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Regioselective supramolecular catalysis. Exploiting multiple binding motifs in propanediurea molecular clips☆

Emmanuelle A. Bugnet, Tracy D. Nixon, Colin A. Kilner, Robert Greatrex and Terence P. Kee*

Department of Chemistry, University of Leeds, Woodhouse Lane, Leeds LS2 9JT, UK

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Abstract—Molecular clips derived from 2,4,6,8-tetraazabicyclo[3.3.1]nonane-3,7-dione promote increased regioselectivity in the SO_2Cl_2-mediated electrophilic aromatic chlorination of *ortho*-cresol leading to *para*/*ortho* ratios ($R_{p/o}$) <25; approximately six times larger than in the absence of the clip. Specific recognition events involving hydrogen-bond, π–π and dative covalent interactions are implicated.

One of the most fruitful areas within supramolecular chemistry is the design of molecular hosts capable of selective and potent binding of neutral guest molecules.[1] Such binding exploits a combination of interactions including hydrogen-bonds, π–π stacking, van der Waals and electrostatic interactions[2] collectively leading to significant advances in the construction of novel supramolecular structures, biomimetic chemistry and supramolecular catalysis.[1] Our interests lie in catalysis, especially biologically inspired forms of catalysis where dative covalent, hydrogen-bond, π–π and van der Waals interactions combine to provide powerful control elements over reaction rates and, most significantly, reaction stereochemistry. Here we describe the application of pre-organised hydrogen-bonding, π–π and dative binding motifs within molecular clips derived from 2,4,6,8-tetraazabicyclo[3.3.1]nonane-3,7-dione for the *para*-selective chlorination of 2-methylphenol (*o*-cresol) as an example of a bio-inspired, non-metal based regioselective catalyst system.

Isomerically pure *ortho*- and *para*-chlorophenols have multiple applications including dyestuffs, preservatives, disinfectants, insecticides and herbicides.[3] 4-Chloro-2-methylphenol (*para*-chlorocresol; PCC), for example, is commercially important in the manufacture of 4-chloro-2-methylphenoxyacetic acid, a major phenoxy herbicide used to control weeds in small grains,[4] cereals and grassland.[5,6] Since regiochemistry of chloro substitution is important for biological activity, considerable efforts have been directed towards controlling *para*-(4-position) selectivity in the chlorination of 2-methylphenol over *ortho*-(6-position) and poly-chlorination. Mild chlorinating agents minimise polychlorination and promote increased *para*:*ortho* ($R_{p/o}$) ratios. Chlorodimethylsulfonium chloride ($Me_2SCl^+Cl^-$),[7] *N*-chloroamines and ammonium salts[8] and sulfuryl chloride (SO_2Cl_2),[9] have been used among others with $R_{p/o}$ ratios >30.[10] However, for the commercially favoured reagent, SO_2Cl_2, $R_{p/o}$ ratios have generally been <10 unless additives such as ethers, organonitrogen or organosulfur compounds are added;[11] raising $R_{p/o}$ values for 2-methylphenol to ca. 20.[12] In almost all cases, the precise role of these additives is unknown.

para-Chlorination is favoured over *ortho*-chlorination as the steric demand of the chlorinating agent increases.[12] Consequently, substituting a cresol ether ($ArCH_2OC_6H_4$-2-CH_3) for 2-methylphenol (HOC_6H_4-2-CH_3) results in $R_{p/o}$ values >60 due principally to increased steric protection *ortho* to the phenoxy function.[13] This allowed us to modify further 2-methylphenol by immobilisation on Merrifield resin, chlorination with SO_2Cl_2 and release from the resin to afford a 4-chloro-2-methylphenol:6-chloro-2-methylphenol mix with $R_{p/o}$ >50.[13] The major problem with this approach is that considerable wet chemistry is necessary. Much more convenient would be the use of a catalyst or additive which could exploit non-covalent interactions with 2-methylphenol to provide improved $R_{p/o}$ ratios.

Previous workers have exploited a molecular recognition cavity effect through structures based on calixarene

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* Corresponding author. Tel.: +44-(0)113-3436421; fax: +44-(0)113-3436565; e-mail: t.p.kee@chem.leeds.ac.uk

