Iodocyclization in Aqueous Media and Supramolecular Reaction Control Using Water-Soluble Hosts

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Supporting Information

ABSTRACT: Iodocyclization of 2-alkynylanisoles is an efficient route for synthesizing substituted benzofurans. Reaction efficiency with copper(II) sulfate and sodium iodide in an aqueous slurry under mild conditions is a manifold higher than in organic solvents. Water-soluble hosts of the cyclodextrin family solubilize the compounds in aqueous media and affect the reaction efficiency through conformation control and steric interactions. Computational chemistry and spectral titration provide information on the host−guest complex structure and insight into the mechanistic basis of the observed effects.

INTRODUCTION

Benzo[b]furans are frequently encountered structural cores in natural compounds1-4 and bioactive molecules.5-11 The significance of the benzofuran framework is evidenced from its ubiquity in plant products and prevalence as the central structures of several biomolecules, especially antimicrobials,12-14 analgesics,15,16 and anti-inflammatory agents.7,17 This biologically useful heterocyclic core structure is also part of several drug molecules (Figure 1).6,18,19 Given its practical significance, there is strong justification for the development of new and efficient synthetic routes to access benzofurans, especially in an environmentally benign and sustainable manner. Currently, there are several synthetic routes reported in the synthetic organic chemistry literature for these compounds that report excellent reaction yields and selectivity.13,14,20,21 However, there are very few reports on improving efficiency of these reactions in a sustainable manner consistent with the principles of green chemistry. We report a convenient and efficient method for the synthesis of substituted benzofurans through the iodocyclization reaction (Scheme 1) in an aqueous environment using economic, safe,

Scheme 1. The Iodocyclization Reaction Yielding Benzo[b]furan

and environmentally benign reagents (CuSO4 and NaI) under mild/moderate conditions. In the aforementioned reaction condition, iodocyclization conversions are at least thrice higher than the reaction in a polar protic solvent such as ethanol. There have been no reports on the in situ generation of I2 for iodocyclization of 2-alkynylanisoles and its efficiency in organic and aqueous media. This work features the unusual

Figure 1. Drug molecules containing a benzo[b]furan core structure.
phenomenon of an organic reaction in an aqueous slurry and the amenability of this reaction toward sustainable synthesis.

Water-soluble hosts, such as cyclodextrins (CDs), calixarenes, and micelles, have been often employed in influencing reaction rates of reactions in aqueous media; both increase (catalysis) and decrease (retardant) in reaction rates have been used to understand the characteristics of the reaction in the aqueous environment. Herein, we report our findings on the influence of cyclodextrin family on the iodocyclization reaction rates in an aqueous environment through encapsulation. Empirical findings of reaction rates coupled with spectral titration and computational investigations provide information about the structural aspects of the host–guest inclusion complex. In addition, the influence of hosts on the reaction rates has been studied in this work, which offers a unique insight into a previously unexplored mechanistic feature of the iodocyclization reaction.

**EXPERIMENTAL SECTION**

The starting substrate, 1-methoxy-2-(phenylethynyl)benzene (1a), was prepared based on the previously reported procedure.22 Stock solutions of the alkyne 1a in dichloromethane and aqueous solutions of copper sulfate and sodium iodide (separately) were prepared in standard flasks. The volume corresponding to the required mass of the substrate was pipetted into a glass vial and the solvent was evaporated off. To the resulting neat substrate in the vial, the required volume of aqueous solution of reagents was dispensed, followed by water to bring the solution to a specific dilution. Typical concentrations of the experiment are 0.3 mmol of the substrate in 25 mL of the aqueous medium. The durations and temperature of the reaction are specified in Table 1. Following the reaction, the slurry was diluted with water and subject to biphasic extraction by stirring the solution with ethyl acetate for 5 h. The organic layer was isolated, the solvent removed in vacuo, and the residue from the reaction analyzed spectroscopically. The proportions of the product and reactant as well as conversions were calculated based on the integration of peak areas in the 1H NMR spectra (Supporting Information) recorded on a 400 MHz Bruker AVANCE spectrometer.

