

# **CHEMISTRY** A European Journal



# **Accepted Article** Title: A synthesis of doubly-annulated m-terphenyl based molecular tweezers and their charge-transfer complexes with DDQ as a quest Authors: Khushabu Thakur, Denan Wang, Sergey V Lindeman, and Rajendra Rathore This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article. To be cited as: Chem. Eur. J. 10.1002/chem.201803137 Link to VoR: http://dx.doi.org/10.1002/chem.201803137 **Supported by**

ACES



## COMMUNICATION

# A synthesis of doubly-annulated *m*-terphenyl based molecular tweezers and their charge-transfer complexes with DDQ as a guest

Khushabu Thakur,<sup>[a]</sup> Denan Wang,<sup>\*[a]</sup> Sergey V. Lindeman<sup>[a]</sup> and Rajendra Rathore<sup>‡[a]</sup>

In memory of Rajendra Rathore

**Abstract:** A synthesis of doubly-annulated *m*-terphenyl-based tweezer plateform has been developed, which affords ready incorporation of various pincer units from monobenzenoid to polybenzenoid electron donors. The complexation study with DDQ as guest has been carried out, and the crystal structure of **T-Py∩DDQ** reveals the sandwich-type binding mode in the solid state.

Molecular tweezers are a class of structures with open cavities that can bind guest molecules, and thus have attracted considerable interest in the recognition/sensing of a variety of guests, including explosives such as trinitrotoluene.<sup>[1-6]</sup> Due to the potential applications of tweezers for the detection of various synthetic, as well as biological, guest molecules, tremendous synthetic effort has been devoted toward the preparation of diverse tweezer platforms.<sup>[5-14]</sup> Zimmerman's tweezer (ZT, Figure 1 (left)) is the most recognized tweezer scaffold. The structural features of **ZT** include a doubly annulated *m*-terphenyl framework, in which the pincers are connected at the 2- and 12-terphenyl positions, and thus are held at a distance of ~7 Å. The ~7 Å separation between cofacially-arrayed pincers allows efficient m- $\pi$  interactions with a sandwiched guest molecule. Despite the effectiveness of the **ZT** platform,<sup>[5-6, 15-16]</sup> the syntheses are rather tedious, and the platform holding the pincers is highly electroactive. Moreover, as the pincers are attached in the beginning steps of the synthesis, ready attachment of different pincers is laborious. Furthermore, the synthetic scheme for ZTs has a number of steps that are rather time consuming and give low product vield.[5-6, 15-16]

In this work, we seek to improve upon the **ZT** platform by exploring the preparation of a common doubly-annulated *m*terphenyl platform, with appropriate functional groups, that would afford a ready attachment of pincers in one synthetic step. A recent report by Rathore and coworkers has described a versatile synthesis for the efficient preparation of doubly annulated *p*terphenyls.<sup>[17]</sup> It can be readily seen (**Figure 1**) that if a similar double annulation is performed onto an *m*-terphenyl derivative, the resulting doubly-annulated derivative with appropriate substitutions at the 2- and 12-positions could serve as a versatile platform for the ready construction of a variety of tweezers with different pincers.

 [a] Dr. K. Thakur, Dr. D. Wang, Dr. S. V. Lindeman, Prof. R. Rathore Department of Chemistry, Marquette University Milwaukee, WI 53201-1881 (USA)
 E-mail: denan.wang@marquette.edu

[‡] Deceased February 16, 2018

Supporting information for this article is given via a link at the end of the document.

Such a doubly-annulated *m*-terphenyl (**TP**) platform holds a number of advantages when compared to the platform utilized for the preparation of Zimmerman's tweezers (**Figure 1**). First, this platform can be readily transformed to a variety of tweezers with different pincers in one synthetic step, as we will demonstrate. Second, the conformation flexibility of the annulating bridges in TP-based tweezers is expected to promote the binding with guests of varied size and shape. Third, unlike the **ZT** platform, which requires the installation of a solubilizing group (see **Figure 1**), the annulating bridges in TP-based tweezers inherently serve as solubilizing groups towards organic solvents. Finally, the platform itself is oxidized at a relatively high potential (~1.7 V vs SCE), and the electronic coupling between the pincers and the platform is minimized due to meta connections.<sup>[18]</sup>



**Figure 1.** Comparison of Zimmerman's tweezer platform (left)<sup>[5-6, 15-16]</sup> with our proposed doubly-annulated *m*-terphenyl (**TP**) platform (right). Due to the conformation flexibility of the annulated bridges center-to-center distance between pincers in **TP** platform may vary.