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and cyclodextrin frameworks to influence the selectivity of aromatic substitution in phenols.[14] In the SO_2Cl_2-mediated chlorination of *o*-cresol, we found both calix[6]arene and β-cyclodextrin structures to be less than effective ($R_{p/o}$ ca. 3–4), we feel, due to the presence of the sterically significant *o*-methyl group. Consequently, we switched our attention to a class of molecular clip derived from tetra-substituted 2,4,6,8-tetraazabicyclo[3.3.1]nonane-3,7-dione derivatives **1** and **2**, which have been demonstrated exquisitely by Nolte and co-workers, to act as hosts for hydroxybenzene guest molecules with high binding affinity (Fig. 1a,b).[15] We envisaged that a combination of hydrogen-bond and π-aromatic interactions between **1** and 2-methylphenol would effectively prevent chlorination at the remaining *ortho*-position of the latter thus directing chlorination preferentially to the *para*-position and increasing the $R_{p/o}$ ratio (Fig. 1c). Indeed, we were inspired in this thought by earlier, seminal work by Guy et al.[16]

Molecular clip **1** was synthesised as described previously[15] and **2** was prepared from **1** upon treatment with aqueous nitric acid (50% w/w) and acetic anhydride.[17] During this work, we were able to analyse the synthetic intermediate 2,4,6,8-tetrakis-methoxymethyl-9,9-dimethyl-2,4,6,8-tetraaza-bicyclo[3.3.1]nonane-3,7-dione **3**, by single crystal X-ray analysis.[18]

Chlorination of 2-methylphenol (0.044 mmol) with SO_2Cl_2 (0.044 mmol) in CH_2Cl_2 solvent (5 cm^3; 298 K) proceeds over 4 h to afford 4-chloro-2-methylphenol and 6-chloro-2-methylphenol as the only products (85% conversion) with an $R_{p/o}$ ratio of ca. 4. Upon repeating the above reaction in the presence of 0.04 mmol (0.9 mol equiv.) of molecular clip **1**, the same two products were obtained exclusively, with an $R_{p/o}$ ratio of ca. 25 (500 MHz NMR; 98% conversion).[19] Although this ratio is decreased somewhat to ca. 15 in the presence of catalytic quantities (4 mol%; 4 h; 95% conversion) of molecular clip, this still represents an almost fourfold increase in product ratio. Revealingly, chlorination under identical conditions in the presence of 0.9 equiv. of clip **2** or the clip precursor derivative **3** both afford a $R_{p/o}$ ratio of 0.7; the *ortho*-product being favoured in

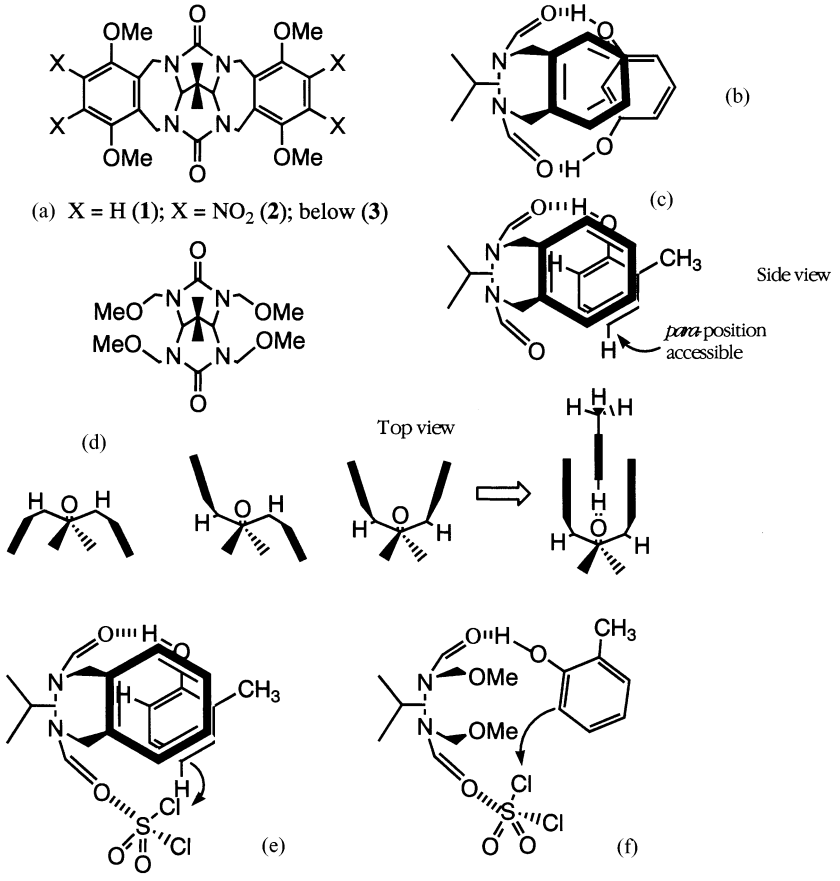

Figure 1. (a) Molecular clips **1** and **2** derived from 2,4,6,8-tetraazabicyclo[3.3.1]nonane-3,7-dione. (b) Interaction between **1** and 1,3-dihydroxybenzenes emphasising hydrogen-bonding and π-aromatic interactions.[15] (c) Envisaged H-bond and π-aromatic interactions between a molecular clip and 2-methylphenol. Hypothetical models for the chlorination of *o*-cresol with SO_2Cl_2 in the presence of molecular clip **1** showing; (d) Molecular clip conformers *ss*, *as*, *aa*; (e) combination of H-bond and π-aromatic interactions leading to *para*-chlorination being favoured whereas, in (f) with ester **3**, lack of a π-stacked groove prevents *o*-cresol being held in an appropriate position to favour *para*-chlorination and we envisage *ortho*-chlorination being favoured as illustrated.

