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Folding-Promoted TBACl-Mediated Chemo- and Regioselective Demethylations of Methoxybenzene-Based Macrocyclic Pentamers

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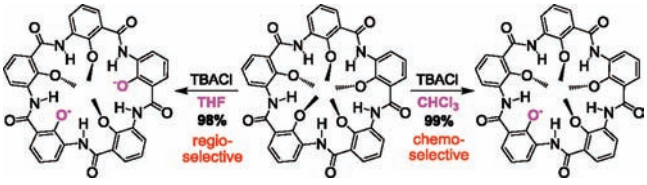
ABSTRACT



Tetrabutylammonium chloride (TBACl) salt alone has not been shown previously to be capable of removing methoxy groups. It is demonstrated here that the use of TBACl achieves efficient folding-promoted chemo- and regioselective demethylations, eliminating up to two out of five methyl groups situated in similar macrocyclic chemical microenvironments.

Differential reactivities along the foldamer backbones composed of repeating units of the same or similar types represent a newly discovered phenomenon that has been scarcely studied. The documented pioneering examples include reactive sieving on methylation of an *m*-phenyleneethynylene foldamer by Moore,[1a,b] selective N-oxidation[1c] and bromination[1d] of pyridine-based helical oligoamides by Huc, and selective hydrogenation of the carbonyl group of 1,10-anthraquinone oligoamides by Chen.[1e]

Internally placed intramolecular H-bonds have been recently shown to be capable of folding methoxybenzene-based[2] or other types of aromatic backbones[1d−e,3,4] into a crescent, circular, or helical structure. In particular, an appropriately sized oligomer such as pentamer **1** can take up a unique pentagon shape, crystallographically revealing the presence of two sterically bulky caps made up of three and two methyl groups that cover either side of the pentamer plane (Figure 1).[2d−h] These differently sized caps twist the pentameric backbone, making it deviate from a planar geometry (Figure 1b−c) and introducing an energetic penalty onto the stability of the pentamer molecule. Indeed, the crowding involving the five interior methyl groups destabilizes the molecules by 2−3 kcal/mol via a stronger E_O repulsion between two *ortho* methyl groups and weaker E_M repulsions among *meta* methyl groups at the B3LYP/6-311+G(d,p) level (Table S1) and, subsequently, may alter the reactivity of these interior methoxy groups to varying extents. This further suggests that under suitable conditions the interior methoxymethyl groups possibly can be selectively removed to expose the cation-binding cavity blocked by hydrophobic methyl groups for the selective recognition of different cations as demonstrated by anionic pentamers **2**−**4**.[2e] Eliminating the interior methyl

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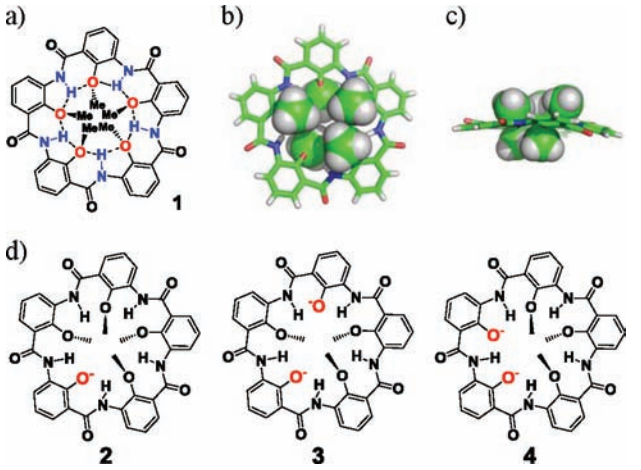

Figure 1. (a) Chemical structure of pentamer **1**. (b) Top and (c) side views of the crystal structure of **1** with methoxymethyl groups in CPK representations, illustrating the steric crowding involving the interior methyl groups.[2d] (d) Structures of anionic pentamers **2**–**4**. The interior methyl groups in anionc **2** point up and down alternatively as revealed by the crystal structure.[2e] Anionic **3** and **4** as shown are the computationally most stable conformers that differ from others by the orientation of the interior methyl groups.

groups not only releases the steric crowding but also generates intermediate anionic phenolates that result in the formation of stronger intramolecular H-bonds,[2e] further stabilizing the resultant anionic pentamers.

