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Redox-Induced Conformational Alteration of *N*,*N*-Diarylamides

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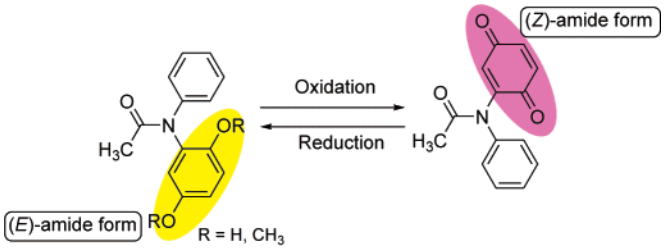
ABSTRACT



We constructed a novel molecular conformational alteration system with an *N*-aryl-*N*-phenylacetamide structure, in which the *N*-aryl group consists of a hydroquinone–*p*-quinone system as a redox-dependent aromatic trigger. The amide conformation depended on the oxidation state of the aryl group, and the two states (compounds 2 and 3) were reversibly converted to each other by redox reactions. Such compounds would be applied as useful structural units for external stimulus-responsive control on the shape and function of large molecules or supramolecules.

The three-dimensional structural and the dynamic behavior of a molecule is an important issue for regulating the molecular function or biological activity.[1] Although it is not easy to control or predict the shape of a large molecule or supramolecule, sometimes conformational change of a small unit can work as a hinge or a trigger of a larger system including functional synthetic polymers and proteins.[2] In such a case, small functionality bearing the conformational alteration in response to external stimuli is of major interest.[3] Thus, molecules that change conformation, depending on pH, solvent, temperature, and so forth, have been developed. On the other hand, redox reaction is very important because many biochemical, electrochemical, and chemical reactions involve redox processes. However, only a few compounds exhibiting redox-induced conformational changes have been reported.[4]

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Among many types of structural units, we have been interested in amide structures, which play important roles in both proteins and many bioactive molecules.[5] We found unique structural properties of aromatic amides, and some of them exhibit external stimulus-responsive conformational alteration.[6−8] Here, we describe a novel molecular system based on redox-responsive alteration of amide conformation.

The hydroquinone−*p*-quinone system was chosen as the redox-dependent aromatic moiety, and was introduced on the amide nitrogen atom of acetanilide. Thus *N*,*N*-diarylacetamides **1**−**3** were designed as redox-responsive molecules (Figure 1).

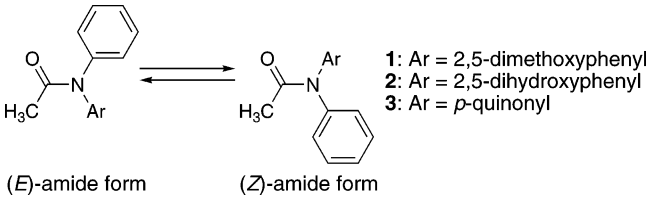

Figure 1. Redox-responsive *N*,*N*-diarylacetamides.

The amides **1**−**3** were synthesized from 2,5-dimethoxy-*N*-phenylaniline by the usual method, and their crystal structures were analyzed (Figure 2). The hydroquinone

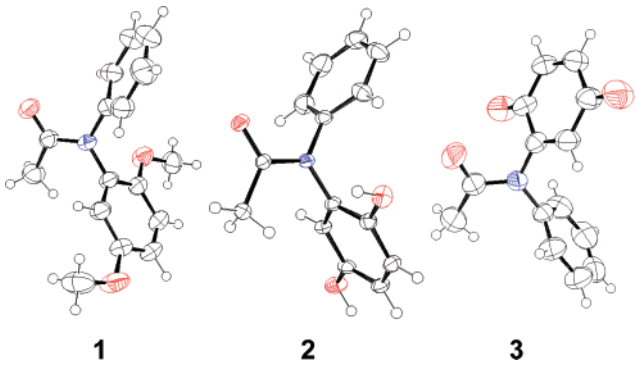

Figure 2. Crystal structures of the amides **1**−**3**.

derivative **2** exists in (*E*)-amide conformation, while the oxidized amide **3** exists in (*Z*)-amide conformation. The dimethoxyl derivative **1**, which lacks intermolecular hydrogen-bonding ability, also exists in (*E*)-amide conformation, like **2**. Each amide exhibits significant distortion of the amide−*N*-aryl framework from planarity.[9]

The conformational preferences, due to electronic repulsion between the carbonyl and the aryl groups, appear consistent with the relative π-electron densities of the two *N*-aromatic parts.[10] Thus the more π-electron-rich *N*-aryl group located trans to the amide oxygen atom (Figure 3). The tendency is

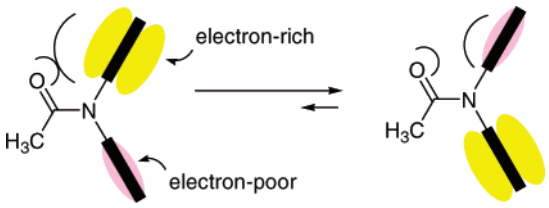

Figure 3. Conformational alteration caused by π-electron density.

also observed in the pH-dependent switching system of acetanilides.[6]

To investigate the conformational preferences of these amides in solution, ^{1}H NMR measurements were performed at various temperatures. Each amide afforded a spectrum with one set of signals at 303 K, whereas the signals of two conformers appeared at low temperature. The major conformers of **1** (73%) and **2** (77%) were assigned as (*E*)-amides based on the chemical shifts and NOE data (Table 1). This

Table 1. Conformational Analyses of Amides by ^{1}H NMR Measurement

amide	major conformer	major ratio (%)	temp (K)	solvent	$\Delta G°$ [a] (kJ/mol)
1	*E*	73	213	CD_2Cl_2	−1.8
2	*E*	77	253	CD_3OD	−2.5
3	*Z*	95	178	CD_2Cl_2	+4.4

[a] $\Delta G° = \Delta G°(E) - \Delta G°(Z)$

was confirmed by time-course measurement after sample preparation at low temperature (Supporting Information). Thus, the crystal of **1** was mixed with frozen CD_2Cl_2 at 143 K and the ^{1}H NMR spectrum was measured when the temperature reached 203 K. The major peak of the acetyl group of compound **1** was predominant, but with the passage

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(9) The dihedral angles between the amide plane and the dioxyphenyl and phenyl planes were 80.61° and 62.45° for **1**, 88.72° and 80.09° for **2**, and 65.11° and 77.80° for **3**, respectively.