For the reaction in organic solvent, 0.3 mmol of alkyne was dissolved in 10 mL of an appropriate solvent followed by the addition of specific amounts of CuSO4·5H2O and NaI. Additional solvent was added such that the final volume was 25 mL. The reaction solutions were stirred at the temperatures and for the durations in Table 2. Following the reactions, ethyl alcohol was removed in vacuo. Residue water and ethyl acetate were added to separate the organic and the inorganic components. The organic layer was separated and evaporated in vacuo after which the products were dried under high vacuum and characterized by 1H NMR spectroscopy.

NMR titration was performed by obtaining a saturated solution of 1a in water by sonicating ~7 mg of the compound in 2 mL D2O followed by removing the ppt through a syringe filter. Then, 0.6 mL of the filtered solution was subject to NMR titration with an addition of the powder form of cyclodextrin(s). Concentration of the saturated solution of 1a in water was sufficient enough to be observed in the spectrometer at with 64 scans.

Computational chemistry of the reactant and its host–guest complexes with cyclodextrin was performed using Gaussian 09 software package. Structures of host–guest complexes were calculated using the ONIOM multilevel theory function in the software. The host molecules (CDs) were treated at the molecular mechanics level (UFF) and the guests were treated at the HF 6-31G basis set. Geometric optimizations and frequency calculations were performed in the gas phase. All normal mode frequencies of optimized structures were positive.

**RESULTS AND DISCUSSION**

Iodocyclization Reaction. Mixtures of copper sulfate and sodium iodide generate molecular iodine (I2) in situ, and the cyclization of 2-phenethynylanisole (1a) is initiated by the electrophilic interaction of I2 with the alkyne. The mechanism of iodocyclization reaction is understood to proceed via the formation of a cyclic iodinium intermediate 3a (Scheme 2).23–25 This electrophilic attack triggers the electrocyclization process involving nucleophilic assistance from the conformationally predisposed ether functionality in the molecule. The

Table 1. Extent of Iodocyclization of 1a in Aqueous Slurry

| time  | ratio (sub/reagent) | conv (%) | temp  |
|-------|---------------------|----------|-------|
| 24 h  | 1:1:1               | 33       | 25 °C |
| 24 h  | 1:3:3               | 58       | 25 °C |
| 24 h  | 1:5:5               | 92       | 25 °C |
| 36 h  | 1:3:3               | 73       | 60 °C |
| 48 h  | 1:3:3               | 81       | 60 °C |

2Quantities of reactants in 25 mL water; 0.3 mmol substrate, relative ratios of CuSO4 and NaI listed in table.2Conversions are the average of three independent, but simultaneous, trials that yield standard deviations less than 5%.

Table 2. Extent of Iodocyclization of 1a in Homogeneous Media

| system     | time | ratio (sub/reagent) | conv (%) | temp  |
|------------|------|---------------------|----------|-------|
| methanol   | 24 h | 1:3:3               | 14       | 25 °C |
| 50% MeOH/H2O | 24 h | 1:3:3               | 45       | 25 °C |
| ethanol    | 24 h | 1:3:3               | 11       | 25 °C |
| ethanol    | 60 h | 1:5:5               | 52       | 25 °C |
| ethanol    | 24 h | 1:5:5               | 62       | 60 °C |

2Quantities of reactants in 25 mL of medium: 0.3 mmol substrate, relative ratios of CuSO4 and NaI listed in table.2Conversions are the average of three independent, but simultaneous, trials that yield standard deviations less than 5%.

Scheme 2. Mechanism of Iodocyclization Reaction
concomitant oxonium ion intermediate 4a reinstates its neutrality through the loss of the methyl group in the presence of the prospective counter-anion in the medium. Due to the involvement of an electrophilic attack in the first step and cationic intermediate that is in conjugation with aromatic rings, substituents with electronic effects greatly influence the reaction rates; electron donating groups increase the reaction rate, whereas electron withdrawing groups reduce the rate.

**Reaction in Homogeneous Aqueous Slurry and Organic Solvents.** Results from the experiments performed at different reagent concentrations, temperatures, and durations are outlined in Table 1. It is evident that even though the reaction mixture was heterogeneous (the reagents and substrates were not in the same macrophase) significant conversion was realized. This was an intriguing finding, as the common knowledge in organic synthesis is that maximization of the reaction speed requires complete solubility of the reactants. While this finding was surprising, trends in the influence of physical factors on the extent of conversion were as expected; conversions increased progressively with time, with an increase in concentration of reagents, and at higher temperatures.

