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Dedicated to Professor Josep Font on the occasion of his 70th birthday

**Abstract:** A new series of 20- and 25-membered polyacetylenic azamacrocycles have been satisfactorily prepared and completely characterised by spectroscopic methods. Various [2+2+2] cyclotrimerisation processes catalysed by the Wilkinson’s catalyst, [RhCl-(PPh₃)₃], were tested in the above-mentioned macrocycles. The 25-membered azamacrocycle (like the previously synthesised 15-membered azamacrocycle) led to the expected cyclotrimerised compound in contrast to the 20-membered macrocycle, which is characterised by its lack of reactivity. The difference in reactivity of the 15-, 20- and 25-membered macrocycles has been rationalised through density functional theory calculations.

**Keywords:** cyclotrimerisation · density functional calculations · macrocycles · reaction mechanisms · rhodium

**Introduction**

Transition-metal-catalysed [2+2+2] cyclotrimerisation reactions involving alkynes, in which three carbon–carbon bonds are formed in one step, is one of the most elegant methods for the construction of polysubstituted aromatics, which have important academic and industrial uses (for recent reviews see references [1–4]) The Wilkinson’s complex [RhCl-(PPh₃)₃] has been widely employed in these reactions. Partially intramolecular approaches or fully intramolecular cycloaddition processes represent efficient entries into various multiple-fused ring compounds. Over the last few years, we have developed an efficient rhodium(I)-catalysed [2+2+2] cyclotrimerisation process of 15-, 16- and 17-membered triynic and enediynic azamacrocycles of type 1 (to give compounds 2) and have described the first examples in the literature of completed closed systems[5–8] (Scheme 1). To broad-

![Scheme 1. Cyclotrimerisation reactions of macrocyclic triynes and enediynes.](image)

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200802548. It contains experimental description of all new compounds shown in Scheme 2 and ¹H and ¹³C NMR spectra for compound 14 and details of the structure determination, including atomic coordinates, bond lengths and angles, thermal parameters, least-squares planes and interatomic contacts of macrocycle 3a. Cartesian xyz coordinates and total energies of all stationary points located are also given.
the scope of these cyclotrimerisation reactions to other macrocyclic systems and to afford new kind of fused tetra
cycles, we have prepared 20-
membered tetraacetylenic azama
crocycle 3a–c and 25-
membered pentaacetylenic azama
crocycle 4 (Scheme 2) and stud
ed their cyclotrimerisation re-
actions catalysed by the Wilkin-
son’s complex.

Later in this paper, we shall
 discuss our finding that unlike
the 15- and 25-membered aza-
macrocycles, the 20-membered
tetraacetylenic azamacrocycles
3a–c do not lead to the expect-
ed \([2+2+2]\) cyclotrimerisation
products. To understand the
origin of this lack of reactivity,
we decided to carry out theo-
retical calculations using densi-
ty functional theory (DFT) with
a hybrid functional.

After a pioneering semiem-
pirical study,\(^9\) several DFT in-
vestigations into the reaction
mechanism of the transition-
metal-catalysed \([2+2+2]\) cyclo-
trimerisation reactions involv-
ing alkynes have been reported
in the last decade. The reaction
mechanism for the alkyne cy-
cloextrimerisation reaction cata-
lysed by \([\text{CoCp}(\text{L})_2]\) (\(\text{Cp} = \text{cyclopentadiene} \); \(\text{L} = \text{CO}, \text{PR}_3,
\text{THF} \) and olefin)\(^{10–13}\) \([\text{RuCpCl}]^{14–17}\) complexes and the
\([\text{RhCp}]^{18}\) and \([\text{RhInd}]\) (\(\text{Ind} = \text{indene}\))\(^{18}\) fragments has been
analysed in these DFT studies. The generally accepted reac-
tion mechanism is drawn in Scheme 3. The reaction begins
with a pair of ligand-alkyne substitution reactions. Then, the
oxidative coupling of the two alkyne ligands generates a
metallacyclopentadiene \(\text{IIIa} ([\text{CoCp}(\text{L})_2]), \text{[RhCp]} \) and
[\(\text{[RhInd]}\) or a metallacyclopentatriene \(\text{IIIb} ([\text{RuCpCl}])\) with
a biscarbene structure. This step has been found to be the
rate-determining step with activation energies typically in
the range \(11–14\) kcal mol\(^{-1}\). Subsequent coordination of a
third alkyne ligand to the metallacyclopentadiene or metal-
acyclopentatriene intermediate is followed by either alkyne
insertion to form a planar aromatic metallacycloheptatriene
\(\text{V} \) (the so-called Schore/C29s mechanism\(^{19}\)) or metal-mediated
\([4+2]\) cycloaddition to yield a 7-metallanorbornadiene com-
plex \(\text{VI} \) or \([2+2]\) cycloaddition to give a metallacyclo-
[3.2.0]heptatriene \(\text{VII} \). Finally, the arene is formed by the re-
ductive elimination of the metal. Although this is the gener-
al picture of the reaction mechanism, differences are found
between catalysts and the presence or absence of coordinat-
ing ligands, such as phosphine groups.\(^{13}\)

