel and A. Fürstner, *Chem. Eur. J.* 2009, **15**, 8558; *Silver in Organic Chemistry*; M. Harmata, Ed.; Wiley-VCH: Weinheim, Germany, 2010; M. Naodovic and Y. Yamamoto, *Chem. Rev.* 2008, **108**, 3132; J.-M. Weibel, A. Blanc and P. Pale, *Chem. Rev.* 2008, **108**, 3149; Z. Li, C. Brouwer and C. He, *Chem. Rev.* 2008, **108**, 3239; E. Jimenez-Nunez and A. M. Echavarren, *Chem. Rev.* 2008, **108**, 3326; N. T. Patil and Y. Yamamoto, *Chem. Rev.* 2008, **108**, 3395; U.-H. Letinois, J.-M. Weibel and P. Pale, *Chem. Soc. Rev.* 2007, **36,** 759.

8 H. Lang, T. Stein, S. Back and G. Rheinwald, *J. Organom. Chem.* 2004, **689**, 2690; H. Lang, N. Mansilla, R. Claus, T. Rüffer and G. Rheinwald, *Inorg. Chim. Acta,* 2001, **373**, 93; S. M. Cortez and R. G. Raptis, *Coord. Chem. Rev.* 1997, **162**, 495; H. Lang, K. Köhler and S. Blau, *Coord. Chem. Rev.* 1995, **143**, 113.

9 A. Das, C. Dash, M. A. Celik, M. Yousufuddin, G. Frenking and H. V. R. Dias, *Organometallics,* 2013, **32**, 3135; A. Reisinger, N. Trapp, I. Krossing, S. Altmannshofer, V. Herz, M. Presnitz and W. Scherer, *Angew. Chem., Int. Ed.* 2007, **46**, 8295; A. Kunze, S. Balalaie, R. Gleiter and F. Rominger, *Eur. J. Org. Chem.* 2006, 2942; R. Gleiter, T. V. Hirschheydt and F. Rominger, *Eur. J. Org. Chem.* 2000, 2127; A. Kunze, R. Gleiter and F. Rominger, *Chem. Commun.* 1999, 171; T. Nishinaga, T. Kawamura and K. Komatsu, *J. Chem. Soc., Chem. Commun.* 1998, 2263; J. D. Ferrara, A. Djebli, C. A. Tessier and W. J. Youngs, *J. Am. Chem. Soc.* 1988, **110**, 647.

10 For seminal works of *ortho*-oligophenylenethynylenes (OPEs): R. A. Blatchly and G. N. Tew, *J. Org. Chem.* 2003, **68**, 8780. T. V. Jones, R. A. Blatchly and G. N. Tew, *Org. Lett.* 2003, **5**, 3297. T. V. Jones, M. M. Slutsky, R. Laos, T. F. A. de Greef and G. N. Tew, *J. Am. Chem. Soc.* 2005, **127**, 17235; R. A. Blatchly and G. N. Tew, *J. Org. Chem.* 2003, **68**, 8780; M. M. Slutsky, T. V. Jones and G. N. Tew, *J. Org. Chem.* 2007, **72**, 342; M.-X. Zhu, W. Lu, N. Zhu and C.-M. Che, *Chem. Eur. J.* 2008, **14**, 9736; J. Jiang, M. M. Slutsky, T. V. Jones and G. N. Tew, *New J. Chem.* 2010, **34**, 307; Y.-T. Shen, N. Zhu, X.-M. Zhang, K. Deng, W. Feng, Q. Yan, S. Lei, D. Zhao, Q.-D.; Zeng, C. and Wang, C. *Chem. Eur. J.* 2011, **17**, 7061; J. Li, G. Hu, N. Wang, T. Hu, Q. Wen, P. Lu and Y. Wang, *J. Org. Chem.* 2013, **78**, 3001.

11 N. Fuentes, A. Martín-Lasanta, L. Álvarez de Cienfuegos, R. Robles, D. Choquesillo-Lazarte, J. M. García-Ruiz, A. J. Mota, L. Martínez-Fernández, I. Corral, D. J. Cárdenas, M. Ribagorda, M. C. Carreño and J. M. Cuerva, *Angew. Chem. Int. Ed.* 2012, **51**, 13036.

