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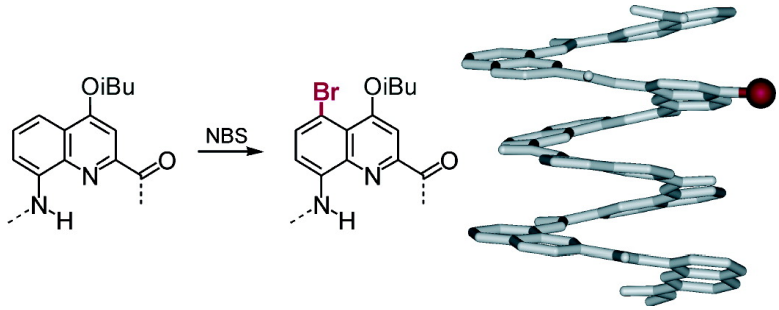

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Remote Substituent Effects and Regioselective Enhancement of Electrophilic Substitutions in Helical Aromatic Oligoamides

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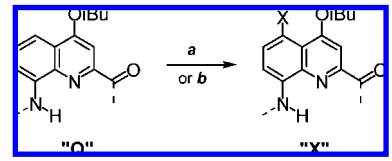
The selective chemical transformation of a multifunctional molecule often rests on the protection of the functions that may interfere in the process. In contrast, enzymes rely on their folded conformations to recognize their substrate and achieve selective transformations without any protecting groups. It might thus be inferred that, if the substrate itself adopts a well-defined folded conformation, specific environments might result that favor reaction at one function in the presence of others without the assistance of an enzyme or the use of protecting groups. Here, we present our discovery of enhanced and remarkably regioselective electrophilic substitutions in helically folded aromatic oligoamides. We also show that this selectivity much depends on the presence of substituents remote from the reaction site.

In solution, oligoamides of 8-amino-4-isobutoxy-2-quinolinecarboxylic acid, ("Q" in Scheme 1) adopt very stable helical conformations having 2.5 units per turn and a helix pitch of 3.5 Å.[1] This study was initiated by the identification of an unexpected byproduct during their synthesis. When tetrameric acid chloride O_2N-Q_4-Cl[2] obtained by refluxing O_2N-Q_4-OH in distilled $SOCl_2$ is coupled to amine H_2N-Q_4-OMe, the expected octamer O_2N-Q_8-OMe is produced[1b] together with a product with a similar retention coefficient (yield = 5−30%). Careful chromatographic separation followed by mass spectrometric and crystallographic analyses allowed us to unambiguously assign its structure to octamer $O_2N-Q_2XQ_5-OMe$. Remarkably, the third quinoline ring of this octamer carried a chlorine in position 5, a site that diverges from the helix and is exposed to the solvent (Scheme 1, conditions a).[3] We concluded that the third ring of tetramer O_2N-Q_4-OH had undergone partial and selective chlorination during activation. The occurrence of electrophilic chlorination in neat $SOCl_2$ is uncommon by itself. It could result from thermal decomposition of $SOCl_2$ into SO_2Cl_2 and S_2Cl_2.[4] But such selectivity is unprecedented and hints at some predisposition of the reaction site toward electrophilic substitution.

Systematic investigations of the bromination of Q oligomers were thus undertaken (Scheme 1, conditions b). Bromination with *N*-bromosuccinimide (NBS) was preferred because it is slower and easier to monitor by ^{1}H NMR than chlorination with NCS. As shown in Table 1, most reactions produced selectively if not exclusively one product and were also carried out on a preparative scale. Identification was made unambiguous by extensive crystallographic characterization (see Supporting Information). Figure 1 illustrates the time course of some of these reactions. Bromination of dimer O_2N-Q_2-OMe into $O_2N-QX-OMe$ (entry 1) is slow yet quantitative and was used as a reference. It showed that the nitro group completely prevented bromination of quinoline ring 1, and that bromination at ring 2 occurred exclusively at position 5. Under the same conditions, O_2N-Q_3-OMe was cleanly converted into O_2N-Q_2X-OMe. Bromination occurred at the third ring even though the second ring is less hindered, being the only one not involved in intramolecular aromatic stacking. Additionally, bro-

Scheme 1. Electrophilic Substitution of Quinoline-Derived Foldamers[a]



[a] Conditions: (a) $SOCl_2$, reflux (X = Cl); (b) NBS, $CDCl_3$, 40°C (X = Br).