On the other hand, the cyclotrimerisation of nitriles and
acetylenes to afford pyridine rings has been also discussed
in a series of theoretical studies.\(^{17,18,20,21}\) The rate-determin-
ing step of the overall catalytic cycle changes to become the
addition of the nitrile molecule to the metallacyclopenta-
diene or metallacyclopentatriene intermediate.\(^{17,18}\) One of

Abstract in Catalan: S’ha sintetitzat i caracteritzat espectros-
còpicament una nova sèrie de macrocicles nitrogenats polia-
cetilènics de 20- i 25-membres. Amb aquests macrocicles s’han dut a terme les reaccions de ciclotrimerització \([2+2+2]\)
catalitzades pel catalitzador de Wilkinson, \([\text{RhCl}_{3}(\text{PPh}_3)_3]\). El
macrocicle nitrogenat de 25-membres (de la mateixa manera
que el macrocicle nitrogenat de 15-membres) permet l’ob-
tenció del compost ciclotrimeritzat. Per contra, el macrocicle
de 20-membres es caracteritza per la seva falta de reactivitat.
El diferent comportament de reactivitat dels macrocicles de
15-, 20-, i 25-membres ha estat estudiat mitjançant càlculs teò-
rics basats en la teoria del funcional de la densitat.
the key aspects in the cyclotrimerisation of nitriles and acetylenes is the competition between arene and pyridine formation. Relevant to our discussion are also several papers that address the co-cyclisation of two acetylene molecules with alkenes or CS₂. [14,22–25] Finally, we can briefly mention here that the uncatalysed thermal cyclotrimerisation is disfavoured entropically and has a high activation barrier. [26,27]

To the best of our knowledge, a theoretical study of the reaction mechanism of the transition-metal-catalysed [2+2+2] cyclotrimerisation reaction in a macrocyclic triyne has yet to be performed. This [2+2+2] reaction should be favoured over cyclotrimerisation reactions involving free acetylene molecules for entropic reasons. [15] In this paper we report the results of our theoretical examination of the mechanism for the cyclotrimerisation catalysed by the Wilkinson’s complex of the 15-, 20- and 25-membered acetylenic azamacrocycles depicted in Scheme 4 with two main goals: 1) to investigate the origin for the different reactivity of the 20-membered tetraacetylenic azamacrocycles and 2) to discuss the chemoselectivity of the trimerisation in the case of the pentaacetylenic azamacrocycles for which more than a single product can be obtained as cycloadDITION can occur between three adjacent or non-adjacent triple bonds. This is, we believe, the first theoretical study that addresses the mechanism of a cyclotrimerisation reaction in a series of acetylenic macrocycles. Furthermore, this is the first time that the Wilkinson’s catalyst has been investigated in a theoretical study of an intramolecular cyclotrimerisation reaction.

