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*iso*-TEtraQuinoline (*i*-TEQ): an inherently chiral N4 macrocyclic quinoline tetramer

Cyclic concatenation of four quinoline units affords a fully  $sp^2$ -hybridized, non-planar macrocycle featuring four inwardly oriented, coordinatively active pyridyl nitrogen atoms. The previously reported tetramer TEtraQuinoline (**TEQ**) exhibits head-to-tail connectivity of its quinoline units, affording an achiral architecture possessing  $S_4$  symmetry. Herein, we report the design and synthesis of *iso*-TEtraQuinoline (*i*-TEQ), an inherently chiral analogue featuring head-to-head connectivity at the 2,2'- and 8,8'-positions, which gives rise to a  $D_2$ -symmetric architecture. Detailed comparative investigations of the connectivity isomers *i*-TEQ and TEQ revealed an array of distinct characteristics.

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Registered charity number: 207890

# Chemical Science

## EDGE ARTICLE

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Cite this: Chem. Sci., 2025, 16, 10714

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 22nd April 2025 Accepted 15th May 2025 DOI: 10.1039/d5sc02937f rsc.li/chemical-science

### Introduction

The chemical space occupied by axially chiral entities has remarkably expanded over the past several decades owing to their diverse applications as chiral ligands,<sup>1</sup> chiral sensing materials,<sup>2</sup> and biologically active natural or artificial products.<sup>3</sup> Due to their high thermodynamic stability and structural robustness, axially chiral molecules composed of sp<sup>2</sup>-hybridized aromatic units have attracted considerable attention for the construction of well-defined chiral environments in catalysis and sensing applications. The 1,1'-binaphthyl unit represents a privileged scaffold for this purpose and is extensively utilized in catalyst design by incorporating chalcogen and pnictogen atoms at 2,2'-positions to promote enantioselective metal- and organocatalysis, and molecular recognition<sup>4</sup> (Fig. 1a). In contrast, the 8,8'-biquinoline framework, which is structurally analogous to the 1,1'-binaphthyl but features an N(sp<sup>2</sup>) atom in place of one  $C(sp^2)$ -H unit, is utilized only sparingly due to its relatively low racemisation barrier<sup>5</sup> (Fig. 1b). Incorporating the



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Chiral macrocycles are attracting growing interest due to their broad applicability as ligands in asymmetric catalysis and as host molecules for chiral recognition. Robustness and high thermodynamic stability can be effectively achieved by strategically linking aromatic panels to construct an axially chiral macrocyclic framework. Cyclic concatenation of four quinoline units affords a fully  $sp^2$ -hybridized, non-planar macrocycle featuring four inwardly oriented, coordinatively active pyridyl nitrogen atoms. The previously reported tetramer TEtraQuinoline (TEQ) exhibits head-to-tail connectivity of its quinoline units, affording an achiral architecture possessing  $S_4$  symmetry. Herein, we report the design and synthesis of *iso*-TEtraQuinoline (*i*-TEQ), an inherently chiral analogue featuring head-to-head connectivity at the 2,2'- and 8,8'-positions, which gives rise to a  $D_2$ -symmetric architecture. Detailed comparative investigations of the connectivity isomers *i*-TEQ and TEQ revealed an array of distinct characteristics, including the overall architecture, intrinsic macrocyclic strain, spatial orientation of nitrogen lone pairs, thermodynamic stability, racemisation behaviour, metal complex stability, and circularly polarised luminescence.



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Open Access Article. Published on 20 2025. Downloaded on 24.06.2025 21:11:17.

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<sup>†</sup> Electronic supplementary information (ESI) available. CCDC 2392427, 2392429, 2392433, 2392428 and 2392430. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d5sc02937f

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quinoline unit is particularly advantageous, as it not only imparts axially chirality but also introduces a functional motif capable of coordinating metal cations, thereby offering dual functionality in a single framework. Inspired by porphyrina representative functional framework ubiquitous in nature that coordinates metal cations through four sp<sup>2</sup>-hybridized nitrogen atoms-we previously designed a tetrameric quinoline construct, TEtraQuinoline (TEQ), as a non-planar analogue of porphyrin.6 While its cyclic concatenation effectively suppresses the flipping of the linked quinoline units, the head-to-tail assembly through the 2- and 8-positions imparts an overall achiral, S<sub>4</sub>-symmetric rigid architecture to the TEQ framework. Given the diverse chemistry exhibited by TEQ in metal coordination, photophysical behaviour, and catalytic applications,<sup>7</sup> the development of its chiral variant is highly desirable. Herein, we report the re-design of a quinoline-based, axially chiral molecular framework that functions as a tetradentate nitrogen ligand: *iso*-TEtraQuinoline (*i*-TEQ).<sup>8</sup> By switching the ring connectivity from head-to-tail to head-to-head at the 2,2'- and 8,8'-positions, *i*-TEO adopts a  $D_2$ -symmetric, inherently chiral architecture.9 Detailed comparative structural analyses uncovered similarities and differences between these connectivity isomers, highlighting the impact of the concatenation pattern on the chemical and photophysical properties.