Table 1. Products and Rates of Bromination of Various Oligomers[a]

entry	reagent	product(s)	initial rate[b]
1	O_2N-**QQ**$-OMe$[2]	O_2N-**QX**$-OMe$	3.1×10^{-4}
2	O_2N-**QQQ**$-OMe$	O_2N-**QQX**$-OMe$	4.5×10^{-3}
3	O_2N-**QQQQ**$-OMe$	O_2N-**QQXQ**$-OMe$[c]	1.1×10^{-2}
4	O_2N-**Q**$_8-OMe$	O_2N-**Q**$_2$**XQ**$_5-OMe$[d]	2.6×10^{-2}
5	Ac−**QQQQ**$-OMe$	mixture[e]	1.9×10^{-3}
6	NC−**QQQQ**$-OMe$[2]	NC−**QQXQ**$-OMe$	8.8×10^{-4}
7	NC−**QQ**$-OMe$[c]	NC−**QX**$-OMe$[c]	2.7×10^{-4}
8	O_2N-**QQQX**$-OMe$	O_2N-**QQXX**$-OMe$	3.6×10^{-5}
9	O_2N-**QXQQ**$-OMe$	O_2N-**QXXQ**$-OMe$	8.1×10^{-6}
10	cyclo-**QQQ**	cyclo-**Q**$_2$**X**, **QX**$_2$, **X**$_3$	3.4×10^{-4}[f]

[a] At 40 mM in $CDCl_3$ at 40 °C using 1 equiv of NBS. [b] In $mmol \cdot L^{-1} \cdot min^{-1}$, variations between duplicate or triplicate independent runs are less than 10%. [c] Some O_2N-**QQXX**$-OMe$ is also produced (<5%). [d] Other products become significant beyond 50% completion. [e] The rate reflects the sum of the products formed. [f] Corrected for degeneracy (/3).

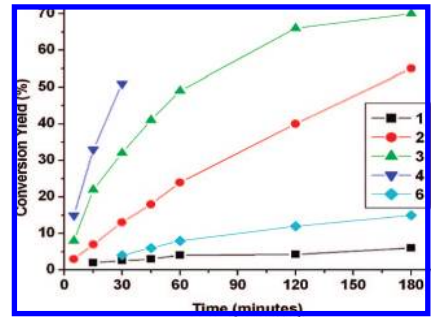


Figure 1. Time course of regioselective monobrominations. The numbers correspond to entries in Table 1. The lines are for guiding the eye only.

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mination was about 15 times faster than in the dimer. A common feature of the brominated quinoline rings in the dimer and the trimer is their position at the C-terminus of the strand. Yet, this feature plays no role as shown by the bromination of tetramer O_2N-Q_4-OMe (entry 3). This reaction proceeded even faster and produced selectively $O_2N-Q_2XQ-OMe$, consistent with the regioselective chlorination mentioned above. A small amount (<5%) of dibromo tetramer $O_2N-Q_2X_2-OMe$ was also identified. Even the octamer O_2N-Q_8-OMe is selectively monobrominated on ring 3 (entry 4), at a rate 85 times faster than the dimer; byproducts became significant (ca. 10%) only when the reaction was conducted beyond 50% completion. For example, residual electron density in the crystal structure of $O_2N-Q_2XQ_5-OMe$ suggested minor amounts of bromination on ring 5.

Our results thus showed that increasing oligomer length resulted in a rate enhancement as well as in a remarkable and surprising regioselectivity. In all cases, NMR showed no intermediates such as *N*-bromoamide or *N*-bromopyridinium in the bromination reaction. Additionally, no indication of preassociation of NBS with the helix, e.g., via intercalation, was observed. Besides, preassociation seems unlikely given that similar effects occurred when Cl_2 was the electrophile. It thus appears that the selectivity results from the *activation* of a particular position due to folding of the molecules.