Results and Discussion

Macrocycles 3 and 4 were prepared following the synthetic pathway outlined in Scheme 2 and they were completely characterised by spectroscopic methods (see Supporting Information for full experimental details). One of the variants these macrocycles can present is the nature of the aryl units of the periphery. Firstly, two macrocycles 3a and 4 containing the same aryl unit, p-tolylsulfonamide, were prepared. The whole synthesis started with the reaction of N-tert-butyloxy-carbonyl (Boc)-protected p-tolylsulfonamide 5 [28] and 0.5 equiv of 2-butyne-1,4-diol under Mitsunobu reaction conditions to give compound 6. The elimination of the Boc groups in compound 6 (to give 7) and the subsequent treatment with two equivalents of bromo derivative 8 [29] resulted...
in the isolation of compound 9 with an 80% yield. The elimination of the Boc groups again with the same reaction conditions as before (TFA in CH₂Cl₂) gave intermediate 10. Compound 10, which already contains three acetylenic chains and four sulfonamide units, was the key intermediate for the preparation of both macrocycles. Cyclisation of 10 with 1,4-dibromo-2-butylene in the presence of KHCO₃ as a base afforded a 60% yield of macrocycle 3a. When intermediate 10 was condensed with the dichloro derivative 11a, previously prepared by us, 25-membered pentaacetylenic macrocycle 4 was obtained with an almost quantitative yield. The p-tolylsulfonamide units give a high level of insolubility in the most common organic solvents in the 20-membered macrocycle. This permitted suitable crystals to be obtained to make X-ray diffraction analysis. Figure 1 shows the Ortep-plot diagram for the compound together with its labelling scheme. Compound 3a crystallises free of solvent molecules with C2 symmetry. Bond lengths and angles are within expected values. The four triple bonds at the macrocyclic ring are located on different planes.

After preparing the macrocycles, the next step was to study how to obtain fused tetracycles 13–15 by [2+2+2] cycloaddition reactions. There is one possible way for macrocycles 3 to cyclise to afford a single 5,5,10-fused benzene derivative. However, in the case of the 25-membered ring 4 there are two possible ways of cyclisation; that is, cycloaddition between three consecutive triple bonds to afford compound 14 or between non-consecutive triple bonds to afford compound 15. The Wilkinson’s catalyst [RhCl(PPh₃)₃] was selected as it had formerly given the best results in our previous studies. When 20-membered macrocycles 3a–c, heated under reflux in toluene, were treated with [RhCl(PPh₃)₃], the reaction did not take place. In all three cases, starting material together with decomposition products were obtained. A stoichiometric amount of [CpCo(CO)₂], another typical catalyst for this chemistry, was also tested. The macrocycle was heated under reflux in toluene and the solution was exposed to light. However, this reaction also failed and the starting macrocycle was recovered. In contrast, when 25-membered macrocycle 4 was treated with a catalytic amount of rhodium complex, the cyclotrimerised compound 14, resulting from the reaction of three contiguous alkenes, was obtained as the only product of the process. Confirmation of the structure of 14 was made by HMBC and 2D NOESY data (see the Supporting Information). Experimentally we observe that 5,5,15-fused core is more favourable than 5,10,10-fused system.

As stated in the Introduction section, we performed B3LYP/cc-pVDZ-PP calculations (see section on Computational Methods for a more detailed description of the method used) to unravel the reaction mechanism of the intramolecular [2+2+2] cycloaddition catalysed by the Wilkinson’s complex of the 15-, 20- and 25-membered acetylenic azamacrocycles (MAAs) depicted in Scheme 4 in order to understand the lack of reactivity of the 20-MAA. As we will see, these DFT computations turned out to be very helpful to rationalise the experimental outcome. To reduce the computational effort required, the SO₂-Ar moieties present in the experimental 15-, 20- and 25-MAA and the three Ph groups of the Wilkinson’s catalyst were substituted by H atoms. Before starting our theoretical study, we checked that the thermodynamics of the 1a–2a conversion is not significantly altered when going from the real system with the p-tolylsulfonamide units to the model system. Our results show that the 1a–2a process in the real system is exothermic by −140.3 kcal mol⁻¹ at the B3LYP/cc-pVDZ-PP level, while in our model system is found to be exothermic by −128.4 kcal mol⁻¹. Thus, substitution of the SO₂-Ar moieties by H atoms reduces the exothermicity of the reaction by approximately 10%. Although this quantity is not negligible, we think that it affects similarly the different reactions studied and, therefore, the conclusions reached by comparison with our model systems should be still valid for the real systems.