During the course of screening some known demethylation conditions[5] that either fail to produce detectable amounts of anionic pentamers such as **2**–**4** or result in a mixture of anionic pentamers containing up to four phenolate moieties (Table S2), we serendipitously found that addition of TBACl into a **1**-containing $CHCl_3$ solution slowly changed the solution from colorless to yellow after a few hours at rt. This color change took place even faster at 60 °C. Since it is highly unlikely for TBACl to form a stable complex with neutral pentamer **1**, certain unexpected reactions must have happened. With this in mind, **1** was treated with 20 equiv of anhydrous TBACl at 60 °C for 12 h in anhydrous $CHCl_3$, and aliquots of reaction solution were taken out at different time intervals for analysis by ^{1}H NMR (Figure 2b). By comparison with the ^{1}H NMR of monoanionic **2** recently reported by us[2e] that contains one

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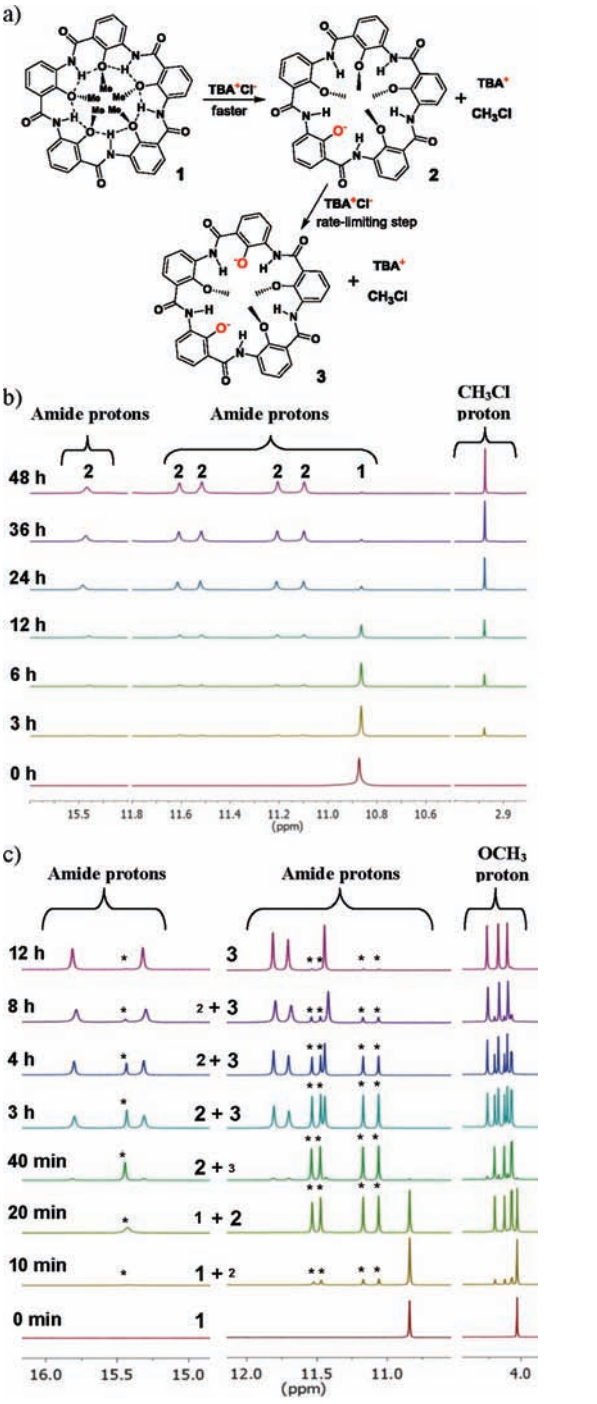

Figure 2. (a) TBACl-mediated demethylation mechanism that can be validated by ^{1}H NMR analyses of both (b) monoanionic **2** and CH_3Cl and (c) dianionic **3** via intermediate **2**, respectively, produced by treating **1** with 20 and 5 equiv of TBACl in anhydrous $CHCl_3$ and THF at 60 °C at different time intervals.

negatively charged O-atom and an array of methyl groups, pointing up and down alternatively (Figure 1d), a new set of ^{1}H NMR signals appearing at ~3 h is confirmed to arise from **2**. The reaction slowly proceeds to completion with a 99%conversion yield in two days with an increasingly intensified new peak at 3.05 ppm ascribable to the protons

from CH_3Cl, a product formed from the demethylation reaction. From these ^1H NMR based analyses, some conclusions can be confidently drawn: (1) TBACl-mediated demethylation allows for producing essentially pure forms of **2** in its anionic state; (2) the monodemethylation is chemoselective, removing one of the two *ortho* methyl groups that are immediately adjacent to each other and that point to the same hydrophobic side containing three methyl groups; and (3) the demethylation mechanism proceeds as shown in Figure 2a whereby a Cl^- anion attacks the methoxy carbon atom and removes the methyl group to produce a phenolate anion as found in **2**.