The conditions employed in the slurry reactions presented in Table 1 are moderate. Near-quantitative conversion (greater than 90%) was achieved at room temperature and in the presence of 5 equiv of copper sulfate and sodium iodide for 24 h. Presence of slightly lesser amounts of reagents (3 equiv) still resulted in moderate conversions of around 50%. The extent of the reaction was significantly higher than that observed for the same reaction in organic media (vide infra). This observation provides an applied significance for our work due to its enhancement of the reaction rate as well as its green chemistry aspect; our work is now expected to be an example, among few others, where the reaction rate is higher in aqueous media compared to that in organic solvents. However, the most notable aspect of the experimental findings is that the reaction proceeds to a significant extent in an environmentally benign solvent, and that without the need of solubilizing agents such as surfactants or crown ethers.

To gain perspective regarding the efficiency of the slurry reaction, we compared the iodocyclization conversions to those in traditional reaction conditions, such as a solution in the organic solvent. Hence the experimental conditions outlined above were employed, except in this case where alcoholic organic solvents were used. Table 2 lists the conversions achieved in various solvents and binary solvent mixtures. The reaction conversions were overall significantly lower than those observed using aqueous slurry conditions. The conversions in pure organic solvents at room temperatures were quite low, wherein for the same duration, the conversion in the slurry was at least five folds higher. Similarly, the conversions were many folds higher at elevated temperatures, as well as in the presence of increased equivalents of the reagents. A comparison of the data in Tables 1 and 2 clearly establishes the fact that the reaction proceeds with a higher rate and improved efficiency in the aqueous environment than in the organic solvent. Time-dependent reaction conversion experiment followed by NMR provides a clear perspective on the progress of the reaction (Figure S4, Supporting Information) where the ratio between proton signals of phenylene (2a) and the methoxy (1a) is proportional to reaction conversion. The importance of water in enhancing the reaction rate is evident from the second entry in Table 2, wherein a 50% v/v mixture of methanol in water was used as the reaction medium. The reaction conversion increased noticeably (about three times higher) and was comparable to that of the reaction in water.

**Supramolecular Influence on Reaction Rate.** While solubility of the inorganic reagents in water increases, solubility of the substrate is starkly reduced. We hypothesized that increasing the solubility of the substrate, acting like a phase-transfer catalyst (PTC), might increase the reaction rate using solubilizing agents. Cavitands, especially cyclodextrins, have been used for this purpose. One specific example is the enhancement of the rate of cyclization of o-aminobenzamides due to its encapsulation reported by Wu et al.26 It is especially relevant due to its structural similarity involving ring closure to form a five-membered benzofuran ring, in which the authors demonstrated the role of CDs acting as a PTC as well as a possible catalyst in stabilizing the reactant transition state. Expecting a similar effect in our reaction involving cyclization of an o-substituted substrate, we employed cyclodextrins to act as a PTC thereby increasing reaction rates (Figure 2). Three cavitands from the cyclodextrin family were used to solubilize the reactant in the aqueous environment (Figure 3).

Cyclodextrins (CD) are bucket-shaped oligomeric structures composed of glucopyranose units (Figure 3, left). The hydroxyl groups of the glucopyranose on the circumference...
of the upper and lower rims of the CD render the molecule water-soluble, while the inner hydrophobic cavity encapsulates smaller organic compounds, such as the substrate (1), in water. The hexameric, heptameric, and octameric oligomer macrocycles are termed α-, β-, γ-CD respectively.

The electrocyclization was performed in aqueous under identical conditions at room temperature as discussed earlier in the presence of 3 equivalents of each CD oligomer (Table 3).

Table 3. Extent of Iodocyclization of 1a Complexed by Water-Soluble Hosts in the Presence of Three Equivalents of Host at 25 °C in the Presence of Five Equivalents of Reagents

| system  | duration | % conv  |
|---------|----------|---------|
| α-CD    | 24 h     | 39      |
| β-CD    | 12 h     | 66      |
| β-CD    | 24 h     | 82      |
| γ-CD    | 12 h     | 73      |
| γ-CD    | 19 h     | > 95    |

“Quantities of reactants in 25 mL water: 0.3 mmol substrate, 1.5 mmol of CuSO4 and NaI; conversions are the average of three independent, but simultaneous, trials that yield standard deviations less than 5%.