Accordingly, here we describe the successful preparation of a doubly-annulated *m*-terphenyl (**TP**) platform, containing trifluoromethane-sulfonate (or triflate, -OTf) groups at the 2- and 12-positions for ready installation of various pincers via a facile and high-yielding Suzuki coupling reaction.<sup>[18-20]</sup> We demonstrate the successful preparation of a number of tweezers based on a **TP**-platform with different pincers varying from monobenzenoid to polybenzenoid electron donors (such as tetramethylbenzene, naphthalene, pyrene). The complexation study with DDQ as guest has been carried out, and complexation product, **T-Py∩DDQ**, has been characterized by X-ray crystallography.

As shown in **Scheme 1**, synthesis of the doubly-annulated *m*terphenyl platform (**TP** or **1g**) begins with commercially available 1,5-dibromo-2,4-diiodobenzene **1a**, which can also be synthesized in excellent yields at a 50-100 gram scale by iodination of *m*-dibromobenzene in concentrated sulfuric acid. Accordingly, an efficient palladium-catalyzed reaction<sup>[21]</sup> of an inexpensive commercially available 2-methyl-3-butyn-2-ol with **1a** leads to a quantitative formation of **1b**, where the more reactive iodo substituents are selectively substituted by acetylenic alcohols. A standard Suzuki coupling of **1b** with 3methoxybenzeneboronic acid in the presence of Pd(PPh<sub>3</sub>)<sub>4</sub> as a

WILEY-VCH

### WILEY-VCH

## COMMUNICATION

catalyst afforded the desired terphenyl **1c** in good overall yield. The resulting diacetylenic-*m*-terphenyl **1c** was subjected to catalytic hydrogenation in ethyl acetate in the presence of 10% palladium on activated carbon as the catalyst. The resulting reduced terphenyl **1d** was sufficiently pure, and thus, was treated directly with methanesulfonic acid in dichloromethane at room temperature to afford the doubly-bridged *m*-terphenyl **1e** via two facile intramolecular Friedel-Crafts cyclizations<sup>[17]</sup> (**Scheme 1**). Conversion of the 2,12- methoxy substituents of **1e** to the corresponding trifluoromethanesulfonates (i.e. **1e** to **1g**) was accomplished in excellent yield by a demethylation reaction<sup>[22]</sup> using BBr<sub>3</sub> followed by a reaction<sup>[23]</sup> with triflic anhydride in a mixture of pyridine and dichloromethane.

The proposed doubly annulated framework may exist in two nearly isoenergetic conformations with varied orientation of the annulated bridge with respect to the plane of the central aromatic moiety (*syn* or *anti*). Indeed, the structural flexibility of the new **TP** platform led to a broad feature between 0.8-1.5 ppm on the <sup>1</sup>H-NMR spectra at 20 °C, which corresponded to the methyl groups in the annulated region. In the case of representative doublybridged *m*-terphenyl **1e**, variable- temperature <sup>1</sup>H NMR spectroscopy in CDCl<sub>3</sub> over a temperature range of +20 to -60 °C (**Figure S2**) showed that the interchange between the two conformers can be frozen at ~ -60 °C, and the estimated activation energy for the interchange between *syn* and *anti*conformers was found to be 11.5 kcal•mol<sup>-1</sup>.



**Scheme 1.** Synthesis of the doubly-annulated *m*-terphenyl platform for the preparation of various tweezers.



**Figure 2.** An ORTEP diagram of the molecular structure of A, the doubly annulated m-terphenyl **1e**; B. **T-Dur** with disordered chloroform solvent. (Thermal ellipsoids drawn at 50% probability, solvent molecules and hydrogen atoms removed for clarity).