### **Results and discussion**

#### Synthesis of iso-TEtraQuinolines (i-TEQs)

Inspired by the **TEQ** framework, we designed a synthetic plan utilizing cyclic diamide 5 with two quinoline units as a key precursor to *i*-**TEQ** *via* a two-fold quinoline forming reaction (Scheme 1). The synthesis of *i*-**TEQ** was initiated by a two-step



Scheme 1 Synthesis of *i*-TEQ 6a, 6b.

benzylic oxidation of 8-bromo-2-methylquinoline 1 mediated by SeO<sub>2</sub> and H<sub>2</sub>O<sub>2</sub>/HCO<sub>2</sub>H to afford carboxylic acid 2. After converting 2 into methyl ester 3 with H<sub>2</sub>SO<sub>4</sub> in MeOH, Suzuki-Miyaura cross-coupling with (2-amino)phenylboronic acid afforded aminoester 4.10 Following brief screening,11 simple cryogenic and highly diluted conditions with LiHMDS engaged 4 in smooth amidative dimerization, furnishing the requisite cyclic diamide 5 in 88% yield. According to Movassaghi's protocol12 and our previous modification for quinoline formation from macrocyclic amides,<sup>6a,h,i</sup> electrophilic activation of the amide functionality using Tf<sub>2</sub>O and 2,4,6-trimethoxypyridine and subsequent formal cycloaddition afforded the *i*-TEQ architecture. Quinoline formation with (triphenylsiloxy)ethylene furnished non-substituted D2symmetric *i*-TEQ 6a, but the yield was only 4%. More reactive panisylacetylene allowed for a more efficient ring reinforcement reaction to give C2-symmetric bis-p-anisylated *i*-TEQ 6b in 23% vield. The *p*-anisyl groups of *i*-TEO 6b can be smoothly demethylated, enabling further structural elaboration.13

A detailed comparative structural analysis was performed on the thus-obtained *i*-TEO 6b-a connectivity isomer of *p*-anisylated TEQ 7b sharing the same atomic composition (Fig. 2). To minimize structural deviations caused by crystal packing effects, DFToptimized structures of both isomers were compared using the B3LYP-D3/6-31G(d,p) level of theory with the IEFPCM(CHCl<sub>3</sub>) solvation model (Fig. 2a).14 Comparison of the top views of these structures revealed a distinct difference in the inner hollow topology: *i*-TEQ 6b features a diamond-shaped 16-membered macrocycle, while TEQ 7b exhibits a square-like counterpart. In contrast, the spatial arrangement of the four nitrogen atoms is similar, with the distances between diagonal nitrogen atoms being nearly identical, ranging from 4.35 to 4.47 Å. Additionally, the  $\tau'_4$  values<sup>15</sup> are close to zero, suggesting that *i*-TEQ 6b, like TEQ 7b, is capable of accommodating metal cations that prefer a square planar coordination mode (Fig. 2a and b). The diamondshaped cavity of *i*-TEQ 6b arises from the head-to-head (2,2' and 8,8') linkage of the quinoline units, leading to an overall laterally distorted structure characterized by reduced dihedral angles and an increased vertical dimension (*i*-TEQ 6b: 6.56 Å vs. TEQ 7b: 6.01 Å). Whereas the  $D_2$ -symmetric *i*-TEQ skeleton is more stable than the S<sub>4</sub>-symmetric **TEQ** skeleton ( $\Delta G = 2.2$  kcal mol<sup>-1</sup>), enthalpic evaluation via a homodesmotic reaction<sup>16</sup> and StrainViz analysis<sup>17</sup> indicated that *i*-TEQ adopts a more strained architecture (difference in total strain: 9.0 kcal mol<sup>-1</sup>), with the local structures of the intrinsic quinoline units being more distorted (Fig. 2b-d). This seemingly contradictory outcome is attributed to electronic repulsion between the lone pairs on the inwardly oriented nitrogen atoms; those of *i*-TEQ are oriented in a mutually more skewed fashion to prevent undesired overlapping. This electronic factor likely outweighs the skeletal distortion, rendering *i*-TEQ more thermodynamically stable than TEQ, as supported by TG-DTA analysis; i-TEQ 6b remains stable above 300 °C, whereas TEQ 7b begins to decompose above 250 °C.18

#### Physicochemical properties of *i*-TEQs

The structural rigidity of the *i*-TEQ framework, a cyclic assembly of four quinoline panels with a hitherto unknown pattern of



