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## Diquats with Robust Chirality: Facile Resolution, Synthesis of Chiral Dyes and Application as Selectors in Chiral Analysis

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**Abstract:** Diquats with extremely high racemization barriers with  $\Delta G^{*}_{theor}$  of 233 kJ mol<sup>-1</sup> at 180°C are described. Reported configurational robustness is due to combination of two structural features: the rigid *o*-xylylene tether connecting the nitrogen atoms and the presence of two substituents in the bay region of the bipyridinium scaffold. Straightforward synthesis of diquats, facile resolution and derivatization make them attractive for chiral application studies. This is demonstrated by (i) synthesis of the first non-racemic diquat dyes with pronounced chiroptical properties and (ii) capability of diquats to interact stereospecifically with chiral molecules. This suggests potential of diquat derivatives to be used as chiral selectors in separation methods.

Diquats are known since 1958 when they have been introduced as powerful herbicides by scientists at Imperial Chemical Industries.<sup>1</sup> Electron deficient systems based on diquat and paraquat<sup>2</sup> have been also instrumental as building blocks for supramolecular chemistry<sup>3</sup> as well as in design of electrontransfer systems.<sup>2,4</sup> Diquats have helical geometry<sup>1b</sup> but typically insufficient configurational stability to allow studies of the two separate enantiomers with opposite helicity (Scheme 1a,  $\Delta G^{\pm}_{theor}$ = 37 kJ mol<sup>-1</sup> at 20°C).<sup>5</sup> In spite of the great general usefulness of diquats, no examples with comfortable configurational stability have been recognized.

It is possible to distinguish in early reports examples of diquat derivatives with potentially elevated configurational stability. Spotswood and Tanzer studied a series of dimethyl-substituted diquats with aliphatic bridge<sup>6</sup> and Vögtle and Bombach reported diquats made by simple quaternization of several 2,2'-bipyridines with *o*-xylylene dibromide.<sup>7</sup> However, aspect of configurational stability as well as resolution of enantiomers were not subject of these reports. More recently, Lacour group revisited some of these dications (Scheme 1b), addressed their resolution and determined racemization barriers. This elegant study found the barriers of the selected example diquats to be relatively low ( $\Delta G^{\neq} = 106-112 \text{ kJ mol}^{-1} \text{ at } 20^{\circ}\text{C}$ ).<sup>8,9</sup>

Non-racemic diquats with comfortably high barriers preventing thermal racemization even at 150-200°C will enable a variety of application studies without being restricted to low temperatures. Such configurational stability would be

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 Supporting information for this article can be found under: XXXX comparable to that of axially chiral binaphthyls which have been widely applied.<sup>10</sup> Here, we report configurationally robust diquats, their synthesis, derivatization and properties (*e.g.* diquat **1**, Scheme 1c). We describe their straightforward resolution, chiral analysis, and derivatization. Their application potential is demonstrated by their use as chiral selectors in capillary electrophoresis as well as synthesis of the first non-racemic diquat dyes.



Scheme 1. (a) Typical diquat with low racemization barrier. (b) Rare diquat with slightly higher barrier allowing resolution of enantiomers. (c) Example of diquat with great configurational robustness studied in this work. TS = transition state.

We became interested in configurationally robust diquats after our theoretical finding that systems such as **1** might have unusually high racemization barriers and would be therefore suitable for chiral applications. Detailed DFT-D calculations revealed relevant non-C<sub>s</sub>-symmetric transition state<sup>11</sup> on the racemization pathway with  $\Delta G^{\neq}_{theor} = 233 \text{ kJ mol}^{-1}$  at 180°C. It corresponds to racemization half-life of more than 800 000 years at 180°C (for details see S49 and supplementary movie file).

At the outset of the experimental investigation, we established a practical route to non-racemic samples of diquat **3**. Starting from commercially available 2,2'-bipyridyl derivative **2**, racemic diquat **3**, [*rac*-**3**][Br]<sub>2</sub>, was synthesized in a single step (Scheme 2,  $2 \rightarrow 3$ ).<sup>7</sup> Next, we addressed resolution of the chiral dication **3** *via* its diastereomeric dibenzoyltartrate salts [*P*-**3**][*R*,*R*-DBT]<sub>2</sub> and [*M*-**3**][*R*,*R*-DBT]<sub>2</sub>.

This resolution is operationally very straightforward and consists of simple mixing of aqueous solutions of [rac-3][Br]<sub>2</sub> and monosodium salt of (R,R)-dibenzoyltartrate, [Na][R,R-DBT]. Efficient precipitation of diastereomerically pure  $[P-3][R,R-DBT]_2$  takes place spontaneously. Subsequently, direct anion exchange using triflic acid in diethyl ether affords virtually enantiopure  $[P-3][TfO]_2$  (98% ee) as evidenced by chiral capillary electrophoresis (CE).<sup>12,13</sup> Similarly, tetramethyl diquat derivative  $[rac-1][Br]_2$  was prepared and resolved using our simple precipitation protocol to obtain  $[P-1][TfO]_2$  (Scheme 3).

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**Scheme 2.** Synthesis and facile resolution of racemic diquat **3** *via* precipitation of diastereomerically pure dibenzoyltartrate salt [*P*-**3**][*R*,*R*-DBT]<sub>2</sub> followed by anion exchange with TfOH.

Absolute configuration of  $[P-1][TfO]_2$  has been unambiguously assigned from the single crystal X-ray structure of the dibenzoyl-L-tartrate salt  $[P-1][R,R-DBT]_2$  (Figure 1a and S89) and absolute configuration of  $[P-3][Br]_2$  has been determined by comparison of experimental and simulated electronic circular dichroism (ECD) data (S78).