Whereas, near quantitative conversion was achieved in an aqueous slurry reaction in 24 h, inclusion of substrate 1a within the smallest oligomer, α-CD, resulted in a 2.4 fold decrease in conversion. This was contradictory to the expected rate enhancement based on the originally hypothesized PTC advantage. Similar outcome was observed for the next larger oligomer β-CD, though the decrease in reaction rate was not as dramatic. The effect of the largest oligomer, γ-CD, continued in the same trend, except in this case an enhancement in conversion was observed compared to the slurry reaction. Near quantitative conversion was observed for γ-CD in less than 20 h, a significantly higher conversion than the corresponding reaction for water in 24 h. This suggested that the effect of CDs on the reaction rates were highly dependent on their cavity sizes suggesting a strong supramolecular control on the reaction mechanism as opposed to a simple PTC phenomenon.

Computational Chemistry. We aimed to understand the effect of CDs on the reaction rates based on the computed geometry of inclusion complexes. Geometry-optimized structures of reactants, products, and their complexes with β-cyclodextrin (all in gas phase) were studied. Initial analysis of the computational structures of the reactant 1a optimized in gas phase (HF 6-31G, Figure 4) and in an aqueous medium (SE PM6, Supporting Information) suggested that the molecule could adopt two possible conformations corresponding to a local minima: one in which the methyl group is pointed away from the alkyne group (conformation 1, C1), and the second in which the methyl group is pointed towards it (conformation 2, C2). Conformation 2 was less stable than conformation 1 in both levels of theory, perhaps due to the possible increased steric interaction between the methyl and alkynyl groups. Based on this information, we realized that our in silico studies should involve complexes of reactants with the CDs in C1 and C2 conformations as well.

$$\Delta \Delta G_{\text{stabilization}} = \Delta G_{\text{nonreactive conf}} - \Delta G_{\text{reactive conf}}$$

In the nonreacting conformation (C1), the methyl group is pointed perpendicular to the alkynyl moiety while in the reactive conformation (C2) it is pointed away, resulting in oxygen’s lone pair predisposed for cyclization. The energies of geometry optimized structures of both conformations in the three CD hosts were performed in two-level ONIOM calculation with the lower level theory (MM, UFF) applied to host and the higher-level theory (HF-6-31G) applied to the guests. Geometry-optimized structures in the gas phase suggested that both phenyl and the anisole rings are conveniently encapsulated within the host cavities. For our analysis, we studied only structures in which the anisole ring is encapsulated as an influence on its conformation will have the most influence on its mechanism.

Comparing the geometry-optimized structure of the reactant conformations C1 and C2 included within the cavity provided a possible explanation for the observed change. For the unbound reactant, computational chemistry suggests that the preferred conformation is the reactive geometry, presumably due to coplanarity of lone pairs for conjugation. Frequency calculations on the geometry-optimized structures allowed us to evaluate the thermochemistry of the isomeric complex structures: C1@CD vs C2@CD (Figure 5).

Comparison of the free energies of the complex formation showed that as the cavity size increases the stability of reactive conformation decreases and that of the nonreactive conformation increases (Figure 6). If stabilization of the reactive geometry (due to oxygen predisposition) is the only factor, then α-CD would be the most reactive and γ-CD the least; however, experimentally this is not the case. Therefore, the second factor that would influence the reaction rate is the accessibility of the molecular iodine to the alkyne moiety to form the cyclic iodonium intermediate. Based on the analysis of complex structures it is evident that as the size of cavity increases, the ability of iodine to react with the substrate would increase. While all CDs enhance the solubility of the substrate, the limited cavity volume of α-CD also imposes a steric barrier on the I2-substrate interaction, which reduces reactivity. On the other hand, the larger cavity volume of γ-CD is able to simultaneously encapsulate the substrate and the reagent while also conferring the solubility advantage for the host without imposing a steric hindrance, which increases the reaction rate; the ability of γ-CD to form ternary complexes is well-documented in literature.