**Fig. 2** Structural comparison of connectivity isomers *i*-**TEQ 6b** and **TEQ 7b** sharing a tetrameric quinoline macrocyclic architecture and two peripheral diagonal *p*-anisyl groups. (a) Optimized structures are calculated at the B3LYP-D3/6-31G(d,p)/IEFPCM(CHCl<sub>3</sub>) level of theory. Colour codes; carbon: grey, nitrogen: blue, oxygen: red, hydrogen atoms are omitted for clarity. <sup>a</sup>Vertical size of the main framework is calculated by the distance between the midpoint of the two quinoline C5 carbons on the upper side and the midpoint of the two quinoline C5 carbons on the lower side. (b) Analysis of local structures. <sup>b</sup>LSP: least squares plane. More detailed analysis is summarized in ESI.† (c) StrainViz analysis and NBO of nitrogen lone pairs. StrainViz calculation was carried out at the B3LYP/6-31G(d) level of theory. (d) Comparison of Gibbs free energy for the formation of non-substituted *i*-**TEQ 6a** and **TEQ 7a**.

connectivity, is great of interest. Racemic samples of  $D_{2^-}$  symmetric non-substituted *i*-TEQ **6a** and  $C_2$ -symmetric *p*-ani-sylated *i*-TEQ **6b** were optically resolved *via* preparative HPLC on a chiral stationary phase (Fig. 3a). **6a** and **6b** were successfully resolved with base-peak separation under identical conditions (DAICEL CHIRALPAK IB-N5, <sup>*n*</sup>hexane/CH<sub>2</sub>Cl<sub>2</sub> mixed solvent



Fig. 3 (a) Partial HPLC chromatogram for optical resolution of *rac-i*-TEQ 6a and 6b separated by DAICEL CHIRALPAK IB-N5 column with <sup>*n*</sup>hexane/CH<sub>2</sub>Cl<sub>2</sub> eluent. (b) Circular dichroism (CD) spectra of optically pure samples of non-substituted (+)- and (-)-*i*-TEQ 6a, and anisylated (+)- and (-)-*i*-TEQ 6b in CH<sub>2</sub>Cl<sub>2</sub> (25  $\mu$ M).

eluent). The initially eluted enantiomers of both **6a** and **6b** displayed a positive Cotton effect in a range of 330–350 nm, corresponding to HOMO–LUMO excitation (Fig. 3b).<sup>19</sup> DFT simulations of electronic CD spectra suggested the absolute configuration shown in Fig. 3a.<sup>20</sup> Intriguingly, optical rotation of the first eluents of **6a** and **6b** were opposite (**6a**: dextrorotatory, **6b**: levorotatory), presumably because the closely located diagonal *p*-anisyl groups of **6b** affected optical rotation at the wavelength of sodium D-lines.

The stereochemical integrity of (-)-*i*-TEQ 6b was traced at a 1 mg mL<sup>-1</sup> concentration in diphenyl ether under various conditions (Table 1). The initial racemisation attempt without any additive confirmed that the stereochemistry of the *i*-TEQ architecture is quite stable; no decomposition or erosion of enantiopurity was observed even at 220 °C for 24 h (Entry 1). DFT calculations on the non-substituted *i*-TEQ 6a successfully reproduced the experimentally observed high racemisation barrier, yielding an inversion barrier of 58.0 kcal  $mol^{-1}$  for the transition state at the B3LYP-D3/6-311+G(2d,p)/SMD(diethyl ether) level of theory (Fig. 4a). Given that structurally similar acyclic azaBINOL is readily racemised (28.4 kcal mol<sup>-1</sup>),<sup>5a</sup> the unusual retention of axial chirality of *i*-TEQ is likely due to its unique concatenated structure. Notably, the inversion barrier of *i*-TEQ 6a is even higher than that of the configurationally stable TEQ 7a (56.9 kcal mol<sup>-1</sup> at the B3LYP-D3/6-31G(d,p) level of theory), and the inversion process proceeds via a stepwise mechanism involving a  $C_i$ -symmetric intermediate, in contrast to the single-step flipping observed for TEQ 7a (Fig. 4a). We

#### Table 1 Racemisation study of *i*-TEQ 6b in the absence or presence of additives



Entry	Additive <sup><i>a</i></sup>	Temp. (°C)	Time (h)	$ee^{b}$ (%)	Rate constant (× $10^{-7}$ s <sup>-1</sup> )	$t_{1/2}$ (h)	$\Delta G_{\exp}^{\ddagger}$ (kcal·mol <sup>-1</sup> )	$\Delta G_{\mathrm{calc}}^{\ddagger c} (\mathrm{kcal} \cdot \mathrm{mol}^{-1})$
1	None	220	24	>99	d	_	_	58.0
2	TFA	140	24	>99	d	_	_	$50.8^{e}, 46.3^{f}$
3		160	56	91	2.18	883	38.9	,
4	$[Pd(MeCN)_4](BF_4)_2$	100	30	63	20.2	95.3	31.8	33.3
5		140	2.5	20	888	2.2	32.1	
6	$CoCl_2$	100	24	>99	d		_	30.6
7		140	56	88	2.99	644	36.8	
8	CuCl <sub>2</sub>	100	24	>99	d		_	34.4
9	-	140	30	72	14.8	130	35.5	