We proceed now by examining the reaction mechanism for the 15-MAA. The energy profile of the [RhCl(PH₃)₃]-catalysed cycloaddition of this 15-MAA is presented in

Figure 1. Ortep plot (50%) of macrocycle 3a.
weakly interacts externally with a triple bond to form the 18-electron complex 15-A1. After that, the distorted trigonal-bypiramidal complex 15-A2 is generated by replacing two phosphines by two internal \( \eta^2 \) interactions with adjacent acetylenic units of the 15-MAA. This process is endoergonic by 10.9 kcalmol\(^{-1}\), although this endoergonicity is probably overestimated as a result of the substitution of the PPh\(_3\) ligands in the Wilkinson/C\(_{29}\) catalyst by a stronger donor such as PH\(_3\).[29] The substitution of the phosphines by acetylene units in the formation of 15-A2 can follow a dissociative or associative mechanism. Although we have not analysed this point in detail, we consider that because of the small cavity size in the 15-MAA, the associative mechanism is very unlikely. Next, the oxidative coupling of the two alkyne groups in 15-A2 leads to the distorted trigonal-bypiramidal bicyclo-rhodacyclopentadiene 15-A3. The TS corresponding to this transformation is depicted in Figure 3.

The C\(_p\)–C\(_a\) distance of 1.948 Å is close to that found for the corresponding TS of the transformation of a 1,6-diyne into a similar ruthenabicyclo complex (2.040 Å).[15] On the other hand, a significant shortening of the Rh–C\(_a\) bond lengths is observed (from 2.247 to 2.078 Å), but the C\(_a\)–C\(_p\) bonds are only slightly elongated with respect to 15-A2. The conversion of 15-A2 into 15-A3 is the rate-determining step of the overall process with a Gibbs free-energy barrier of 10.9 kcalmol\(^{-1}\) and a Gibbs free-reaction energy of −31.9 kcalmol\(^{-1}\). These values are in line with those obtained for the conversion of a bisacetylene [RuClCp] complex into a ruthenacicyclopentatriene in three different studies of about 13 and −35 kcalmol\(^{-1}\), respectively.[14,15,17] On the other hand, similar barriers but lower exothermicities were reported for RhCp and CoCp-catalysed cyclotrimerisations.[10,17,18] As found previously in similar Co and Rh complexes, the 15-A3 complex exhibits \( \pi \) localisation with C\(_a\)–C\(_p\) and C\(_p\)–C\(_p\) bond lengths of 1.351 and 1.453 Å, respectively, despite the presence of metal lone pairs that could favour the formation of an aromatic ring.[10,18] The Rh–C bond length of 2.04 Å is not far from the average crystallographic bond length of 2.01 Å.[19] The Rh–C bond lengths for the C atoms of the triple bond still present in this complex, suggest that the \( \pi \)-electronic structure interacts with the metal in an \( \eta^2 \) fashion in 15-A3. This complex resem-
We have not investigated the possible formation of η⁴-cyclobutadiene-like complexes as a result of a thermal cyclodimerisation from 15-A2, because this process was found to be kinetically quite unfavourable in similar species. The photochemical process instead is more favourable. The 16-electron 15-A3 complex adds a phosphine molecule to yield the 18-electron species 15-A4 with a Gibbs free-energy stabilisation of 13.1 kcal mol⁻¹. The coordination of this PH₃ promotes an elongation from 2.033 to 2.076 Å of the bond length between the Rh and the C on the opposite side of this PH₃. The process that converts 15-A4 into 15-A5 is an intramolecular [4+2] cycloaddition of the coordinated alkyne of the 15-MAA to the rhodacyclopentadiene. This reaction has a small barrier of only 3.8 kcal mol⁻¹ and is exoergic by 55.4 kcal mol⁻¹ in line with previous studies. The driving force for this reaction comes from the formation of two new C-C σ-bonds and a partially aromatic distorted six-carbon arene ring. The possible formation of rhodacycloheptatriene or 7-rhodanorbornadiene or rhodabi-cyclo [3.2.0] heptatriene intermediates was also investigated. None of these intermediates were located in our potential-energy surface for the 15-membered macrocycle. In the 18-electron 15-A5 complex the benzene formed ring is attached to the Rh through an η⁴-interaction. The coordinated butadiene portion of the six-membered ring displays a significant short–long bond length alternation (BLA of 1.357/1.469 Å), which is an indication of the loss of ring aromaticity as compared to the free benzene ring and of the significant ring–metal interaction (both donation from the π system of the benzene ring to the metal and back-donation). This ring exhibits a hinge angle of 30⁰, similar to the 37⁰ found by BLYP/TZP calculations in the [Rh(η⁴-benzene)Cp] species or the 42⁰ measured in the X-ray structure of [Rh[η⁴-C₆(CH₃)₅]η⁴-C₆(CH₃)₅] complex. The transformation from 15-A5 into distorted tetrahedral 15-A6 involves a ring slippage with a change of the arene-ring hapticity from η⁴ to η². The barrier for this conversion is low (2.4 kcal mol⁻¹) and, somewhat unexpected when going from the 18- to 16-electron species, quite exoergic by 18.6 kcal mol⁻¹. The thermodynamic driving force of this process is likely the partial recovery of aromaticity of the arene ring, which becomes planar and has a small BLA. Completion of the catalytic cycle occurs upon exoergic (by 20.3 kcal mol⁻¹) displacement of the arene by a phosphine molecule to regenerate the [RhCl(PH₃)₃] catalyst.

