This work presents a straightforward method for the preparation of an isoindoline bridged \([M(\text{arene})_2]^{+}\) \((M = \text{Re}, 99mTc)\) ansa-arenophane. This intramolecular formation of an ansa-complex is accompanied by the intermolecular formation of a pair of isoindoline bridged macrocyclic dinuclear sandwich complexes, one of which exhibits axial chirality.

**Introduction**

Cyclopentadienyl-based ansa-metalloccenes and arene-based \([n]\)arenophanes \((n = \text{number of bridging atoms})\) are the backbone of olefin polymerization and other catalytic processes. Ansa-derivatives of ferrocene and group 4 elements have been studied particularly extensive due to their impressive chemical and catalytic diversity. There is a plethora of literature precedent for late transition metal ansa-complexes including group 7 elements. Ansa-technocene complexes with Re were reported by Heinkekey et al. and Conway and coworkers. They reported the synthesis of \(\text{C}(\text{CH}_3)_2\) and \(\text{Si}(\text{CH}_3)_2\) bridged technocenes respectively. These interesting compounds suffer though from shortcomings; e.g. the Si(CH₃)₂ bridged compound is thermally unstable at room temperature \((t_{1/2} = 2\ h)\) and decomposes under methane elimination. The C(CH₃)₂ linked complex can only be isolated in very low yields. Ansa-[n]arenophanes are far less known and mainly reported since their discovery by Schneider et al. in the 1990s for group 6 and for group 8 elements. They are unknown at all for rhenium and technetium thus far and represent an unanswered challenge. Given the existence of arenophanes with group 6 ansa-metalloccenes and ansa-[n]arenophane with group 8 elements, stable group 7 ansa-[n]arenophanes would fill a knowledge gap.

An attractive entry into ansa-chemistry is the \([M(\eta^6-\text{arene})_2]^{+}\) \((M = \text{Re}, 99mTc)\) family of compounds. These cationic, arene-based sandwich complexes are water-soluble and air- and moisture stable. Alkyl derivatized \([\text{Re(\eta^6-\text{arene})}_2]^{+}\) complexes can directly be synthesized from Na[ReO₄] under Fischer-Hafner conditions. Lithiation of \([\text{Re(\eta^6-C_6H_6)_2}]^{+}\) and quenching with electrophiles leads to an array of mono- and bis-substituted compounds. Alternatively, naphthalene in \([\text{Re(\eta^6-naphth)_2}]^{+}\) can be exchanged by functionalized arenes with a high degree of functional group tolerance.

Technetium chemistry is developed *in tandem* with the one of rhenium. \(^{99m}\text{Tc}\) complexes are of special interest for diagnostic, medicinal chemistry due to their potential application as radio-pharmaceuticals. A distinct advantage of \([^{99m}\text{Tc}(\eta^6-\text{arene})_2]^{+}\) complexes is their direct synthesis in water and under mild conditions with vast substrate scope.

We present in this report the first example of stable \([M(\eta^6-\text{arene})_2]^{+}\) \((M = \text{Re}, 99mTc)\) type anza-complex, featuring an isoindoline unit as the bridge between the two arene ligands, and an uncommon dinuclear macrocycle formed by intermolecular isoindoline formation starting from \([\text{Re(\eta^6-C_6H_6-NH_2)_2}]^{+}\).

**Results and discussion**

Since the aforementioned silyl- or carbon-bridged anza-metalloccenes of Re are temperature, oxygen and moisture sensitive, we hypothesized that ansa-[n]arenophanes would be more persistent. We targeted to exploit the literature reported condensation reaction between 2 eq. of aniline or amino pyridines and ortho-phenyldialdehyde (OPA) which is known to form heterocyclic isoindolines units in a straight-forward manner (Scheme 1, left). We rationalized that a 1,1-diamino sandwich complex might replace the individual anilines in the organic template reaction to form the corresponding anza-complex. With \([\text{M(aniline)}_2]^{+}\) \((M = \text{Re}; \text{[4]}; M = 99m\text{Tc}; \text{[7]})\) as synthetic precurso an isoindoline-bridged anza-[3]arenoophane should be accessible by treatment with OPA (Scheme 1).
Complex [4][PF₆] was prepared via two different synthetic routes (Scheme 2). Starting from [1][PF₆], [4][PF₆] can be obtained in 21% yield over two steps according to a literature procedure by arene exchange of naphthalene with aniline.¹⁵ The literature yields were improved from 39 to 88% by employing a large excess of aniline as compared to the literature report. An alternative route is an adapted Gabriel amine synthesis inspired by the preparation of 1,1′-diaminoferrocene as reported by Abdulmalic and Rüffer.²⁵ Bis-chlorinated [2][PF₆]¹⁷ was treated with potassium phthalimide (KPhth) in the presence of copper to provide [3][PF₆] in excellent yields (97%). The X-ray structure of [3][PF₆] was elucidated (ESI, Fig. S24†).

