Phase-transfer-mediated electrochemical reaction: anodic disulfide bond formation under biphasic condition

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ABSTRACT

The use of bromide ion as a redox mediator promotes electrochemical reactions in the non-conductive cyclohexane phase. Anodically oxidized species of bromide ion in the conductive methanol phase can bring oxidizing power across phases to induce oxidative disulfide bond formation of a hydrophobically-tagged tripeptide, which is located predominantly in the cyclohexane phase. In addition to commonly used tetraalkylammonium salts, inorganic sodium salt can also be effective alternatives for the bromide source.

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Introduction

Chemical events between two substances located in different phases of a heterogeneous mixture are often ineffective because the accessibility of reagents is limited. A typical example is an organic molecule and an inorganic salt in a biphasic solution of a less-polar solvent and water in which the reaction is generally slow or sometimes barely takes place. Phase-transfer catalysis, which facilitates the migration of a reactant from one phase into another phase, has been proposed to solve this problem.[1] This early finding has led to the development of chiral phase-transfer catalysts that have been widely applied in academic research and industrial production.[2]

Organic electrochemistry has provided a straightforward method to trigger electron transfer events at the surface of electrodes, including anodic oxidation and cathodic reduction, which can generate reactive intermediates.[3] The fundamental limitation for this methodology is the requirement of conductivity, namely, the solvent must be sufficiently polar to dissolve the ionic supporting electrolyte. This also means that substrates should be less hydrophobic to maintain a homogeneous condition; otherwise they are not able to access the surface of electrodes effectively, severely inhibiting electron transfer events. In a similar fashion to a phase-transfer catalyst, a 'phase-transfer mediator' that can bring anodic oxidizing and/or cathodic reducing power across phases could

significantly enhance the utility of this methodology, especially for hydrophobic substrates that are not soluble in polar electrolyte solutions. Although various redox mediators have been developed and have found creative applications in organic electrochemistry,[4] the construction of mediators that function across phases in biphasic conditions remains challenging.

We have been developing soluble tag-assisted chemistry, which employs hydrophobic benzyl alcohols as supports for various organic processes.[5] The tagged substrates are soluble in less-polar solvents to realize effective liquid phase reactions, also enabling selective precipitation or extraction from polar solvents that can facilitate their separation. Our ongoing challenge is to apply the tagged substrates for electrochemical reactions, mainly focusing on how to obtain homogeneous solutions suitable for both the hydrophobic tag and ionic supporting electrolyte. We have demonstrated two strategies so far, one uses a tetrahydrofuran/methanol monophasic mixture[6] and the other takes advantage of a 'thermomorphic' cyclohexane/methanol biphasic mixture,[7] where the system is heated to form a monophasic, relatively 'less-polar' electrolyte solution. When oxidative disulfide bond formation was used as a model for the former strategy, we found that both direct anodic oxidation of the tagged substrate and an indirect mediated mechanism can occur. If the mediator can bring anodic oxidizing power across the phases, it might function even in a biphasic mixture. Described herein is a 'phase-transfer-mediated' electrochemical reaction in which the desired anodic disulfide bond formation can be induced in such a biphasic mixture where the substrate cannot access the surface of the electrodes.

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Results and discussion

The present work began with the investigation of a biphasic cyclohexane/methanol mixture as a potential electrolyte solution. 1.0 M lithium perchlorate/methanol formed a clear biphasic solution with cyclohexane in the presence of a tagged tripeptide (**1**), even after vigorous mechanical stirring. Lithium perchlorate was exclusively located in the methanol phase; only <1% was recovered from the cyclohexane phase. On the other hand, the tagged tripeptide (**1**) was predominantly recovered from the cyclohexane phase, while <0.1% was located in the methanol phase. The cyclohexane phase had no reasonable conductivity, in that cyclic voltammetry did not show any redox wave.

Under this condition, the tagged cyclic peptide (**2**) was not obtained and starting tagged tripeptide (**1**) was recovered even after 4.8 F/mol of electricity was passed through the solution (Table 1, entry 1). This result clearly shows that the tagged tripeptide (**1**) hardly accesses the surface of the electrodes which are located in the methanol phase. As expected when 10 mM of tetraethylammonium bromide was added to the biphasic mixture as a redox mediator, disulfide bond formation took place to give tagged cyclic peptide (**2**) (Table 1, entry 2). The addition of tetraethylammonium bromide did not affect the localization of either lithium perchlorate or tagged tripeptide (**1**), which suggested that the anodically oxidized species of bromide ion was able to induce the disulfide bond formation of tagged tripeptide (**1**) located in the cyclohexane phase (Scheme 1). Whether the reaction occurred at the interface between the two phases or in the cyclohexane phase is unclear, however, the anodic oxidizing power was indeed brought across over the phases. We also found that a lower concentration of tetraethylammonium bromide gave better results to give purer tagged cyclic peptide (**2**) (Table 1, entries 3 and 4). Because the tagged cyclic peptide (**2**) was exclusively located in the cyclohexane phase, only liquid–liquid extraction was required as a work-up.