<sup>*a*</sup> 1 Equivalent of additives was added. <sup>*b*</sup> Determined by chiral stationary phase HPLC analysis. <sup>*c*</sup>  $\Delta G_{calc}^{\ddagger}$  was calculated on non-substituted *i*-TEQ 6a at the B3LYP-D3/6-311+G(2d,p)-SDD(Co,Cu,Pd)/SMD(diethyl ether) level of theory. Compared with Fig. 4, a more extended basis set was employed and an appropriate solvation model was applied. <sup>*d*</sup> No racemisation occurred. <sup>*e*</sup> Calculated on the monoprotonated model. <sup>*f*</sup> Calculated on the diprotonated model.

reasoned that mitigating the repulsive orbital interactions of the four inwardly oriented nitrogen atoms enhanced the racemisation. While racemisation of (–)-*i*-**TEQ 6b** barely proceeded in the presence of 1 equivalent of trifluoroacetic acid (TFA) at 140 °C, a higher temperature (160 °C) induced slow the racemisation ( $t_{1/2} = ca.$  37 days) (Table 1, Entries 2,3). Quinoline ring flipping was significantly accelerated by the addition of [Pd(MeCN)<sub>4</sub>](BF<sub>4</sub>)<sub>2</sub> with  $t_{1/2}$  of 2.2 h at 140 °C (20% ee after 2.5 h), which corresponds to an empirically determined flipping barrier of 32.1 kcal mol<sup>-1</sup> (Entries 4,5). Intriguingly, *p*-anisylated (–)-**TEQ** 7**b**, featuring head-to-tail concatenation, was significantly more reluctant to racemise and remained at 88% ee even after 24 h of stirring under identical conditions (with Pd salt at 140 °C).<sup>21</sup> This distinct response to the Pd<sup>2+</sup> cation was reproduced by DFT calculations (Fig. 4b); the pathway from the *i*-**TEQ 6a**/Pd<sup>2+</sup> complex to its antipode involves a series of local minima connected by partially flipped  $C_1$ - and  $C_s$ -symmetric transition states, which significantly lower the inversion barrier.



Fig. 4 Stereoinversion of non-substituted quinoline tetramers in the absence and presence of  $Pd^{2+}$  cation. Calculated at the B3LYP-D3/6-31G(d,p)-SDD(Pd) level of theory. (a) *i*-TEQ 6a and TEQ 7a, and (b) *i*-TEQ 6a/Pd<sup>2+</sup> complex and TEQ 7a/Pd<sup>2+</sup> complexes.

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Fig. 5 Racemisation profile of enantiopure (–)-*i*-TEQ 6b in the presence of additives (1 eq) at 140 °C in diphenyl ether (1 mg mL<sup>-1</sup>). A plot of enantiomeric excess (%) *versus* time is shown. Enantiomeric excess was determined by chiral stationary phase HPLC analysis.

In contrast, the **TEQ 7a**/Pd<sup>2+</sup> complex undergoes a high-energy  $S_4$ -symmetric transition state to achieve stereoinversion. Other azophilic metal cations featuring a square planar coordination mode, *e.g.* Co<sup>2+</sup> or Cu<sup>2+</sup> rendered racemisation, whereas acceleration was significantly smaller than that of Pd<sup>2+</sup> and no racemization occurred at a temperature not exceeding 100 °C (Table 1, Entries 6–9). A plot of enantiomeric excess and elapsed time clearly demonstrates the substantial rigidity and characteristic response to Pd<sup>2+</sup> in the racemisation of (–)-*i*-TEQ 6b (Fig. 5). DFT calculations located energetically more favourable transition states by protonation or metal coordination.<sup>22</sup>

The accelerated racemisation of (-)-*i*-**TEQ 6b** in the presence of Pd<sup>2+</sup> demonstrates that *i*-**TEQ** is capable of accommodating Pd<sup>2+</sup> cations despite the highly twisted configuration of the lone pair orbitals of the four quinoline nitrogen atoms (Fig. 2c). Indeed, treatment of *i*-**TEQ 6b** with [Pd(MeCN)<sub>4</sub>](BF<sub>4</sub>)<sub>2</sub> in MeOH at 50 °C furnished the *i*-**TEQ 6b**/Pd(BF<sub>4</sub>)<sub>2</sub> complex in excellent yield (Scheme 2). Comparative X-ray diffraction analysis of the crystal structures of *i*-**TEQ 6b** and *i*-**TEQ 6b**/Pd(BF<sub>4</sub>)<sub>2</sub> revealed that both the averaged torsion angle at 8,8'-biquinoline units and the averaged distance of the diagonal nitrogen atoms



Scheme 2 Complexation of *i*-TEQ 6b with  $[Pd(MeCN_4)](BF_4)_2$ , and crystal structures of the 6b and 6b/Pd(BF\_4)\_2 complex. ORTEP drawings are shown at 50% probability ellipsoids. Colour codes; carbon: grey, nitrogen: blue, oxygen: red, palladium: dark blue. Hydrogen atoms, *p*-anisyl substituents, and counter anions were omitted for clarity.

decreased upon complexation from  $53.9^{\circ}$  to  $49.3^{\circ}$  and from 4.32 to 4.06 Å, respectively, leading to a vertically collapsed architecture.