Hydrazine mediated phthalimide elimination delivered [4][PF₆] in a satisfactory yield of 65% (Scheme 2). The formation of [4][PF₆] was monitored over the course of the reaction by UPLC-ESI-MS. Based on results thus obtained, we propose a step-by-step mechanism shown in Scheme 3. This proposal is based on a similar pathway as described by Chebolu et al. for the synthesis of 1,2-disubstituted benzimidazoles.²² Two possible routes lead to the ansa-species [5]+, namely formation of a symmetrical di-imine followed by cyclization or a sequence of mono-imine formation followed by a sigmatropic rearrangement. According to our data, the second pathway is more likely to be at play. Imine formation between [4]+ and OPA (observed as [M + H₂O]+; m/z = 507.05) followed by nucleophilic attack of the second aniline nitrogen generates the A ring. Subsequent imine formation between the second-ary amine and the remaining aldehyde moiety results in the fused A–B–C ring system, supported by the observation of the key intermediate I. Elimination of water and rapid [1,3] sigmatropic rearrangement finally delivers [5]+. The dinuclear species [6a]²⁺ and [6b]²⁺ are the result of intermolecular imine formations instead of an intramolecular pathway. A detailed overview of all observed intermediates and pathways is provided in the ESI (Scheme S1†).

Scheme 1 Concept for the synthesis of novel isoindoline bridged ansa-complexes. OPA = ortho-phenyldialdehyde; M = Re, ⁹⁹mTc.

Scheme 2 Overall synthetic route to the ansa-complex [5]+ and the dinuclear species [6a]²⁺ and [6b]²⁺. Reaction conditions: (i) Zn, AlCl₃, naphthalene, 100 °C, 18 h; (ii) aniline, N-methyl pyrrolidone, 1,4-dioxane, 120 °C, 4 h; (iii) Cu turnings, potassium phthalimide, THF, 70 °C, 22 h; (iv) aq. hydrazine, CH₂CN, 25 °C, 24 h; (v) OPA, 0.1 vol% TFA in H₂O, CH₂CN, 25 °C, 2 h, then 80 °C, 3.6 h; (vi) conc. HCl, 70 °C, 24 h.

Scheme 3 Mechanistic reaction scheme of the formation of [5]+ from [4]+. Indicated m/z values and retention times (Rt) correspond to observed intermediates.
Complex [5][PF₆] crystallized in the monoclinic space group P2₁/c with one CH₃CN solvent molecule in the asymmetric unit (Fig. 1). The centroid–Re–centroid angle (169.66(7)°) is significantly smaller than the optimal 180° but still larger than the one reported by Heinekey et al. for their ansa-rhenocene (145.2(16)°).⁷ The angle between the η⁶-C₆H₆ planes is 15.23(9)°, indicating an exposure of the rhenium center. The arene ligands are in an almost perfectly eclipsed conformation. The bridging isoindoline unit is arranged perpendicular to the π-surfaces of the sandwich scaffold.

We were interested in reactivities of [5]⁺, particularly in the question if oxidative addition to the exposed rhenium center would occur, given the strain imposed on the arene ligands by the bridging isoindoline. Such reactivities would be desirable if the ansa-complexes were supposed to enter some catalytic processes. For their application in radiopharmacy, however, any metal-based reactivity has to be omitted. Treatment of [5][TFA] with CH₃I however did not lead to an oxidative addition and reaction with HBF₄ did not lead to rhenium protonation. Clean hydrolysis of the imine was observed with aqueous acids (77% yield, see ESI†) to yield compound [8][TFA]. This reaction is however, ligand-rather than metal-based. The strain of the arene ligands is thus too small to expose the rhenium center and facilitating e.g. oxidative addition reactions.

Analytically pure samples of [6a][TFA]₂ were obtained by fractional crystallization. Complex [6b][TFA]₂ could not be fully separated from [6a][TFA]₂. A structure elucidation revealed axial chirality in [6a]²⁺, thus both (P)- and (M)-enantiomers are present in the crystals as evident from a combination of NMR and crystallographic data. Moreover, classical coalescence behavior of the ¹H NMR signals was observed between 270 K and 330 K (ESI, Fig. S28†). This coalescence process describes the rapid interconversion between (P)- and (M)-enantiomers of [6a]²⁺. The process has a free activation energy barrier of ΔG‡ = 64.0 ± 0.4 kJ mol⁻¹, which corresponds to a first order rate constant k = 65.76 s⁻¹ at 298 K (ESI chapter 4†). The best estimate for the coalescence temperature is 323 K. Thus, the solution structure of [6a]²⁺ at room temperature is described as a rapid equilibrium between its enantiomers. In combination with ROESY correlation data (ESI, Fig. S31†), we assessed that only [6a]²⁺ but not [6b]²⁺ is involved in the coalescence behavior. The crystallographic data of [6a][TFA]₂ confirmed the axial chirality and the presence of a racemate (Fig. 2). It crystallized in the centrosymmetric space group C2/c and the two rhenium centers lie on a two-fold axis. The asymmetric unit features both helical enantiomers. We assigned the (P)- and (M)-enantiomers based on rotational direction of the head-to-head oriented helices.²⁶ Bond lengths and angles of the isoindoline units are in the same range as those of [5][PF₆]·CH₃CN. The crystal structure of [6b][TFA]₂ shows a flytrap-like head-to-tail geometry of the two isoindoline-units bridging the two [Re(η⁶-C₆H₆)₂]⁺ scaffolds (Fig. 1).