DFT calculations at M06-2X/6-31G(d) with an implicit treatment of  $CH_2CI_2$  as a solvent predict that the energetic difference between *syn* and *anti* is indeed small, i.e., only

0.06 kcal/mol. Yet, X-ray crystallographic analysis of the doubly annulated *m*-terphenyl **1e** showed that in the solid state it exists only in the *anti*-conformation, due to stabilization by packing forces (**Figure 2A**).

Synthesis of various tweezers (see structures below) containing duryl (**T-Dur**), naphthyl (**T-Nap**) and pyrenyl (**T-Py**) groups as pincers was readily accomplished by a standard Suzuki coupling of the doubly-annulated *m*-terphenyl-ditriflate **1g** with various boronic acids (i.e. durylboronic acid or 2-naphthylboronic acid or 2-pyrenylboronic acid) in the presence of  $Pd(PPh_3)_4$  as a catalyst in toluene as a solvent (**Scheme 2**). All three molecular tweezers are fully characterized with <sup>1</sup>H/<sup>13</sup>C NMR and MALDI-TOF mass spectra (**Figure S1**).



Scheme 2. Synthesis of various tweezers: T-Dur, T-Nap and T-Py.

In the context of application of a TP platform in molecular recognition, a syn conformation is preferred, as its relative arrangement of the pincers would favor the trapping of the guest molecule. Indeed, according to the DFT calculations of T-Dur, T-Nap and T-Py, the syn configuration is the preferred conformation, lower by 0.4-1.3 kcal/mol lower than the anti conformation. This difference due to the geometrical architecture of the TPframework, which leads to more favorable CH- $\pi$  interactions in the syn conformation (Figure S11 in the Supporting Information). As the result, the relative orientation of the pincers is non-parallel, with interplanar angles in a wide 6-74° range. In the solid state, T-Dur exists in a syn-conformation with a disordered chloroform solvent molecule positioned in the cleft between two terminal durene moieties that have an interplanar angle of 74° (Figure 2B). However, in the presence of the quest molecule, the relative energetics of the syn/anti conformations of the tweezer will change depending on the nature of host/guest interactions.

To probe whether the TP-based tweezers can effectively host a guest molecule, we next studied their binding affinity with **DDQ**—a powerful electron acceptor ( $E_{red} = 0.56$  V vs SCE).<sup>[24]</sup> Mixing of **DDQ** with **T-Dur**, **T-Nap** and **T-Py** in CH<sub>2</sub>Cl<sub>2</sub> resulted in the appearance of a characteristic charge-transfer band in their UV-vis absorption spectra (**Figures S4-S6** in the Supporting Information), suggesting formation of electron donor-acceptor (EDA) complexes. Interestingly, analysis of the Benesi-Hildebrand plots showed that as the size of the aromatic pincer increases, the binding constant (*K*) also increases, from 26 M<sup>-1</sup> in **T-Dur**, to 196 M<sup>-1</sup> in **T-Nap**, to 415 M<sup>-1</sup> in **T-Py**.

## COMMUNICATION

It is well known that the formation constant of EDA complexes is highly dependent on the free energy of the electron transfer (i.e.,  $\Delta G_{\text{ET}} = E_{\text{ox}}[\text{donor}] - E_{\text{red}}[\text{acceptor}])$ ;<sup>[25]</sup> and the oxidation potentials of polycyclic aromatic hydrocarbons generally decrease with an increasing number of aromatic rings.<sup>[26]</sup> Indeed, a plot of *K* against  $\Delta G_{\text{ET}}$  shows a strong dependence that is well described by the linear plot in the range of  $\Delta G_{\text{ET}} = 1.2$  to 0.7 V (**Figure S7** in the Supporting Information).<sup>[25]</sup>



**Figure 3.** Showing the side and top views (A/B) and a space-filling representation (C) of the X-ray structures of 1:1 EDA complex of **T-Py** $\cap$ **DDQ** together with a solvent molecule (i.e. CH<sub>2</sub>Cl<sub>2</sub>). (Thermal ellipsoids drawn at 50% probability).