To probe the thermodynamic stability of the Pd<sup>2+</sup> complexes of *i*-TEQ 6b and TEQ 7b, structural isomers with an identical elemental composition, a ligand metathesis experiment was conducted (Scheme 3). The *i*-TEQ  $6b/Pd(BF_4)_2$  complex and metal-free TEQ 7b were mixed in CDCl<sub>3</sub> and heated under reflux. <sup>1</sup>H NMR revealed that the signals derived from both the *i*-TEQ  $6b/Pd(BF_4)_2$  complex and the TEQ 7b completely disappeared (Scheme 3, (i,ii) vs. (iii)). Instead, newly observed peaks corresponded to the free forms of *i*-TEQ 6b and the TEQ  $7b/Pd(BF_4)_2$  complex (Scheme 3, (iii) vs. (iv, v)). In contrast, under identical conditions, a mixture of the free form of *i*-TEQ **6b** with the **TEQ**  $7b/Pd(BF_4)_2$  complex displayed virtually no change in <sup>1</sup>H NMR analysis, confirming the unidirectional Pd<sup>2+</sup> cation swapping from *i*-TEQ 6b to TEQ 7b (Scheme 3 (iv,v) vs. (vi)). The empirically observed higher stability of the  $Pd^{2+}$ complex of TEQ 7b over that of *i*-TEQ 6b was reproduced by DFT calculations at the B3LYP-D3/6-31G(d,p)-SDD(Pd)/



Scheme 3 Unidirectional Pd<sup>2+</sup> cation swapping between *i*-TEQ 6b and TEQ 7b. Partial <sup>1</sup>H NMR spectra in CDCl<sub>3</sub> (i) *i*-TEQ 6b/Pd(BF<sub>4</sub>)<sub>2</sub>; (ii) TEQ 7b; (iii) *i*-TEQ 6b/Pd(BF<sub>4</sub>)<sub>2</sub> + TEQ 7b at reflux temperature after 4 h; (iv) *i*-TEQ 6b; (v) TEQ 7b/Pd(BF<sub>4</sub>)<sub>2</sub>; (vi) TEQ 7b/Pd(BF<sub>4</sub>)<sub>2</sub> + *i*-TEQ 6b at reflux temperature after 4 h.



Fig. 6 Photophysical properties of *i*-TEQ 6b. Fluorescence spectra of *i*-TEQ 6b in  $CH_2Cl_2$  (20  $\mu$ M) were recorded upon incremental addition of TFA in  $CH_2Cl_2$  (excitation at 385.5 nm).

IEFPCM(CHCl<sub>3</sub>) level of theory; [*i*-TEQ 6b + TEQ 7b/Pd<sup>2+</sup>] is 27.7 kcal mol<sup>-1</sup> more stable than [*i*-TEQ 6b/Pd<sup>2+</sup> + TEQ 7b].

The photophysical properties of *i*-TEQ 6b were systematically investigated. Although i-TEQ 6b is inherently barely emissive, the addition of TFA induced a pronounced fluorescence enhancement in an equivalence-dependent manner (Fig. 6). In CH<sub>2</sub>Cl<sub>2</sub>, the fluorescence intensity of *i*-TEQ 6b increased progressively with the incremental addition of TFA, reaching a plateau at 4 equivalents (460 nm,  $\Phi_{\rm F} = 0.41$ ). This acid-responsive fluorescence behaviour, combined with the inherent chirality of 6b, prompted us to explore its potential in circularly polarized luminescence (CPL). Enantiomerically pure samples of (+)-6b and (-)-6b exhibited mirror-image CPL spectra upon the addition of 4 equivalents of TFA, with an absolute luminescence dissymmetry factor ( $|g_{\text{lum}}|$ ) of 4.95 × 10<sup>-3</sup>.<sup>23</sup> Notably, this value is an order of magnitude greater than that of ring-connectivity isomer TEQ  $7b_{,6\alpha}^{,6\alpha}$  highlighting the strong influence of the concatenation pattern on the resultant physicochemical properties.24

#### Derivatization from cyclic diamide

Cyclic diamide 5, a key intermediate in the synthesis of *i*-TEQs, serves as a flexible N4 macrocyclic scaffold (Scheme 4). Partial reduction of the amide moiety of 5 using the Zr-based Schwartz reagent<sup>25</sup> afforded diimine 8 in 54% yield. Reduction to secondary amines was achieved via Ir-catalysed silane conditions,26 affording tetradentate ligand 9. While electrophilic activation of the amide with Tf<sub>2</sub>O followed by formal cycloaddition with alkynes furnishes the quinoline ring en route to *i*-TEQs (vide supra), a two-fold intramolecular cyclization by the neighbouring quinoline proceeded in the absence of an external nucleophile to afford a warped, tetraaza dicationic  $\pi$ -material 10. A brief base screening identified electron-deficient 2-chloropyridine as optimal, providing 10 in 79% yield. 10 was readily reduced to furnish a more stable, neutral fused polycyclic material 11,27 whose unique three-dimensional structure was unambiguously determined by X-ray crystallographic analysis.