Next, we examined the two possible reaction mechanisms for the [2+2+2] cyclotrimerisation catalysed by the [RhCl(PH₃)₃] complex in the 20-MAA. The Gibbs free-energy profile of this cyclotrimerisation is drawn in Figure 4. The overall transformation is also very exoergic (–122.0 kcal mol⁻¹), so the reason for the lack of reactivity of the 20-MAA must be kinetic. Although, the reaction...
mechanism is similar to that found for the 15-MMA, there are three remarkable differences. First, 18-electron complex 20-A2 is generated by replacing a single (instead of two) phosphine ligand by two internal $\eta^2$ interactions with adjacent acetylenic units of the 20-MAA. This process is endergonic by 2.8 kcal mol$^{-1}$. Second, there are two possible ways of coordinating two alkyne units in the macrocycle. Thus, species 20-A2’, with two internal $\eta^2$ interactions with non-adjacent acetylenic units of the 20-MAA, can also be formed but it is less stable than 20-A2 by 12.8 kcal mol$^{-1}$. The conversion of 20-A2 and 20-A2’ into bicyclorhodacyclopentadiene 20-A3 and 20-A3’, respectively, takes place by oxidative coupling of the two coordinated alkyne moieties through the TSs depicted in Figure 5 with Gibbs free-energy barriers of 30.7 and 15.3 kcal mol$^{-1}$, respectively. These values are clearly larger than those found for the same rate-determining step in the 15-MAA. The reasons for these higher energy barriers, which are in agreement with the experimental lack of formation of 13, will be discussed later. Although the barrier for the transformation of 20-A2’ into 20-A3’ is lower than that for the equivalent 20-A2 into 20-A3 conversion, the two TSs differ by only 2.6 kcal mol$^{-1}$ and we decided to continue the analysis of the reaction mechanism only from the 20-A3 species. The rearrangement converting 20-A3 into the distorted octahedral 20-A4 complex requires 3.6 kcal mol$^{-1}$ and attaches one uncoordinated triple bond of the 20-MAA to the metal. Since no transition state connecting 20-A3 to 20-A4 was found, the barrier for this step is expected to be very low or absent. At this stage the third important difference arises. The process that transforms 20-A4 into 20-A5 is not a [4+2] cycloaddition, but rather a [2+2] asymmetric addition that results in the formation a non-planar rhodacycloheptatriene complex (see Figure 6) through the TS depicted in Figure 7. This process has a low barrier (4.7 kcal mol$^{-1}$) and is exergonic by 20.3 kcal mol$^{-1}$. All attempts to find the TS corresponding to the [4+2] cycloaddition were unsuccessful. Thus, even small changes in the macrocycle can lead to important differences in the reaction mechanism of the [2+2+2] intramolecular cyclotrimerisation. A seven-membered ruthenacycle was also found in the reaction mechanism of the [2+2+2] cyclotrimerisation of alkynes. Experimentally, the crystal structure of an iridacycloheptatriene with a tub-shaped conformation has been reported. Our 20-A5 rhodacyclohepta-
triene complex has a tub-shaped conformation with a short-long BLA of 1.347/1.475 Å similar to that found in the iridacycloheptatriene of 1.344/1.484 Å. On the other hand, the bond length between the two carbons atoms not linked is 2.648 Å to be compared with the 2.885 Å found in the iridacycloheptatriene. Final ring closure in 20-A5 provides 20-A6 in which the arene ring is coordinated in an η² fashion. The barrier for this reaction is only 1.3 kcal mol⁻¹ and the exoergonicity is as large as 50.1 kcal mol⁻¹. Finally, the catalytic cycle is closed upon exoergonic displacement (by 20.7 kcal mol⁻¹) of the arene by a phosphine molecule to regenerate the [RhCl(PH₃)₃] catalyst.