12 For other approaches to covalently lock supramolecular arrangements, see: S. Hecht and A. Khan, *Angew. Chem. Int. Ed.* 2003, **42**, 6021–6024; R. A. Smaldone, E.-C. Lin and J. S. Moore, *J. Pol. Sci., Part A: Pol. Chem.* 2010, **48**, 927; C. E. Schafmeister, J. Po and G. L. Verdine, *J. Am. Chem. Soc.* 2000, **122**, 5891; Y.-K. Kim, P. S. Kutchukian and G. L. Verdine, *Org. Lett.* 2010, **12**, 3046; H. E. Blackwell and R. H. Grubbs, *Angew. Chem. Int. Ed.* 1998, **37**, 3281: D. J. Yeo, S. L. Warriner and A. J. Wilson, *Chem. Commun.* 2013, **49**, 9131; M. J. Kim, Y. R. Choi, H. G. Jeon, P. Kang, M.-G. Choi and K.-S. Jeong, Chem. *Commun.* 2013, **49**, 11412; J. Yu, J. R. Horsley, K. E. Moore, J. G. Shapter and A. D. Abell, *Chem. Commun.* 2014, **50**, 1652; I.-E. S. Müller, B. Bernet, C. Dengiz, W. B. Schweizer and F. Diederich, *Eur. J. Org. Chem.* 2014, 941.

13 P. D. Frischmann and M. J. MacLachlan, *Chem. Soc. Rev.* 2013, **42**, 871.

14 N. Fuentes, L. Álvarez de Cienfuegos, A. Parra, D. Choquesillo-Lazarte, J. M. García-Ruiz, M.; Marcos, E. Buñuel, M. Ribagorda, M. C. Carreño, D. J. Cárdenas and J. M. Cuerva, *Chem. Commun.* 2011, **47**, 1586; S. Rodríguez-Bolívar, F. M. Gómez-Campos, L. Álvarez de Cienfuegos, N. Fuentes, D. J. Cárdenas, E. Buñuel, J. E. Carceller, A. Parra and J. M. Cuerva, *Phys. Rev. B*, 2011, **83**, 125424; N. Fuentes, A. Martín-Lasanta, L. Álvarez de Cienfuegos, M. Ribagorda, A. Parra and J. M. Cuerva, *Nanoscale* 2011, **3**, 4003; A. J. Mota, L. Álvarez de Cienfuegos, S. P. Morcillo, N. Fuentes, D. Miguel, S. Rodríguez-Bolívar, F. M. Gómez-Campos, D. J. Cárdenas and J. M. Cuerva, *ChemPhysChem* 2012, ***13***, 3857; A. Martín-Lasanta, D. Miguel, T. García, J. A. López-Villanueva, S. Rodríguez-Bolivar, F. M. Gómez-Campos, E. Buñuel, D. J. Cárdenas, L.