Scheme 4 Derivatization from cyclic diamide 5.

### Conclusions

Here, we describe the design and synthesis of a  $D_2$ -symmetric *iso*-TEtraQuinoline (*i*-TEQ) as an inherently, three-dimensional analogue of porphyrin. *i*-TEQ is a head-to-head quinoline tetramer and a connectivity isomer of previously reported  $S_4$ -symmetric, achiral TEQ, in which four quinoline units are concatenated in a head-to-tail fashion. Comprehensive and systematic comparable analyses of *i*-TEQ and TEQ revealed the unique features of these closely related molecular entities in terms of their overall architecture, stereochemical integrity, intrinsic ring strain, metal complexation abilities, and photophysical behaviour. Given its built-in chirality, *i*-TEQ represents a unique molecular scaffold that will serve as a cornerstone in the development of chiral porphyrinoids, thereby expanding the chemical space of porphyrin-based materials.

### Data availability

Experimental and characterization data, including crystallographic data [5 (CCDC 2392427), **6b** (CCDC 2392429), and **6d** (CCDC 2392433), **6b**/Pd(BF<sub>4</sub>)<sub>2</sub> (CCDC 2392430), **11** (CCDC 2392428)], photophysical measurements, and NMR spectra, as well as computational investigations. The data supporting this article have been included as part of the ESI.†

### Author contributions

N. K. and W. X. conceived and directed the project. R. Y. and W. X. synthesised, analysed, and characterised all compounds. T. K. performed theoretical calculations with partial support

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from N. K. Y. N. carried out CPL measurement and related data analysis. The draft manuscript was written by W. X. and N. K., and all the authors contributed to finalize manuscript though proofreading. All authors approved the final version of the manuscript.

### Conflicts of interest

There are no conflicts to declare.

### Acknowledgements

This work was financially supported by KAKENHI grant JP22K19037 (Grant-in-Aid for Exploratory Research; to N. K.), JP23H01952 (Grant-in-Aid for Scientific Research (B); to N. K.), and MEXT KAKENHI grant 23H03809 (Grant-in-Aid for Transformative Research Areas (B); to N. K.). N. K. thanks the Mitsubishi Foundation and Mukai Science and Technology Foundation for financial support. W. X. thanks TOBE MAKI foundation for financial support. T. K. thanks Izumi Science and Technology Foundation for financial support. Dr Tomoyuki Kimura at the Institute of Microbial Chemistry is gratefully acknowledged for X-ray crystallographic analysis. Computational calculations were performed using the resources of the Research Center for the Computational Science at Okazaki, Japan (Project No. 23-IMS-C081, 24-IMS-C077).

### Notes and references

- 1 (a) Y.-B. Wang and B. Tan, Acc. Chem. Res., 2018, 51, 534–547;
  (b) J. K. Cheng, S.-H. Xiang, S. Li, L. Ye and B. Tan, Chem. Rev., 2021, 121, 4805–4902;
  (c) G.-J. Mei, W. L. Koay, C.-Y. Guan and Y. Lu, Chem, 2022, 8, 1855–1893.
- 2 (a) L. Pu, Chem. Rev., 1998, 98, 2405-2494; (b) L. Pu, Acc. Chem. Res., 2012, 45, 150-163.
- 3 (a) G. Bringmann, T. Gulder, T. A. M. Gulder and M. Breuning, *Chem. Rev.*, 2011, 111, 563–639; (b)
  S. R. LaPlante, L. D. Fader, K. R. Fandrick, D. R. Fandrick, O. Hucke, R. Kemper, S. P. F. Miller and P. J. Edwards, *J. Med. Chem.*, 2011, 54, 7005–7022; (c) M. Basilaia, M. H. Chen, J. Secka and J. L. Gustafson, *Acc. Chem. Res.*, 2022, 55, 2904–2919; (d) B. A. Lanman, A. T. Parsons and S. G. Zech, *Acc. Chem. Res.*, 2022, 55, 2892–2903; (e)
  Z. Wang, L. Meng, X. Liu, L. Zhang, Z. Yu and G. Wu, *Eur. J. Med. Chem.*, 2022, 243, 114700.
- 4 For selected reviews on asymmetric catalysis with 1,1'-bi-2-naphthol (BINOL); (a) Y. Chen, S. Yekta and A. K. Yudin, Chem. Rev., 2003, 103, 3155-3212; (b) L. Eberhardt, D. Armspach, J. Harrowfield and D. Matta, Chem. Soc. Rev., 2008, 37, 839-864; (c) P. W. N. M. van Leeuwen, P. C. J. Kamer, C. Claver, O. Pàmies and M. Diéguez, Chem. Rev., 2011, 111, 2077-2118; (d) D. Parmar, E. Sugiono, S. Raja and M. Rueping, Chem. Rev., 2014, 114, 9047-9153; (e) L. Pu, Chem. Rev., 2024, 124, 6643-6689. For lanthanum-lithium-BINOL (LLB) complexes; (f) M. Shibasaki and N. Yoshikawa, Chem. Rev., 2002, 102, 2187-2210; (g) N. Kumagai, M. Kanai and H. Sasai, ACS