Fortunately, we have obtained crystals of the charge-transfer complex of T-Py and DDQ (i.e., T-Py∩DDQ) suitable for X-ray crystallography. Dark-colored crystals of the 1:1 complex were isolated from an equimolar solution of T-Py and DDQ in a mixture of dichloromethane and acetonitrile, by a very slow evaporation of the solution at ambient temperatures. X-ray crystallographic analysis of the T-PyODDQ charge-transfer complex revealed that DDQ is bound in a sandwich configuration between a pair of pyrenyl donors. Figure 3. In addition, the entire complex contains a local symmetry plane, and the *m*-terphenyl platform of the **T-Py** tweezer adopts an achiral syn conformation (Figure 3). The pyrene pincers are oriented almost parallel to each other with a dihedral angle of 13.2°, and DDQ is located between the two pyrenyl with equivalent interplanar distances of 3.2 Å. The remaining empty space near the central benzene ring of the mterphenyl platform in the T-Py∩DDQ complex is filled by a solvent (i.e.  $CH_2CI_2$ ) molecule, which makes  $C-H...\pi$  and C-H...Ocontacts, providing the weak intermolecular forces for the solid state assembly (see Figure 3).

Comparing the geometry of **T-Py** in the crystal structure of **T-Py∩DDQ** EDA complex with that of the calculated *syn* **T-Py**, we note that weak CH- $\pi$  interactions between tilted **Py** moieties in isolated **T-Py** are diminished in favor of the formation of sandwich-like arrangement stabilized by the charge-transfer interactions in the EDA complex (**Figure 3**). Besides pure electronic effects discussed above, entropic effects may also contribute to the observed difference in the binding between **T-Dur**, **T-Nap** and **T-Py**. For example, the crystal structure of **T-Py∩DDQ** reveals that the **DDQ** binds near the end rather than at the center of the **Py** 

moiety (Figure 3). A smaller contact area of the Dur- and Napbased pincers may prevent efficient stacking with DDQ leading to diminished values of the binding constant.

In conclusion, we have successfully developed an efficient method to synthesize a doubly-annulated m-terphenyl tweezer platform, containing trifluoromethane-sulfonate groups at the 2and 12-positions for ready installation of various pincers. In comparison with the Zimmerman tweezers, this new platform has a higher oxidation potential and more structural flexibility to bind with guest molecules, and the synthetic strategy affords incorporation of pincers late in the synthesis. Thus, the successful preparation of a number of tweezers based on a TPplatform with different pincers varying from monobenzenoid to polybenzenoid electron donors as pincers has been described, and their binding affinity has been examined with DDQ as the guest molecule. Among investigated tweezers, the pyrene-based tweezer (T-Py) shows the strongest association with DDQ, with a binding constant of 415 M<sup>-1</sup> in a dichloromethane solution, and the crystal structure reveals the sandwich-type complexation in the solid state. Thus, the binding constants are of the same order of magnitude as original Zimmerman tweezers,<sup>[6]</sup> and therefore this novel framework holds potential in recognition/sensing of a variety of guests. Future studies may involve introduction of the pincers with large graphitic cores such as HBC. More applications of molecular tweezers exploiting the reported novel framework are under investigation.

#### Acknowledgements

We thank the NSF (CHE-1508677) for financial support, Professor Scott A. Reid (Marquette University) for helpful discussions and Dr. Maxim V. Ivanov (Marquette University) for calculations and helpful discussions. The calculations were performed on the high-performance computing cluster Père at Marquette University and XSEDE.

#### **Conflict of interest**

The authors declare no conflict of interest.

**Keywords:** molecular tweezers • self-assembly • supramolecular chemistry • charge transfer • DDQ

- A. Petitjean, R. G. Khoury, N. Kyritsakas, J.-M. Lehn, J Am Chem Soc 2004, 126, 6637-6647.
- [2] M. Harmata, Accounts Chem Res 2004, 37, 862-873.
  [3] F.-G. Klärner, B. Kahlert, Accounts Chem Res 2003, 36,
- [3] F.-G. Klärner, B. Kahlert, Accounts Chem Res 2003, 36, 919-932.
- [4] C. W. Chen, H. W. Whitlock, J Am Chem Soc 1978, 100, 4921-4922.
- [5] S. C. Zimmerman, in Supramolecular Chemistry I Directed Synthesis and Molecular Recognition (Eds.: J. Canceill, J. C. Chambron, A. Collet, C. Dietrich-Buchecker, H. D. Durst, J. P. Dutasta, F. H. Kohnke, B. Lozach, J. P. Mathias, S. Misumi, J. P. Sauvage, J. F. Stoddart, D. A. Tomalia, S. C. Zimmerman), Springer Berlin Heidelberg, Berlin, Heidelberg, **1993**, pp. 71-102.