each case (>95% conversion; 4 h). We feel that this serves to highlight the differences in solution interaction between clips **1**, **2** and **3** and 2-methylphenol and offer a hypothesis below.

Experimental studies have revealed that **1** binds resorcinols with association constants (K_a) of 10,000 L mol^{-1} and above, due principally to the stereochemically favourable disposition of hydrogen bonding and non-covalent π-aromatic interactions.[15] When aromatic nuclei bearing a single hydrogen-bond donor (e.g. phenols) are employed as guest molecules, the association constants with **1** drop precipitously to around the 10–1000 region, depending upon the nature of substitution on the guest molecule. We envisaged that similar low association might also result between **1** and 2-methylphenol on account of the steric presence of the methyl substituent limiting the possibilities of effective binding whilst binding should increase somewhat for 4-chloro-2-methylphenol in line with the trend observed previously for phenol. Indeed, this proved to be the case. Job analyses confirmed 1:1 interaction stoichiometry between **1** and 2-methylphenol, 4-chloro-2-methylphenol and 6-chloro-2-methylphenol as guests whilst NMR titrations at 298 K in $CDCl_3$ returned associations constants of 8, 39 and <1 L mol^{-1} for these three substrates respectively.[20] We took the liberty of re-recording, as a reference, the association constant between **1** and phenol which has been previously found[15] to be 22 L mol^{-1}. In our hands we returned exactly the same value, allowing us some confidence over our measurements for cresols. We expected that since 2-methylphenol is more electron-releasing than phenol, a less electron-rich molecular clip than **1** may improve binding of cresols. However, both Job analyses and NMR titrations of **2** with 2-methylphenol do not support 1:1 binding in the manner of phenols with **1** consistent with a different interaction profile leading to different regioselectivities in *o*-cresol chlorination. Futhermore, semi-empirical analyses at the AM1 level[22] suggests that methoxy-clip **1** is more stable in the cavitated conformation (*aa*) shown in Figure 1d by ca. 9 kJ mol^{-1} than a form in which the aromatic side-walls are not facing each other (*ss* and *as* conformers in Fig. 1d), similar calculations suggest that the same cavitated form of (**2**) is within ca. 1 kJ mol^{-1} of alternative, non-cavitated conformations.

Although the association constant between **1** and 2-methylphenol is very small, equating to a ΔG of complexation of ca. 5 kJ mol^{-1} at 298 K this translates, in a 1:1 mixture of the two at 298 K, to 88% of 2-methylphenol being bound at any one time. Revealingly, 4-chloro-2-methylphenol binds more strongly to **1** than 2-methylphenol, worth ca. 9 kJ mol^{-1} (298 K), which indicates the former to be a competitive, reversible inhibitor in the binding of the latter to clip **1**. However, since complexation should be fairly labile, we envisage that such non-reactive inhibition should not adversely affect the regiochemical outcome of reaction.[2] Given the low binding constant of 2-methylphenol to **1**, we were intrigued as to why the $R_{p/o}$ ratios were increased so in the presence of the latter and why molecular clip **1** should favour the *para*-product but close neighbour **2** and precursor molecule 2,4,6,8-tetrakis-methoxymethyl-9,9-dimethyl-2,4,6,8-tetraaza-bicyclo-[3.3.1]nonane-3,7-dione **3** favour the *ortho*-product. We hypothesise that molecular clip **1** binds 2-methylcresol via hydrogen bonding and π–π molecular interactions as proposed by Nolte[15] and in so doing, activates the phenol to electrophilic attack; as has been proposed earlier.[16] Crucially, we hypothesise further that the sulfuryl chloride is also activated by interaction with clip **1** in a manner illustrated in Figure 1e. Similar activation of SO_2Cl_2 in the presence of oxygen donors has been reported.[12] The effect of this dual activation of substrate and reagent is that chlorination of 2-methylphenol is both faster and more *para*-selective when the latter engages in interaction with the clip. Should this hypothesis be correct, an $R_{p/o}$ ratio of ca. 25 for the 1:1 **1**:*o*-cresol system implies that 4-chlorination of *o*-cresol is some 25 times faster than that for 6-chlorination under normal kinetic controlled conditions; implying a $\Delta\Delta G^{\ddagger}$ of ca. 8 kJ mol^{-1}, energies accessible via a combination of *o*-cresol binding and activation of SO_2Cl_2 by the clip. Intriguingly, our observations also suggest that chlorination of *o*-cresol using either clip **2** or precursor **3** affords an $R_{p/o}$ ratio of ca. 0.7 suggesting that the presence of π–π-stacking interactions are vitally important in the regioselective-determining action of clip **1**.