- Catal., 2016, 6, 4699–4709. For the other phosphines, amides, and others; (*h*) Q.-H. Fan, Y.-M. Li and A. S. C. Chan, *Chem. Rev.*, 2002, **102**, 3385–3466; (*i*) M. Berthod, G. Mignani, G. Woodward and M. Lemaire, *Chem. Rev.*, 2005, **105**, 1801–1836; (*j*) T. Akiyama and K. Mori, *Chem. Rev.*, 2015, **115**, 9277–9306; (*k*) H. Ni, W.-L. Chan and Y. Lu, *Chem. Rev.*, 2018, **118**, 9344–9411; For 1,1'-binaphthyl-based macrocycles; (*l*) R. Ning, H. Zhou, S.-X. Nie, Y.-F. Ao, D.-X. Wang and Q.-Q. Wang, *Angew. Chem., Int. Ed.*, 2020, **59**, 10894–10898; (*m*) G. Sun, X. Zhang, Z. Zheng, Z.-Y. Zhang, M. Dong, J. L. Sessler and C. Li, J. Am. Chem. Soc., 2024, **146**, 26233–26242.
- 5 (a) P. R. Blakemore, C. Kilner and S. D. Milicevic, J. Org. Chem., 2006, 71, 8212–8218; (b) J. Xiao and T.-P. Loh, Org. Lett., 2009, 11, 2876–2879; (c) S.-M. Sephton, C. Wang, L. N. Zakharov and P. R. Blakemore, Eur. J. Org Chem., 2012, 3249–3260; (d) J. V. Chocholoušová, J. Vacek, A. Andronova, J. Míšek, O. Songis, M. Šámal, I. G. Stará, M. Meyer, M. Bourdillon, L. Pospíšil and I. Starý, Chem.– Eur. J., 2014, 20, 877–893.
- 6 (a) W. Xu, Y. Nagata and N. Kumagai, J. Am. Chem. Soc., 2023, 145, 2609-2618. Other examples of quinoline-based macrocycles; (b) P. S. Shirude, E. R. Gillies, S. Ladame, F. Godde, K. Shin-ya, I. Huc and S. Balasubramanian, J. Am. Chem. Soc., 2007, 129, 11890-11891; (c) T. Shimasaki, R. Kuroda, M. Akao, T. Akimoto, T. Ishikawa, T. Iwanaga, N. Teramoto and M. Shibata, Chem. Lett., 2019, 48, 133-136; (d) S. Adachi, M. Shibasaki and N. Kumagai, Nat. Commun., 2019, 10, 3820; (e) D. Yang, J. L. Greenfield, T. K. Ronson, L. K. S. von Krbek, L. Yu and J. R. Nitschke, J. Am. Chem. Soc., 2020, 142, 19856-19861; (f) T. Kobayashi and N. Kumagai, Angew. Chem., Int. Ed., 2023, 62, e202307896; (g) T. Kobayashi, T. Sakurai and N. Kumagai, Bull. Chem. Soc. Jpn., 2023, 96, 1139-1143; (h) K. Kihara, T. Kobayashi, W. Xu and N. Kumagai, Chem.-Eur. J., 2024, 30, e202304176; (i) T. Karimata, W. Xu and N. Kumagai, Chem.-Eur. J., 2025, 31, e202404335.
- 7 M. Nishiwaki, W. Xu and N. Kumagai, *Asian J. Org. Chem.*, 2023, **12**, e202300261.
- 8 For the naphthalene analogue; (*a*) Y. Nojima, M. Hasegawa, N. Hara, Y. Imai and Y. Mazakia, *Chem. Commun.*, 2019, 55, 2749–2752; (*b*) Y. Nojima, M. Hasegawa, N. Hara, Y. Imai and Y. Mazaki, *Chem.–Eur. J.*, 2021, 27, 5923–5929.
- 9 For other inherently chiral macrocyclic compounds, see: (a)
  S. Tong, J.-T. Li, D.-D. Liang, Y.-E. Zhang, Q.-Y. Feng,
  X. Zhang, J. Zhu and M.-X. Wang, J. Am. Chem. Soc., 2020,
  142, 14432–14436; (b) H. Han, X.-G. Wang, S. Tong, J. Zhu and M.-X. Wang, ACS Catal., 2025, 15, 6018–6024; (c)
  S. J. Nemat, H. Jędrzejewska, A. Prescimone, A. Szumna and K. Tiefenbacher, Org. Lett., 2020, 22, 5506–5510; (d)
  G. E. Arnott, Chem.-Eur. J., 2018, 24, 1744–1754; (e)
  F. Sannicolò, P. R. Mussini, T. Benincori, R. Cirilli,
  S. Abbate, S. Arnaboldi, S. Casolo, E. Castiglioni,
  G. Longhi, R. Martinazzo, M. Panigati, M. Pappini,
  E. Q. Procopio and S. Rizzo, Chem.-Eur. J., 2014, 20, 15298–15302.
- 10 A. Suzuki, Angew. Chem., Int. Ed., 2011, 50, 6722-6737.