**Scheme 3.** Synthesis of non-racemic diquat dyes. Conditions: a) 110°C, sealed tube, 72 h, 84%, b) resolution *via* direct precipitation of diastereomerically pure dibenzoyltartrate salt [*P*-1][*R*,*R*-DBT]<sub>2</sub> followed by anion exchange with TfOH, 56%, c) RT, 2 h, 94%, d) 70°C, 72 h, 65%.

The calculated barrier of diquat  $1 \Delta G^{\neq}_{theor}$  of 233 kJ mol<sup>-1</sup> at 180°C corresponds to racemization half-life of more than 800 000 years. In line with this theoretical assessment of the racemization barrier, prolonged exposure of [*P*-1][TfO]<sub>2</sub> solution to 180°C did not show any signs of racemization as evidenced by enantiocomposition analysis by CE with sulfated  $\gamma$ -cyclodextrin chiral selector (see S54 for details). Similarly,

absence of racemization in diquat  $[P-3][TfO]_2$  at 180°C was found (S55).



**Figure 1.** X-ray crystal structures of: a) diquat  $[P-1][R,R-DBT]_2$  (CCDC 1447598) and b) diquat dyes **5** (CCDC 1447601) and **6** (CCDC 1447600). Anions are omitted for clarity (see S87).

Presence of two active methyl groups in system 1 calls for derivatization via methods established for pyridinium type systems.<sup>13</sup> Interestingly, synthesis of non-racemic diquat dyes has never been addressed so far.14 To this end, we converted [P-1][TfO]2 to non-racemic dye [P-5][TfO]2 in presence of triethylamine (Scheme 3). By contrast, reaction of [P-1][TfO]2 amino-substituted benzaldehvde with derivative via Knoevenagel condensation in presence of pyrrolidine as catalyst failed to give the expected [P-6][TfO]2 and only complex reaction mixture was obtained. To our delight, the desired dye [P-6][TfO]2 can be successfully prepared in absence of pyrrolidine. Synthesis of the dyes having M configuration, [M-5][TfO]2 and [M-6][TfO]2, has been accomplished starting from [M-1][TfO]2 precursor (S38, S41).



Figure 2. ECD of the individual enantiomers of diquat dyes  $[5][\mbox{TfO}]_2$  and  $[6][\mbox{Br}]_2.$ 

Identity of both dyes **5** and **6** has been unambiguously confirmed by X-ray crystal structure data in the racemic series (Figure 1b). ECD of the non-racemic dye samples **6** in the visible spectral region showed bisignate Cotton effect characteristic for exciton chirality<sup>15</sup> contrary to ECD of the non-racemic dye samples **5** with large monosignate feature (Figure 2). TD-DFT calculations of **5** and **6** were performed (see S78), however without success for compound **5**. The similar discrepancy was already reported in literature<sup>16</sup> showing the limitation in applicability of the standard exciton chirality to systems where the intrinsic (origin-independent) magnetic transition moment is negligible.

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**Figure 3.** a) Enantiodiscrimination of chiral analytes with diquat  $[P-1][TfO]_2$  as a selector in capillary electrophoretic separation. b)-d) Experimental arrangement of CE chiral separation in counter-flow of diquat selector: b) Narrow zone of injected racemic analyte; c) Snapshot in the course of separation; d) Separated enantiomers of the analyte in the detector area.

We used capillary electrophoresis for rapid investigation<sup>17</sup> of chiral discrimination capabilities of diquat 1 (Figure 3a). Flexible CE setup with both analytes and chiral selector in free solution (Figure 3b-d) was beneficial in identification of important chiral molecules specifically interacting with optically pure diquat enantiomers. Structural diversity of successfully resolved analytes is a promising starting point for application of novel diquats as chiral selectors for electrophoresis and chromatography. Then, principal availability of both diquat enantiomers is advantageous to control elution order of chiral analytes. For analysis of trace amounts of optical impurities, it is beneficial that the minor enantiomer elutes first. This is difficult to achieve for chiral selectors typically available in only one optical form, such as cyclodextrins. Extension of this proof-ofconcept study towards design of configurationally robust diquats as a central stereorecognition motif for enantioseparations of chiral pharmaceuticals and metabolites or for uses as sensors thus seems attractive.

In summary, this report introduces detailed experimental and theoretical investigation of diquats with notably high racemization barriers. The presented results are significant from several perspectives: (i) Facile and inexpensive preparative resolution of two parent diquat systems is described. (ii) The facilitated by enantiocomposition analysis by capillary using well available electrophoresis cyclodextrin-based selectors. (iii) Comfortably robust configurational stability of the title diquats permits their exploration for range of applications in chiral science. We demonstrate in conditions of capillary electrophoresis that diquat 1 can act as a chiral selector to investigate enantiocomposition of example acidic aromatic analytes with axial and central chirality. The enantiodiscrimination aspect shown suggests more general potential of the dications in chiral separation methods and chiral supramolecular recognition with prospective use in sensorics. (iv) Synthesis of non-racemic diquat dyes is described. This is the first time chiral dyes of that type have been synthesized and their prominently large chiroptical responses documented. To this end, their intense ECD in the visible region is of interest towards applications in polarization-related photonics for data storage and communication. Overall, our results show diquats as a class of attractive chiral dicationic scaffolds, which constitute useful platforms for chiral application studies. Work towards application of the title diquats as a recognition motif in chiral stationary phases for liquid chromatography is underway.

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## COMMUNICATION

Configurationally robust diquats

facile resolution

flexible derivatization to make dyes applied as chiral selectors

- thermal racemization via chiral TS
- ⊿G<sup>‡</sup><sub>theor</sub> = 233 kJ mol<sup>-1</sup> at 180°C



Facile access to enantiopure diquats with extreme configurational stability is described for the first time along their derivatization and application as chiral selectors.

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