We shall now examine the reaction profile of the 25-MAA depicted in Figure 8. Due to the size of the 25-MAA, these calculations are extremely computationally demanding. For this reason, we only located the TSs corresponding to the first steps of the reaction mechanisms. As we have seen for the 15- and 20-MAA, the barriers involved in the last steps of the reaction mechanism are low and are expected to have little influence on the overall kinetics of the reaction. As shown in Scheme 4, there are two possible products (14 and 15) of the cyclotrimerisation of the 25-MAA. From a thermodynamic point of view, the reaction is favoured for the two products with exoergonicities of 121.6 and 98.8 kcal mol⁻¹ for 14 and 15, respectively. It is interesting, however, that the product experimentally observed is the most stable by 22.8 kcal mol⁻¹. It is likely that the greater stability of 14 relative to 15 is a result of the triple bonds in ten-membered rings being particularly strained. Indeed the ζ,CCC angle including the two carbon atoms linked by a triple bond is far from linear (around of 160° as compared to 179° in the 15-membered ring of 14). This is in line with the fact that the exoergonicity of the trimerisation substantially decreases when going from the product of the 15-MAA (no ten-membered rings with triple bonds) to that of the 20-MAA (one ten-membered ring with triple bonds) to 15 (two ten-membered rings with triple bonds). Despite this, the thermodynamics alone cannot explain the formation of only 14. As can be seen in Figure 8, 18-electron complexes 25-A2 and 25-A2' are formed by replacing a single phosphine ligand by two internal η² interactions either with adjacent or non-adjacent acetylenic units of the 25-MAA. For the non-adjacent coordinated triple bonds species, the process is endoergonic by 13.5 kcal mol⁻¹. The subsequent oxidative coupling takes place through a very high Gibbs free-energy barrier of 52.9 kcal mol⁻¹. Therefore, this reaction pathway is inaccessible at the temperature of the reaction. Instead, coordination of two adjacent triple bonds requires only 2.3 kcal mol⁻¹ and the barrier for the oxidative coupling to yield the rhodacyclopentadiene 25-A3 is low (of only 6.4 kcal mol⁻¹). The TSs for the transformation of 25-A2 into 25-A3 and 25-A2' into 25-A3' are depicted in Figure 9. We attribute the large barri-
er found in the conversion of $25\text{-}A_2'$ into $25\text{-}A_3'$ in part to the deformation of the 20-MAA required in order to form two strained ten-membered rings. The deformation energy is 28.6 kcalmol$^{-1}$ higher in the TS for the $25\text{-}A_2'$ into $25\text{-}A_3'$ than for the $25\text{-}A_2$ into $25\text{-}A_3$ transformation. Again in $25\text{-}A_3$ there are two possibilities for the coordination of a triple bond. The triple bond can be adjacent to those involved in the oxidative coupling that lead to the rhodacyclopentadiene $25\text{-}A_3$ or non-adjacent. In the former process, the complex $25\text{-}A_4$ is formed with a stabilisation of 18.2 kcalmol$^{-1}$, while in the latter the formation of the product $25\text{-}A_4'$ releases only 3.5 kcalmol$^{-1}$. In addition, the subsequent [2+2] cycloaddition to form the rhodacyclotetraene complexes $25\text{-}A_5$ and $25\text{-}A_5'$ depicted in Figure 10 through the corresponding TSs (see Figure 11) is favoured in the case of the adjacent triple bond (Gibbs free-energy barrier of 5.8 kcalmol$^{-1}$ with respect to 10.1 kcalmol$^{-1}$ for the non-adjacent triple bond). Therefore, the reaction pathway involving addition of the three contiguous triple bonds is favoured, which explains the experimental formation of 14 and not of 15. Final ring closure in $25\text{-}A_5$ provides $25\text{-}A_6$ in which the arene ring is coordinated in an $\eta^1$ fashion. Conversion of $25\text{-}A_6$ into $25\text{-}A_7$ occurs after ring slippage and final displacement of the arene by a phosphine molecule regenerates the [RhCl(PH$_3$)$_3$] catalyst.