## WILEY-VCH

# COMMUNICATION

- [6] S. C. Zimmerman, C. M. VanZyl, G. S. Hamilton, J Am Chem Soc 1989, 111, 1373-1381.
- [7] Z. Gao, Y. Han, S. Chen, Z. Li, H. Tong, F. Wang, ACS Macro Lett. 2017, 6, 541-545.
- [8] H. Yoon, J. M. Lim, H.-C. Gee, C.-H. Lee, Y.-H. Jeong, D. Kim, W.-D. Jang, J. Am. Chem. Soc. 2014, 136, 1672-1679.
- [9] B. Legouin, P. Uriac, S. Tomasi, L. Toupet, A. Bondon, P. van de Weghe, *Org. Lett.* **2009**, *11*, 745-748.
- [10] T. Schaller, U. P. Buechele, F.-G. Klaerner, D. Blaeser, R. Boese, S. P. Brown, H. W. Spiess, F. Koziol, J. Kussmann, C. Ochsenfeld, J. Am. Chem. Soc. 2007, 129, 1293-1303.
- [11] V. Balzani, H. Bandmann, P. Ceroni, C. Giansante, U. Hahn, F.-G. Klaerner, U. Mueller, W. M. Mueller, C. Verhaelen, V. Vicinelli, F. Voegtle, *J. Am. Chem. Soc.* 2006, *128*, 637-648.
- [12] M. Fokkens, T. Schrader, F.-G. Klaerner, J. Am. Chem. Soc. 2005, 127, 14415-14421.
- [13] M. Harmata, C. L. Barnes, J. Am. Chem. Soc. 1990, 112, 5655-5657.
- [14] S. C. Zimmerman, M. Mrksich, M. Baloga, J. Am. Chem. Soc. 1989, 111, 8528-8530.
- [15] S. C. Zimmerman, Z. Zeng, W. Wu, D. E. Reichert, *J Am Chem Soc* 1991, *113*, 183-196.
- [16] S. C. Zimmerman, C. M. VanZyl, J Am Chem Soc 1987, 109, 7894-7896.
- [17] M. Modjewski, S. V. Lindeman, R. Rathore, *Org Lett* **2009**, *11*, 4656-4659.
- [18] C. Patoux, C. Coudret, J.-P. Launay, C. Joachim, A. Gourdon, *Inorg Chem* **1997**, *36*, 5037-5049.
- [19] A. Suzuki, Chem Commun 2005, 4759-4763.
- [20] J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem Rev* 2002, 102, 1359-1470.
- [21] A. Elangovan, Y.-H. Wang, T.-I. Ho, Org Lett 2003, 5, 1841-1844.
- [22] J. E. Van Epp, D. R. Boyd, G. A. Berchtold, *The Journal of Organic Chemistry* **1981**, *46*, 1817-1820.
- [23] L. J. Goossen, N. Rodríguez, C. Linder, J Am Chem Soc 2008, 130, 15248-15249.
- [24] R. D. Srivastava, G. Prasad, Bull. Chem. Soc. Jap. 1970, 43, 1611-1614.
- [25] S. M. Hubig, R. Rathore, J. K. Kochi, J. Am. Chem. Soc. 1999, 121, 617-626.
- [26] M. V. Ivanov, D. N. Wang, R. Rathore, J Am Chem Soc 2018, 140, 4765-4769.



## WILEY-VCH

# COMMUNICATION

## Entry for the Table of Contents

## COMMUNICATION



A synthesis of m-terphenyl-based tweezer plateform has been developed, which affords ready incorporation of various pincer units as electron donors.

Khushabu Thakur,<sup>[a]</sup> Denan Wang,<sup>\*[a]</sup> Sergey V. Lindeman<sup>[a]</sup> and Rajendra Rathore<sup>‡[a]</sup>

#### Page 1. – Page 4.

A synthesis of doubly-annulated *m*terphenyl based molecular tweezers and their charge-transfer complexes with DDQ as a guest