It was tempting to investigate, if ⁹⁹ᵐTc would yield the same ansa-[n]arenophane complex directly in water and despite the presence of water, which affects imine formation. To verify this hypothesis, the same route as with rhenium was employed. Aqueous [⁹⁹ᵐTcO₄]⁻ was treated with aniline and zinc (impossible for Re) in saline which produced exclusively [⁹⁹ᵐTc(η⁶-aniline)₂]⁺ ([7], Scheme 4). To remove excess aniline, the crude reaction mixture was purified via HPLC and peaks containing [7]⁺ collected. The resulting solution was treated with OPA which gave the ⁹⁹ᵐTc homologue ansa-complex [⁹⁹ᵐTc][5]⁺ in a clean reaction. Complex [⁹⁹ᵐTc][5]⁺ was isolated in excellent radiochemical purity of >98% after HPLC purification. Its chemical identity was confirmed by chromatographic cojunction with the rhenium homologue [5][TFA]₂ (Fig. 3). Complex [⁹⁹ᵐTc][5]⁺ represents the first example of a technetium ansa-complex. Although a two-step reaction, it is amazing that this kind of structurally diverse complexes can be prepared in water and in good yields. Analysis of the reaction solution did not indicate the formation

![Fig. 1 ORTEP representation of the cations [5]⁺ of the crystal structure [5][PF₆]·CH₃CN (left), and [6b]²⁺ of the crystal structure [6b][TFA]₂·2H₂O (right). Thermal ellipsoids represent 50% probability. Hydrogens and counterions were omitted for clarity.†](image)

![Fig. 2 Side-by-side ORTEP representations of the cations (P)-[6a]²⁺ (left) and (M)-[6a]²⁺ of the crystal structure [6a][TFA]₂·H₂O. Counterions, hydrogen atoms and labels were omitted for clarity.† The black bar represents the mirror plane relating the two enantiomers.](image)

![Scheme 4 Synthesis of the ⁹⁹ᵐTc ansa-complex [⁹⁹ᵐTc][5]⁺. Reaction conditions: (i) zinc, aniline, 100 °C, 30 min, microwave; (ii) OPA, 80 °C, 40 min.](image)
of dinuclear species, analogous to \(6a^{2+}\). The high dilution of \(\text{\textsuperscript{99m}Tc}\) (around \(10^{-15}\) M) would require an extremely fast process to form dinuclear species, which appeared not to be the case with the reaction between \(7^{+}\) and OPA.\(^{27}\)

Especially the well-established synergy between rhenium and technetium renders the presented compounds interesting candidates for the development of chemical and radioactive probes.

**Conclusions**

We report the first examples of \(\textit{ansa-}[M(\text{\textsuperscript{16}arene})_{2}]^{+} \) (\(M = \text{Re, \text{\textsuperscript{99m}Tc}}\)) complexes, featuring an isoindoline as the bridging unit. The high degree of stability coupled with the biorelevant properties of the isoindoline unit\(^{24}\) renders \([5][\text{TFA}]\) an attractive candidate as building block for bioorganometallic chemistry. The 1,2-dialdehyde unit can thereby act as an anchoring group to an active pharmaceutical or be even part of it. The fact that the analogous \(\text{\textsuperscript{99m}Tc}\) complex is readily available further underlines the potential of the system in a radiopharmaceutical context. We assess that further exposure of the rhenium is required to explore eventual catalytic applications of \([5]^{+}\) and therefore, a more straining bridging unit is required.

Moreover, two dinuclear macrocyclic complexes, featuring comparably rare axial chirality for dinuclear species, were isolated and fully characterized. Perspective studies of the dinuclear species point to the preparation of heteronuclear \(\text{Re}^{–}\text{\textsuperscript{99m}Tc}\) dimers to probe them as potential theranostic pairs.

**Author contributions**

JC wrote and edited the manuscript, conceptualized the project and performed experiments, DKJ performed experiments and edited the initial manuscript, QN performed \(\text{\textsuperscript{99m}Tc}\) chemistry, OB performed all crystallographic measurements, TF recorded NMR spectra of \(6a[\text{TFA}]_{2}\) at various tempera-

tures, HB advised \(\text{\textsuperscript{99m}Tc}\) experiments, RA revised the manuscript and initiated the project.

**Conflicts of interest**

There are no conflicts to declare.

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**Notes and references**

\(^{†}\)The crystallographic data is available in the electronic ESI.

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