Álvarez de Cienfuegos and J. M. Cuerva, *ChemPhysChem* 2012, **13**, 860.
15 B. H. Zimm and J. K. Bragg, *J. Chem. Phys.* 1959, **31**, 526.
16 R. Chinchilla and C. Najera, *Chem. Soc. Rev.* 2011, **40**, 5084; R. Chinchilla, R. and C. Najera, *Chem. Rev.* 2007, **107**, 874; K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.* 1975, **16**, 4467.
17 J. E. Gano, G. Subramaniam and R. Birnbaum, *J. Org. Chem.* 1990, **55**, 4760; H. C. Kang, A. W. Hanson, B. Eaton and V. Boelelheide, *J. Am. Chem. Soc*. 1985, **107**, 1979; J. L. Pierre, P. Baret, P. Chautemps and M. Armand, *J. Am. Chem. Soc.* 1981, **103**, 2986.
18 A mechanistic study of a silver-catalyzed Sonogashira protocol based on ^{1}H, ^{13}C and ^{109}Ag-NMR data reported by Pale *et al.* provided several data to contrast our findings: U. Létinois-Halbes, P. Pale and S. Berger, S. *J. Org. Chem.* 2005, **70**, 9185-9190. See Figure S1 in ESI for details.
19 AgOTf was also tested in the titration experiments as silver source but best results were obtained using $AgBF_4$. This fact is related to the less coordinating character of the BF_4^- in comparison to the triflate anion.
20 P. Kuzmic, *Analytical Biochemistry*, 1996, **237**, 260.
21 See ESI for details.
22 Titrations of compounds **1**, **7** and **8** were repeated several times at different concentrations and the same titration curves were obtained in all the trials.
23 Tolane and bis-alkynyl trimer were also titrated and sequential changes in the chemical shift were recorded indicating that Ag(I)-alkyne coordination occurred. However, titration curves showed no clear break point over the range investigated, suggesting the coexistence of several complexes with different stoichiometries in solution. In addition, an isomer of compound **9** in which the central benzene in 1,3-substituted also led to similar results evidencing that at the least three alkynes located in *ortho* position (adjacent coordination sites) were required for the metal-assisted folding. See Figure S2 in ESI for details.
24 Modern NMR instruments can register good quality spectra with sub-millimolar concentrations and therefore NMR might be suitable for measuring association constants up to and even above 10^6 M^{-1}, although many literature references will state that 10^5 M^{-1} is the limit for NMR titration experiments. See: P. Thordarson, *Chem. Soc. Rev.,* 2011, **40**, 1305.
25 M. J. Chmielewski, T. Zielinski and J. Jurczak, *Pure Appl. Chem.* 2007, **79**, 1087.
26 A mono-hydroxylated *o*-OPE was synthesized and titrated giving a values of K_{as}= 16.8 ± 0.8 M^{-1}, closer to the ones obtained for **8.** See Figure S3 in ESI for details.
27 Poly-hydroxylated backbones turn out to be quite insoluble products hence their non-substituted analogs were chosen for the study.
28 The Ag(I)-alkyne values are shorter than the ones reported for the **II·Ag(I)** complex (ca. 2.7-2.8Å, from ref. 9g) but they are quite similar to that measured for [(cyclooctyne)$_3$Ag][PF6] (ca. 2.3-2.4Å, from ref. 9a).
29 A. G. Young and L. R. Hanton, *Coord. Chem. Rev.* 2008, **252**, 1346.
30 G. F.Swiegers, T.J. Malefetse, *Chem. Rev.* 2000, **100**, 3483.
31 E. C. Constable, *Chem. Soc. Rev.* 2013, **42**, 1637; Y. Wang, J. Xu, Y. Wang and H. Chen, *Chem. Soc. Rev.* 2013, **42**, 2930; J. Crassous, *Chem. Comm.* 2012, **48**, 9684.
32 T. M. Figueira-Duarte and K. Müllen, *Chem. Rev.* 2011, **111**, 7260; S. H. Lee, S. H. Kim, K. S. Kim, J. H. Jung and J. S. Kim, *J. Org. Chem.* 2005, **70**, 9288; H. Yuasa, N. Miyagawa, T. Izumi, M. Nakatani and I. Hashimoto, *Org. Lett.* 2004, **6**, 1489; F. M. Winnick, *Chem. Rev.* 1993, **93**, 587.
33 The fluorescence emission profiles were invariant with concentration in the range of 10^{-5}-10^{-7} M.
34 P. Reynders, W. Kühnle and K. A. Zachariasse, *J. Am. Chem. Soc.* 1990, **112**, 3929.
35 See for example: H. Maede, T. Maeda, K. Mizuno, K. Fujimoto, H. Shimizu and M. Inouye, *Chem. Eur. J.* 2006, **12**, 824; A. C. Benniston, A. Harriman, D. J. Lawrie and S. A. Rostron, *Tetrahedron Lett.* 2004, **45**, 2503.
36 A. M. Maçanita and K. A. Zachariasse, *J. Phys. Chem. A* 2011, **115**, 3183.
37 W. Y. Yang, R. B. Prince, J. Sabelko, J. S. Moore and M. Grubele, *J. Am. Chem. Soc.* 2000, ***122***, 3248; Z. Yu, S. Weidner, T. Risse and S. Hecht, *Chem. Sci.* 2013, **4**, 4156-4167.
38 G. Maayan, M. D. Ward and K. Kirshenbaum, *Chem. Commun*. 2009, 56-58