Empirical Observation of Host-Guest Complex. Complex formation was experimentally ascertained through NMR host-guest titrations (Figure 7). Compound 1a is soluble enough in D2O (saturated solution) for 1H NMR analysis. Addition of aliquots of β- and γ-CDs showed peak broadening indicating complexation. Surprisingly, there was no observable shift in signals, which is unusual. The extent of peak
broadening was significant for γ-CD even at 1 equivalent, while it was minimal (though noticeable) for β-CD. The extent of peak broadening was similar for all nine aromatic protons, suggesting complexation of the host to both the phenyl and phenoxy sides. The presence of a single set of peaks indicated complexation kinetics faster than the NMR time scale, consistent with a weak complexation dynamic typically observed for CDs in general.

Complexation of the guest to CDs was further ascertained through UV−vis and fluorometric titrations (section D, Supporting Information). UV−vis titration of 1a with β-CD showed increase in extinction coefficient of the chromophore (absorbance increase) with each addition. Similarly, there was a significant decrease in fluorescence of the chromophore in the presence of the host compared to that of the free guest. Spectral analysis of guest 1a in the presence and absence of water-soluble hosts indicated inclusion complex formation, which considered along with the NMR titration experiments, confirmed inclusion of the guest within the cavitand. Therefore, the changes in reaction conversion that we observed in our experiments were evidently the result of supramolecular (weak) interactions between the host and guest.

Figure 5. Geometry-optimized of host−guest complex of 1a bound to CDs and relative stabilities based on free energies of formation as deduced from eq 1.

Figure 6. Chart showing the trend in stabilization energy of the nonreacting conformer (ΔΔGstabilization eq 1, maroon, left axis) and its correlation with experimental reaction conversion (green, right axis).

Figure 7. Partial ¹H NMR spectra of the saturated solution of 1a in D₂O (top) and its complexes with two equivalents of β-CD (middle) and γ-CD (bottom).
Effect of Substituents. The effect of substituents on the reaction outcome, performed under the reported conditions, was explored. Two additional substrates were used, namely 4-methoxy- and a 4-cyano-substituted derivatives. As iodocyclization involves a cationic iodonium intermediate, it is expected that electronically activated substrates would enhance the reaction rate and vice versa. The 4-methoxy derivative of 1a underwent near quantitative conversion in 20 h under unmediated conditions, while the 4-cyano derivative resulted in no significant conversion under similar conditions (Table 4). These results were consistent with expectations. Similar to the experiments with 1a, the reaction was performed in the presence of CDs. Consistent with the earlier findings, the reaction conversions were enhanced for all substrates, substantiating our hypothesis that the complexation of substrates to CDs increases interaction between I₂ and the alkynyl bond along with PTC effect.

### Table 4. Substituent Effect on Extent of Reaction in Presence and Absence of Macrocyclic Cavitand 

| R        | time | conv (%) |
|----------|------|----------|
| Phenol   | 20 h | >95      |
| Acetone  | 20 h | >95      |
| Cyano    | 36 h | 11       |

“Quantities of reactants in 25 mL water: 0.3 mmol substrate, in the presence of five equivalents of reagents and three equivalents of host; conversions are the average of three independent, but simultaneous, trials that yield standard deviations less than 5%.

**CONCLUSIONS**

This work reports enhancement of the iodocyclization reaction of 1-alkoxyphenyl-2-phenyl acetylene in the presence of copper sulfate and sodium iodide to yield the corresponding benzofuran. The reaction has been observed to proceed faster in an aqueous environment as a homogeneous slurry than in the solution in organic solvents. We speculate that this is due to the increased solubility of the inorganic reagents in water leading to an increase in the local concentration of the reactants and reagents. High reaction conversions were achieved under moderate conditions in an environmentally friendly solvent. We attempted to improve the reaction conversions by utilizing solubilizers to enhance the aqueous solubility of the substrate, which yielded mixed results: the large host γ-CD enhanced reaction rate compared to the aq slurry while the smaller hosts showing reduced rates exhibiting a clear size-dependent trend. Energy-minimized structures of the reactant and the complex suggested that the gradation in reaction rates is due to the differential stabilization of two different conformations (reactive and nonreactive) of the substrate. While all three hosts increase solubility of the substrate in water, the smaller hosts also prevent their reactivity through steric hindrance; the larger cavity volume of γ-CD does not impose such physical limitation, which results in an overall rate enhancement.

**ASSOCIATED CONTENT**

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.9b02466.
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