Finally, it is clear that molecular clips **1** and **2** have a differential effect upon the rate of *o*-cresol chlorination at the 4- and 6-positions. As yet we do not know whether the effects we are seeing reflect an enhancement of 4-chlorination or attenuation of 6-chlorination. These and further semi-empirical computational analyses are in progress to probe this regioselective effect in more detail and apply the approach to other regioselective processes involving aromatic substrates.

Supplementary data. The following information is available on-line: (i) synthesis and characterising data for all compounds, (ii) Job analyses and (iii) ^{1}H NMR titration analyses of the interactions between molecular clip **1** and substituted *o*-cresol.

Acknowledgements

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17. In a 25 cm^3 round-bottomed flask equipped with a magnetic stirrer, 0.55 cm^3 of HNO_3 50% aqueous solution was added dropwise at 0°C to the methoxy-clip **1** derived from 2,4,6,8-tetraazabicyclo[3.3.1]nonane-3,7-dione (70.4 mg, 0.138 mmol) in acetic anhydride (2 cm^3). The mixture was stirred for 20 min at 0°C, before being allowed to warm to room temperature and stirred overnight. After 17 h, water was added and the solution extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed once with 2 M KOH solution, once with water, dried over $MgSO_4$, filtered and the volatiles removed under reduced pressure to leave nitro-methoxy clip **2**. Yield: 87 mg, 91.6%. Found: C, 47.1; H, 4.6; N, 15.2. $C_{27}H_{28}N_8O_{14}$ requires: C, 47.1; H, 4.1; N, 16.3%. Mass spectrum: ES m/z 1399 [$2C_{27}H_{28}N_8O_{14}^+$+Na], 711 [$C_{27}H_{28}N_8O_{14}^+$+Na]. IR (KBr disk): ν 1664 (CO), 1359, 1544 (NO_2). ^{1}H NMR δ ($CDCl_3$): 1.50 (s, 6H, CH_3), 3.74 (d, 4H, $^2J_{HaHb}$ 16.3 Hz, Ha), 4.02 (s, 12H, OCH_3), 4.50 (s, 2H, CH), 5.74 (d, 4H, $^2J_{HaHb}$ 16.3 Hz, Hb). ^{13}C NMR δ ($CDCl_3$): 22.7 (CH_3), 32.5 ($\underline{C}(CH_3)_2$), 46.3 (CH_2), 64.4 (OCH_3), 81.9 (CH), 139.3 ($\underline{Ar}NO_2$, $\underline{A}rCH$).
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19. We find that molecular clips **1** and **2** do not lead to polychlorination of the *o*-cresol, nor to chlorination of the clip itself when the clip is not present in excess. When clip **1** is exploited in excess, it does become mono-chlorinated once all *o*-cresol has been chlorinated.[18] Dynamic range issues effectively limit precise 500 MHz intensity measurements to ratios but problems are not expected below ratio values of 100 (Fisher, J., personal communication). All $R_{p/o}$ ratio measurements were made using 500 MHz NMR spectroscopy with extended relaxation delay times (>3 s) as reported in a previous study (Ref. 13).
20. 1:1 Association constants, K_a, (as supported by Job analyses) were determined by ^{1}H NMR titrations at 500 MHz on a Bruker DRX500 instrument at 298 K in freshly distilled $CDCl_3$ solvent referenced to internal TMS as 0 ppm. In each case concentrations of molecular clip **1** and **2** were measured precisely between 5.5 and 7.7 mM and the concentration of the guest component varied between 15-times and beyond the concentration of host as required for compliance with standard double reciprocal Benesi–Hildebrand treatments.[21] In each case, we have monitored the change in host aromatic signals [for molecular clip **1**] and backbone proton environments for molecular clip (**2**) upon increasing concentrations of guest molecule.
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22. Molecular mechanics and semi-empirical analyses were performed at the MM+ and AM1 levels respectively using the HyperChem 7.0 package (HyperCube Inc., 1115 NW 4th St., Gainsville, FL, USA).