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of time at 203 K, a minor peak appeared, with a rate constant of 4.2×10^{-5} s^{-1} (from *E* to *Z* isomer).

On the other hand, the quinone form **3** existed predominantly (95%) in (*Z*)-amide conformation, as assigned from the chemical shifts and NOE data.[11] The major conformers of these amides **1**−**3** in solution are consistent with the crystal structures, with the amide oxygen atom being located trans to the more electron-rich *N*-substituents.

Redox properties of these amides were investigated by cyclic voltammetry. Figure 4 shows the voltammograms of

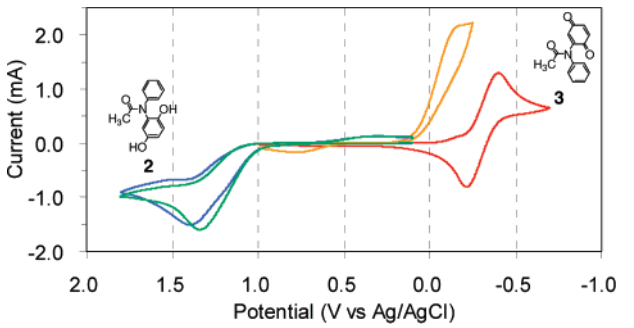

Figure 4. Cyclic voltammograms of **2** (blue curve), **2** containing 200 equiv of acetic acid (green curve), **3** (red curve), and **3** containing 200 equiv of acetic acid (orange curve). Each sample was measured in an acetonitrile solution (4.0 mM) containing 0.1 M tetra-*n*-butylammonium perchlorate at a platinum electrode. Sweep rate: 100 mV/s.

2 and **3** in the presence of excess acetic acid as a proton source, and in its absence. An irreversible oxidation wave was observed for **2** in the presence or absence of acetic acid, resulting from oxidation of the hydroquinone moiety. In contrast, **3** showed a reversible redox wave, which became irreversible and shifted to the positive direction in the presence of acetic acid, due to reduction of the quinone moiety. These irreversible redox waves in the presence of acid suggest that electrochemical conversion can occur.[12]

Based on these data, the electrochemical interconversion was investigated.[13] The amide **2** was oxidized in a constant potential manner at +1.40 V (vs Ag/AgCl) to give **3** in 82% yield, and **3** was reduced similarly at −0.15 V with acetic acid as the proton source to give **2** in 92% yield. The electrochemical redox reaction can be carried out reversibly, and therefore amide conformational alteration under redox control is suitable for providing direct output.

In summary, the aromatic amides **1** and **2** exist in (*E*)-amide form, while **3** exists in (*Z*)-amide form, both in the crystal and in solution. Redox reaction of the hydroquinone−benzoquinone moiety on the acetamide skeleton could be performed reversibly, and would be accompanied by amide conformational alteration (Figure 5). This system provides

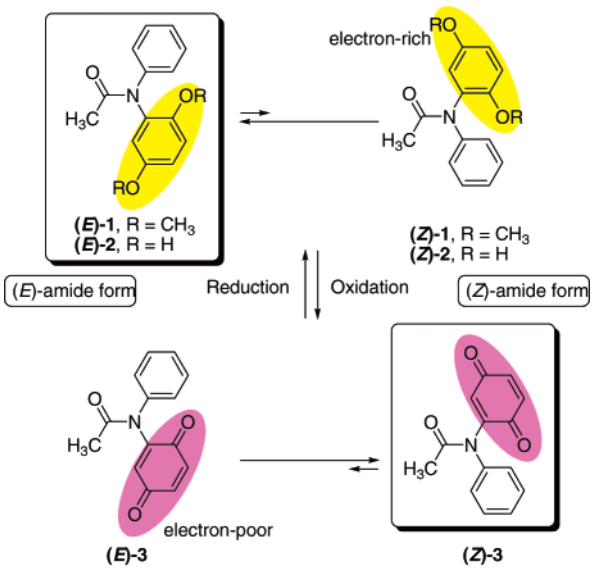

Figure 5. Redox-dependent conformational alteration.

a simple example of conformational alteration, in which the redox reaction controls the predominant amide conformation in equilibrium. These results are also important in order to understand the behavior of *N*-quinonyl-type bioactive compounds in nature.[14] At the same time, this redox-responsive type of conformational control has wide potential for controlling the shape and function of large molecules or supramolecules.

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Supporting Information Available: Experimental details for synthesis and electrochemical reactions, ^{1}H NMR spectra, and X-ray crystallographic data for **1**, **2**, and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Similar preference was observed in THF-d_8 at 168 K, thus **3** exists in (*Z*)-amide form predominantly (96%).

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(13) Electrochemical oxidation was performed in a solution of 0.1 M tetra-*n*-butylammonium perchlorate in acetonitrile, using platinum mesh as working and counter electrodes, and Ag/AgCl electrodes as the reference for constant potential oxidation. Acetic acid (200 equiv) was added as a proton source. Constant potential reduction was performed similarly.

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