We noted that, in the helically folded conformation, the site of bromination on ring 3 is relatively close in space to the terminal nitro group ($d = 3.5$ Å). To test whether the nitro group played any role, bromination was performed on acetamido tetramer $Ac-Q_4-OMe$ and, indeed, a complex mixture of products was obtained (entry 5). The reaction was also slower than with a terminal nitro group. However, cyano tetramer $NC-Q_4-OMe$[2] is brominated regioselectively on ring 3; the rate is 12 times slower than for O_2N-Q_4-OMe (entry 6). Cyano and nitro are both electron withdrawing substituents but of quite different strength. They do not possess other obvious common features and it is unclear how they could both favor the reaction on ring 3 through space. Additionally, the trend of reaction rates as a function of end group ($O_2N > CH_3CONH > CN$) is inconsistent with classical inductive or mesomeric donor and acceptor effects that would remotely propagate through the helix backbone. This was confirmed by the bromination of dimers O_2N-Q_2-OMe (entry 1) and $NC-Q_2-OMe$[2] (entry 7): both compounds are too short to possess any helicity and are brominated on ring 2 at comparable rates.

Further remote substituent effects were observed during the bromination of tetramers that already possess a bromine atom on ring 4 (entry 8, $O_2N-QQQX-OMe$) or ring 2 (entry 9, $O_2N-QXQQ-OMe$). Both tetramers were prepared by stepwise assembly of the corresponding monomers (see Supporting Information). In both cases, bromination occurred selectively on ring 3, as expected, but reactions were slower than that of O_2N-Q_4-OMe by factors of 300 and 1300, respectively—they thus reacted more slowly than a dimer. It should be pointed that bromine substituents on ring 2 or ring 4 are almost radially opposed to the reaction site on ring 3, at a distance around 12 Å.

The high stability of helically folded Q oligomers,[1,6] even in $SOCl_2$ (see Supporting Information), made it difficult to find media in which to monitor bromination of unfolded conformations. Yet, bromination in a nonhelical conformation could be assessed using the flat cyclo-Q_3 (entry 10).[1f] It proceeded at the same rate as for crescent dimer O_2N-Q_2-OMe and showed no substituent effect after the first and second bromination steps.

Taken altogether, these results show that (i) unusual regioselectivity and enhanced reaction rates resulted from a helical conformation of the oligomer; (ii) the distances between substituents are in some cases much too large for through-space effects to be involved; (iii) classical inductive or mesomeric substituent effects can also be ruled out. How does the helical aromatic backbone convey the effects of substituents? What is the exact origin of the rate enhancement and how is the steric hindrance expected in a helical conformation overcome? One may envisage that the large dispersive forces and ring current effects associated with tight aromatic stacking may enhance reactivity, and that regioselectivity might arise from local variations of steric hindrance associated with conformation dynamics such as helix springlike extension[5] or helix handedness inversion.[6]

The enhancement of a chemical reaction within a helical aromatic oligomer has been observed in two other instances, namely the quaternization of a pyridine ring into an *N*-methyl-pyridinium,[7] and the *N*-oxidation of pyridine rings.[8] Pyridine quaternization, *N*-oxidation, and aromatic electrophilic substitution all proceed through the intermediate build up of a positive charge on the aromatic backbone. It might be proposed that cation-π interactions come into play to stabilize transition states,[9] though this hypothesis was dismissed in the case of quaternization.[7d] The presumably larger polarizability of longer helices would then results in enhanced reaction rates.[9]

Our observation of the specific reaction of a given site in an oligomeric sequence in the presence of other, a priori equivalent, reaction sites is, to the best of our knowledge, unprecedented, and so are the remote substituent effects. Extensive additional investigations, including theoretical calculations will be necessary to elucidate these phenomena. The reaction behavior of conformationally folded aromatic oligomers emerges as a field full of surprises and new challenges for chemists.

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Supporting Information Available: Synthetic procedures, characterization of new compounds, NMR kinetic studies, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(2) In this abbreviation, the nitro or cyano groups replace the terminal NH.

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