The observed chemoselectivity can be explained on the basis of the ring strain resulting from electrostatic repulsions among the five interior methyl groups. The repulsive $CH_3\cdots CH_3$ interactions engaging methyl groups can be classified to have two types according to whether the interacting methyl groups are *ortho* (E_O, Figure S1b) or *meta* (E_M, Figure S1b) to each other, with the former being stronger than the latter. The respective values of E_O and E_M in $CHCl_3$ were determined to be 1.57 and 0.27 kcal/mol at the B3LYP/6- 31G* level with the single-point energy calculation carried out at the B3LYP/6-311+G(d,p) level (Figures S1−S2 and Table S1). From these values, it can be estimated that the five interior methyl groups energetically destabilize **1** by 2.40 kcal/mol. From Figure 3a, it can be seen that **2**, $\mathbf{2_{II}}$, and $\mathbf{2_{III}}$ contain $2E_M$, $2E_M + 1E_O$, and $1E_M + 1E_O$, respectively. The absence of E_O repulsion in **2** makes **2** energetically more stable than $\mathbf{2_{II}}$ and $\mathbf{2_{III}}$ by 1.18 and 1.30 kcal/mol in $CHCl_3$, respectively. Accordingly, if demethylation takes place at one of the two methyl groups that are *ortho* to each other and whose methyl groups point to the same side, resulting in the formation of **2** where one *ortho* and one *meta* $CH_3\cdots CH_3$ interaction is eliminated, the folding-induced ring strain can be maximally released with regard to the removal of any one of the other three methoxy groups that eliminates only *meta* $CH_3\cdots CH_3$ interaction, producing either $\mathbf{2_{II}}$ or $\mathbf{2_{III}}$ (Figure 3a). The importance of folding-induced ring strain can be corroborated by the fact that, under the identical conditions, TBACl-mediated demethylation does not take place at all for a compound as simple as monomer **1a**, a macrocyclic repeating unit found in **1** (Figure 3b). A decreased nucleophilicity of the phenolate anions as a result of their participation in forming stronger intramolecular H-bonds[2e] is another reason why the resultant phenolate anions do not easily undergo further alkylation with the *in situ* generated CH_3Cl molecules. Additionally, the strong repulsive interactions among the possibly generated negatively charged O-atoms as in **3** or **4** may prevent the excessive demethylation from happening, resulting in the chemoselective removal of only one methyl group at an energetically more favored site in $CHCl_3$.

Screening against 20 equiv of anhydrous TBA salts was then carried out, and the demethylation efficiencies of these salts in terms of producing anionic **2** can be ranked in the order of TBACl (99%) > TBABr (84%) > TBAI (52%) > TBAF (0%). We also found that demethylation reactions can also be carried out in HPLC grade $CHCl_3$ (≤0.02% water) without comprimising the efficiencies and yields. A further test of other HPLC grade solvents such as acetonitrile (≤0.01% water), acetone (≤0.5% water), toluene (≤0.02% water), dioxane (≤0.2% water), dimethyl sulfoxide (≤0.2% water), and NMP (≤0.05% water) by using 5 equiv of TBACl at 60 °C for 12 h shows that (1) no demethylation occurs in acetonitrile and (2) a reaction mixture is produced that contains anionic **2** and **3** in most cases where other solvents are used. With the use of 20 equiv of TBACl in HPLC grade or anhydrous acetronitrile, dianionic **3** can be produced in 11% and 30% yields, respectively.

Highly desirably, the use of only 5 equiv of TBACl in anhydrous or HPLC grade THF (< 0.02% water) gives dianionic pentamer **3**, rather than **4**, as the regiospecific

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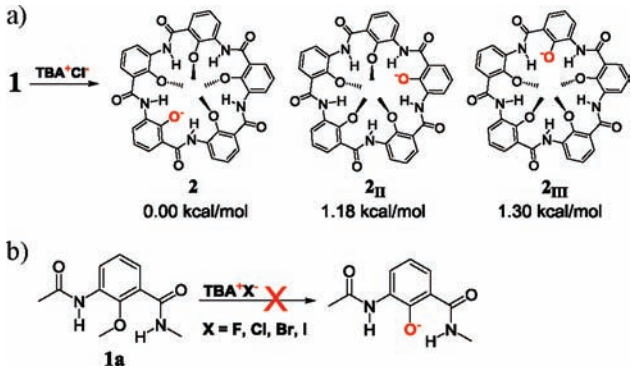