As reported in previous studies,[10–18] we have also found that the rate-determining step in the [2+2+2] cyclotrimerisation of ethynes is the initial oxidative coupling to yield the metallacyclopentadiene or metallacyclopentatriene intermediate. The Gibbs free-energy barriers obtained for this process in the 15-, 20- and 25-MAA are calculated to be 21.8, 30.9 and 8.7 kcalmol$^{-1}$ with respect to separated reactants. The values obtained are in line with the experimental observations. To investigate the origin of the barriers, we divided the energy difference between the TS and the separated reactants into deformation energy and interaction energy ($\Delta E_{\text{def}}$ and $\Delta E_{\text{int}}$). The deformation energy ($\Delta E_{\text{def}}$) is the energy needed to modify the geometry of the free reactants to attain the geometry they have in the TS. The interaction energy ($\Delta E_{\text{int}}$) is the energy released when the two free de-

![Figure 9. Optimised structure (B3LYP/cc-pVDZ-PP) for 25-TS(A2,A3) (top) and 25-TS(A2',A3') (bottom) with the most relevant bond lengths [Å] and angles [°].](image)

![Figure 10. Optimised structure (B3LYP/cc-pVDZ-PP) for 25-A5 (top) and 25-A5' (bottom) with the most relevant bond lengths [Å] and angles [°].](image)
formed reactants are brought to the position that they have in the TS. The calculated deformation energies for the 20- and 25-TS(A2,A3) are 95.9 and 104.4 kcal mol\(^{-1}\), respectively. We have not included the 15-TS(A2,A3) in the analysis as the different number of phosphine ligands hamper the comparison. Clearly, the deformation energy in the TS is not the origin of the larger barrier for the 20-TS(A2,A3).

The interaction energies are in turn 62.4 and 95.7 kcal mol\(^{-1}\) for the 20- and 25-TS(A2,A3), respectively. The main interaction in TS(A2.A3) occurs between the LUMO of the catalyst and the HOMO of the macrocycle. By comparing the HOMO and LUMO energies involved in the 20- and 25-TS(A2,A3), it can be seen that the main difference is the energy of the HOMO of the 20-MAA (\(-0.192\) au) as compared to that of the 25-MAA (\(-0.172\) au.). The HOMO–LUMO overlaps are quite similar in the two cases. A picture of the two HOMOs is given in Figure 12, showing a higher delocalisation of the HOMO in the deformed 20-MAA, which apparently is responsible for its greater stabilisation and, as a consequence, its lower reactivity. So, we concluded that the two factors that make the 20-MAA less reactive are 1) a more stable and delocalised HOMO orbital and 2) the formation of a strained ten-membered ring.