Table 1
Optimization of the reaction condition for a phase-transfer-mediated anodic disulfide bond formation
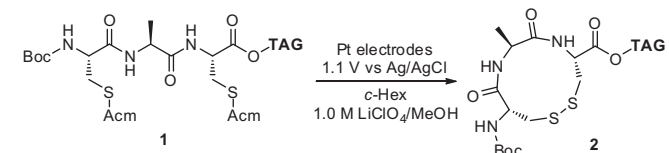
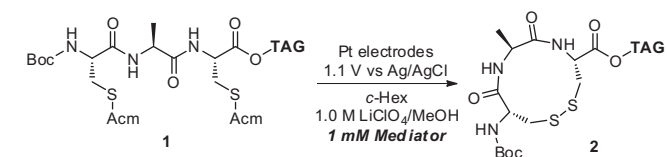| Entry	Mediator	Yield[a]
1	–	0 (100)
2	Et$_4$NBr (10 mM)	49 (3)
3	Et$_4$NBr (6 mM)	86 (0)
4	Et$_4$NBr (1 mM)	87 (0)

[a] Recovered tagged tripeptide (**1**) was reported in parentheses.
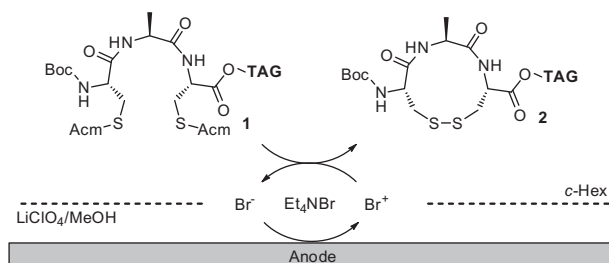
Scheme 1. Possible reaction mechanism of a phase-transfer-mediated anodic disulfide bond formation.

Table 2
Phase-transfer-mediated anodic disulfide bond formations using several redox mediators

| Entry	Mediator	Yield[a]
1	Et$_4$NBr	87 (0)
2	Bu$_4$NBr	86 (0)
3	NH$_4$Br	42 (37)
4	LiBr	57 (27)
5	NaBr	77 (4)
6	KBr	34 (48)
7	NaCl	6 (74)
8	NaI	30 (60)
9	PyHBr	81 (0)

[a] Recovered tagged tripeptide (**1**) was reported in parentheses.

With the phase-transfer-mediated anodic disulfide bond formation in hand, we then focused on various redox mediators (Table 2). As expected, tetrabutylammonium bromide gave a comparable result (entry 2), while ammonium bromide negatively affected conversion (entry 3). At first glance, this could be because tetraalkylammonium ions are required, similar to typical phase transfer catalysts. However, we found that inorganic sodium bromide was an efficient alternative (entry 5). Additionally, lithium bromide gave a moderate yield (entry 4) while potassium bromide seemed to be a poor redox mediator (entry 6), generating a large amount of unidentified by-product, apparently due to its poor solubility. Furthermore, we also tried other sodium halides (entries 7 and 8); however, neither chloride nor iodide were effective redox mediators. These sodium halides possibly contain trace bromide, which might induce the disulfide bond formation at low levels. It should be noted that pyridinium bromide was also able to offer an alternative to the use of tetraalkylammonium bromides (entry 9).

It has been well-documented that an intramolecular disulfide bond formation in tripeptide sequences is not favorable,[8]

Table 3
Phase-transfer-mediated anodic disulfide bond formations in several tagged tripeptides
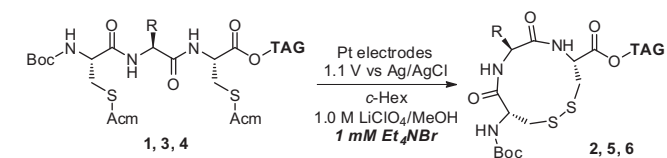
Entry	Side chain	Yield[a]
1	**1, 2** (Ala)	87 (0)
2	**3, 5** (Leu)	80 (2)
3	**4, 6** (Phe)	84 (0)

[a] Recovered tagged tripeptide (**1**) was reported in parentheses.

apparently due to their relatively constrained small ring sizes, while such a disulfide motif is commonly found in tetrapeptide sequences, especially in the active site of thiol-disulfide oxidoreductases.[9] Therefore, we finally prepared the tagged tripeptides (**3**, **4**), containing bulky side chains, which might inhibit the intramolecular disulfide formation. To our satisfaction, the anodic disulfide bond formations took place effectively under optimized biphasic condition to give the corresponding tagged cyclic peptides (**5**, **6**), respectively (Table 3, entries 2 and 3).

Conclusion

In conclusion, we have developed a phase-transfer-mediated electrochemical reaction using anodic disulfide bond formation as a model. Bromide ions derived from tetraalkylammonium and sodium salts can function as efficient redox mediators in a cyclohexane/methanol biphasic mixture. Although further experiments are required to understand the whole picture of the reaction mechanism, the results described herein suggest that anodic oxidizing power can be brought across phases, which may broaden the applications of organic electrochemistry.

Acknowledgment

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.04. 116.

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