- 11 See ESI Section 2.6<sup>†</sup> for details.
- 12 M. Movassaghi and M. D. Hill, J. Am. Chem. Soc., 2006, **128**, 14254–14255.
- 13 See ESI Section 2.9 and 2.10 $\dagger$  for details.
- 14 X-ray crystallographic analysis of *i*-TEQ 6b and TEQ 7b revealed that crystal structures and calculated structures of the main frameworks are almost identical.
- 15 A. Okuniewski, D. Rosiak, J. Chojnacki and B. Becker, *Polyhedron*, 2015, **90**, 47–57.
- 16 See ESI Section 7.7† for details.
- 17 C. E. Colwell, T. W. Price, T. Stauch and R. Jasti, *Chem. Sci.*, 2020, **11**, 3923–3930.
- 18 See ESI Fig. S28 and S29.†
- 19 See ESI Table S4<sup>†</sup> for details.
- 20 See ESI Fig. S17 and S18.†
- 21 See ESI Section 5.3<sup>†</sup> for details.
- 22 See ESI Section 6† for details.
- 23 G. Longhi, E. Castiglioni, J. Koshoubu, G. Mazzeo and S. Abbate, *Chirality*, 2016, 28, 696–707. See ESI Section 7.5<sup>+</sup> for experimental details.
- 24 See ESI Section 7.6<sup>†</sup> for calculational details.
- 25 J. Schwartz and J. A. Labinger, *Angew. Chem., Int. Ed.*, 1976, 15, 333–340.
- 26 C. Cheng and M. Brookhart, J. Am. Chem. Soc., 2012, 134, 11304–11307.
- 27 For fused polycyclic material see following reviews or latest articles; (a) H. Ito, K. Ozaki and K. Itami, Angew. Chem., Int. Ed., 2017, 56, 11144-11164; (b) S. H. Pun and Q. Miao, Acc. Chem. Res., 2018, 51, 1630-1642; (c) G. G. Miera, S. Matsubara, H. Kono, K. Murakami and K. Itami, Chem. Sci., 2022, 13, 1848-1868; (d) S. M. Elbert, O. T. A. Paine, T. Kirschbaum, M. P. Schuldt, L. Weber, F. Rominger and M. Mastalerz, J. Am. Chem. Soc., 2024, 146, 27324-27334. For aza-substituted warped nano-sheets; (e) S. Ito, Y. Tokimaru and K. Nozaki, Angew. Chem., Int. Ed., 2015, 54, 7256-7260; (f) H. Yokoi, Y. Hiraoka, S. Hiroto, D. Sakamaki, S. Seki and H. Shinokubo, Nat. Commun., 2015, 6, 8215; (g) S. Higashibayashi, P. Pandit, R. Haruki, S. Adachi and R. Kumai, Angew. Chem., Int. Ed., 2016, 55, 10830-10834; (h) K. Oki, M. Takase, S. Mori, A. Shiotari, Y. Sugimoto, K. Ohara, T. Okujima and H. Uno, J. Am. Chem. Soc., 2018, 140, 10430-10434; (i) T. Kirschbaum, F. Rominger and M. Mastalerz, Chem.-Eur. J., 2020, 26, 14560-14564; (j) P. An, R. Li, B. Ma, R.-Y. He, Y.-K. Zhang, M.-J. Xiao and B. Zhang, Angew. Chem., Int. Ed., 2021, 60, 24478-24483; (k) J. Wagner, P. Z. Crocomo, M. A. Kochman, A. Kubas, P. Data and M. Lindner, Angew. Chem., Int. Ed., 2022, 61, e202202232; (l) M. Krzeszewski, Ł. Dobrzycki, A. L. Sobolewski, M. K. Cyrański and D. T. Gryko, Chem. Sci., 2023, 14, 2353-2360.