Figure 3. (a) Chemoselective demethylation of **1** produces **2** rather than $\mathbf{2_{II}}$ and $\mathbf{2_{III}}$. (b) TBAX salts do not mediate demethylation to a detectable extent on **1a**, a macrocyclic repeating unit of **1**. Relative energies in (a) were computed at the B3LYP/6-311+G(d,p) level in $CHCl_3$. Other energetically equivalent mirror images or isomers are not considered.

product in 98% yield (Figure 2c). The first new set of ^{1}H NMR signals appearing at ~3 min arises from **2**, and the second new set of ^{1}H NMR signals emerging at ~40 min comes from **3**. It is evidenced that the first monodemethylation reaction is rapid and a nearly complete conversion of **1** into **2** can be achieved in about 30 min, around which time **2** is maximally observed to reach a 97% yield (Figure 2c). A second monodemethylation, constituting the rate-determining step, then takes place detectably in ~40 min, transforming **2** into **3** with an accumulated yield of 3% within the first 40 min. It takes ~120 min from the start of the reaction to convert 50% of **2** into **3** and another 480 min to reach a 98% conversion of **2** into **3**. By comparing the relative energies of anionic **3** and **4** computed at the B3LYP/6-311+G(d,p) level in THF, the regioselective transformation of **2** into **3** rather than **4** becomes very obvious: the process producing **3** is energetically more advantageous than that producing **4** by 5.44 kcal/mol. Therefore, after the first chemoselective demethylation reaction, the second demethylation preferentially takes place at the methoxy group *meta* to the first demethylation site to produce **3**, avoiding producing strongly repulsive negatively charged *ortho* O-atoms as found in **4**. This also explains a lack of other anionic pentameric products containing more than two phenolate anions that invariably shall introduce strongly repulsive interactions between *ortho* phenolate O-atoms.

The TBACl-mediated didemethylation apparently proceeds in two sequential monodemethylation steps via **2** as the intermediate with the first monodemethylation step faster than the second step. Our calculations show that the repulsive *ortho* and *meta* $CH_3\cdots CH_3$ interactions are worth 1.61 and 0.27 kcal/mol in THF (Table S1), respectively. Transforming **1** to **2** by the first monodemethylation reaction therefore results in a release of molecular strain of ~1.88 kcal/mol by removing one E_O and one E_M interaction. This process is unfavorably accompanied by two repulsive interactions among a newly generated negatively charged phenolate O-atom and its two neighboring methoxy O-atoms (distances among the *ortho* O-atoms = ~3.4 Å, Figure 2a). Comparatively, producing **3** from **2** by the second monodemethylation step allows releasing a much smaller molecular strain worth about 0.27 kcal/mol by eliminating only one E_M interaction and undesirably, however, introduces four repulsive interactions among two negatively charged phenolate O-atoms and two adjacent methoxy O-atoms (Figure 2a). This smaller release in molecular ring strain coupled with the increased energetic penalty makes the second monodemethylation a rate-determining step in the TBACl-mediated didemethylation reaction in THF.

In short, we show here that highly efficient chemoselective monodemethylation and regioselective didemethylation, eliminating up to two out of five aromatic methyl groups, can be achieved by TBACl salt in an almost quantitative yield. This is a very surprising finding given that TBACl salt alone has not been demonstrated previously to be able to demethylate aromatic methoxy groups even though diverse demethylating reagents have been developed for varying purposes.[5] By combining with the one-pot synthesis of **1** in 46% yields,[2f,g] anionic **2** and **3** now can be prepared in just two steps with an overall yield of ~45% within a day rather than an ~10% yield after months of effort.[2e] Efficient construction of anionic pentamers such as **2**–**4** is important given their recently proven abilities to differentiate between Na^+/K^+ and Rb^+/Cs^+ ions in a highly selective and tight fashion.[2e] Along this line, we are currently exploring different demethylation methodologies for generating anionic pentamers of varying types to fine-tune the cation-binding affinities and selectivities.[2e]

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Supporting Information Available. Other demethylation conditions tested, general procedures for demethylations and *ab initio* computations on the repulsive interactions among interior methyl groups. This material is available free of charge via the Internet at http://pubs.acs.org.