**Conclusions**

In summary, we report an efficient stepwise preparation of 20- and 25-membered macrocycles featuring four and five triple bonds, respectively, with different arylsulfonyl moieties in their structure. All new compounds are completely characterised by spectroscopic methods and additional evidence for structure was secured by X-ray diffraction for 3a.

An efficient rhodium(I)-catalysed \([2+2+2]\) cyclotrimerisation of 25-membered pentaacetylenic azamacrocycle 4 chemoselectively afforded the cyclotrimerised compound 14 resulting from the reaction of three adjacent alkynes instead of the cyclotrimerisation between non-adjacent triple bonds. In contrast, the 20-membered tetraacetylenic azamacrocycles 3 did not lead to the expected cyclotrimerised compounds. DFT calculations to unravel the reaction mechanism of the 15-, 20- and 25-MAA revealed that there are two main factors that contribute to the lack of reactivity of the 20-MAA: 1) the 20-MAA has a more stable and delocalised HOMO orbital and 2) the formation of a strained ten-membered ring during the cyclotrimerisation of the 20-MAA. These two factors increase the free-energy barriers of the rate-determining step and difficult the intramolecular cyclotrimerisation of the 20-MAA.

**Experimental Section**

\([2+2+2]\) Cyclotrimerisation of macrocycle 4: A degassed solution of macrocycle 4 (0.05 g, 0.045 mmol) and chlorotris(triphenylphosphane)-rhodium(I) (0.0020 g, 0.0022 mmol) in anhydrous toluene (10 mL) was heated under reflux for 30 h (TLC monitoring). The solvent was then evaporated and the residue was purified by column chromatography on silica gel with dichloromethane/ethyl acetate (20:1) to afford 14 (0.025 g, 50%) as a colourless solid. M.p. 194–196\(^\circ\)C; \(^1\)H NMR (500 MHz, CDCl\(_3\), 25\(^\circ\)C, TMS): \(\delta = \) 2.40 (s, 12H), 2.45 (s, 6H), 3.59 (s, 2H), 3.72 (s, 4H), 4.14 (s, 4H), 4.33 (s, 4H), 4.48 (s, 4H), 7.15 (AA\'BB\' system, \(J = \) 8.0 Hz, 4H), 7.35–7.38 (m, 10H), 7.63 (AA\'BB\' system, \(J = \) 8.2 Hz, 2H),
In addition, we have checked that, despite the electronic and computational differences with the Gaussian 03[29] method used in the present calculations, the reported relative Gibbs free energies (ΔG⧧) are consistent within about 12 kcal mol⁻¹, while in [RhCl(PPh₃)₃] it is exergonic but by about 12 kcal mol⁻¹, while in [RhCl₂(PPh₃)₂] it is exergonic but by only 0.3 kcal mol⁻¹ (A. Dachs, S. Osuna, A. Roglans, M. Solá, unpublished results).

Indeed, at the same level of theory, substitution of two phosphine ligands by acetylene molecules in [RhCl₂(PPh₃)₂] is exergonic by about 12 kcal mol⁻¹, while in [RhCl₂(PPh₃)₂] it is exergonic but by only 0.3 kcal mol⁻¹ (A. Dachs, S. Osuna, A. Roglans, M. Solá, unpublished results).


[48] For the cyclotrimerisation of three acetylene molecules catalysed by [RhCl(H3C)C2H4(PR3)3], the reaction energy is –165.2 kcalmol⁻¹ for both R = H and Ph3, while the energy barrier for the rate-determining step is 11.9 and 12.9 kcalmol⁻¹ for R = H and Ph3, respectively (A. Dachs, S. Osuna, A. Roglans, M. Solà, unpublished results).

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