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Published on Web 06/16/2010

Nitrone [2]Rotaxanes: Simultaneous Chemical Protection and Electrochemical Activation of a Functional Group

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Abstract: We report on the use of the hydrogen-bond-accepting properties of neutral nitrone moieties to prepare benzylic amide macrocycle-containing [2]rotaxanes in yields as high as 70%. X-ray crystallography showed the presence of up to four intercomponent hydrogen bonds between the amide groups of the macrocycle and the two nitrone groups of the thread. Dynamic ^{1}H NMR studies of the rates of macrocycle pirouetting in nonpolar solutions indicated that the amide−nitrone hydrogen bonds are particularly strong (~1.3 and ~0.2 kcal mol^{-1} stronger than similar amide−ester and amide−amide interactions, respectively). In addition to polarizing the N−O bond through hydrogen bonding, the rotaxane structure affects the chemistry of the nitrone groups in two significant ways: first, the intercomponent hydrogen bonding *activates* the nitrone groups to electrochemical reduction, a one-electron-reduction of the rotaxane being stabilized by a remarkable 400 mV (8.1 kcal mol^{-1}) with respect to the same process in the thread; second, however, encapsulation *protects* the same functional groups from chemical reduction with an external reagent (and slows electron transfer to and from the electroactive groups in cyclic voltammetry experiments). Mechanical interlocking with a hydrogen-bonding molecular sheath thus provides a route to an encapsulated polarized functional group and radical anions of significant kinetic and thermodynamic stability.

Introduction

The rich and diverse covalent chemistry of nitrones[1] [generally depicted as C═N$^+$(R)−O$^-$, although the C$^-$−N$^+$(R)═O canonical form makes a significant contribution to their properties] has led to their being exploited in many different ways: they serve as potent oxidants in many chemical reactions,[2] are readily reduced to amines and hydroxylamines,[3] and act as starting materials for various heterocyclic skeletons via cycloaddition reactions.[4] They have also found utility as diagnostic spin traps,[5] potential antioxidant therapeutics,[6] precursors to radical initiators for living and other controlled polymerizations,[7] and components in multifunctional materials.[8] However, with the notable exception of the α-nitronyl nitroxide organic magnet systems,[9] the use of nitrones and related synthons in molecular-level assembly processes remains largely unexplored, certainly in comparison with the use of ethers, amides, imines, ureas, and guanidinium units.[10] This is somewhat surprising given their desirable intrinsic properties: nitrones possess one of the largest dipole moments known for any functional-group type (3.37−3.47 D[11]), making them potentially useful for NLO applications and control of molecular orientation; they offer a simple route to stable radicals via one-electron electrochemical reduction[12] or conjugate addition to C═N followed by oxidation;[13] and the N$^+$−O$^-$ motif is a powerful hydrogen-bond acceptor.[14]

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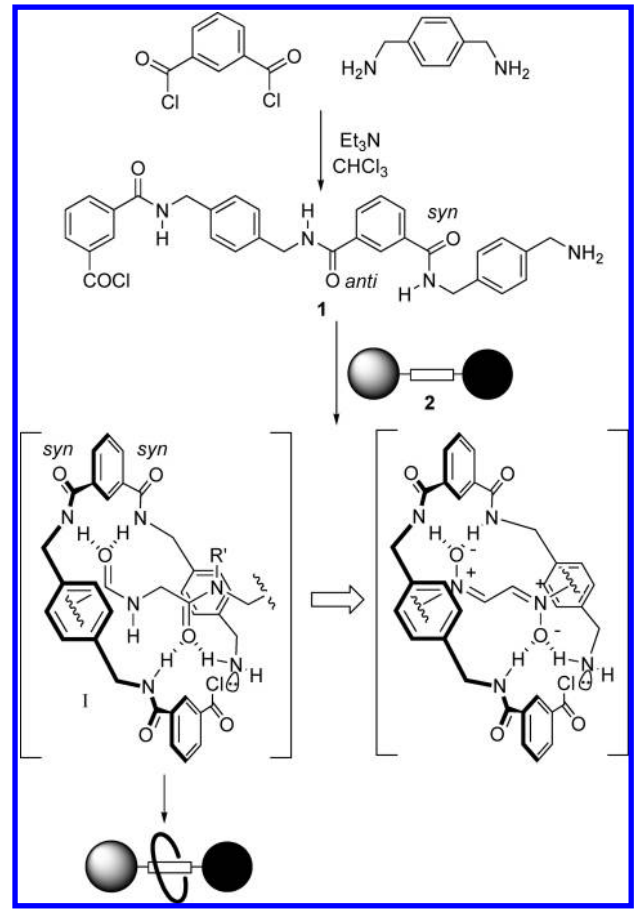
Hydrogen bonding has previously been used[15−24] to assemble benzylic amide macrocycles around various amide,[16,17] ester,[17,18] squaraine,[19] phenolate,[20] urea,[21] pyridone,[22] and ion-pair[23] templates to generate rotaxanes and catenanes.[25] Tuning of structural rigidity and preorganization has been reported to effect yields as high as 97% for [2]rotaxanes incorporating amide threads.[17] Although threading protocols using preformed macrocycles have been successfully used in some cases,[21,22,24] the poor solubility of most benzylic amide macrocycles in the nonpolar solvents needed to promote intercomponent hydrogen bonding has meant that templated assembly of building blocks about the thread to form the macrocycle is most often used to construct such rotaxanes.[15] These five-component "clipping"

Scheme 1. Hydrogen-Bonding Modes of Dipeptide and Bisnitrone Templates for Rotaxane Synthesis



reactions (Scheme 1) produce interlocked architectures because multipoint hydrogen bonding between the open-chain precursor **1** (which in the absence of a suitable template preferentially adopts a linear syn−anti conformation) and the thread **2** promotes a conformational change that brings the reactive end groups close together, leading to rapid cyclization of **1** about the axle.[16a,b,i,17] The key factors determining the efficiency of rotaxane formation in such reactions are the following:

(i) the spatial arrangement of hydrogen-bonding sites on the thread (ideally chosen so a low-energy conformation of the macrocycle precursor **1** can bind in a multidentate manner to the thread, as shown in **I** in Scheme 1);[16a,b]

(ii) the rigidity of the template unit (as few as possible internal degrees of freedom of the thread or intramolecular hydrogen bonds should be lost upon complexation with **1** to form **I**).[17]

(iii) the efficacy of the hydrogen-bonding motifs in the thread (e.g., amides are much more effective than esters).[17]

The majority of neutral hydrogen-bond-accepting groups employed in such threads to date have been amides, squaraine

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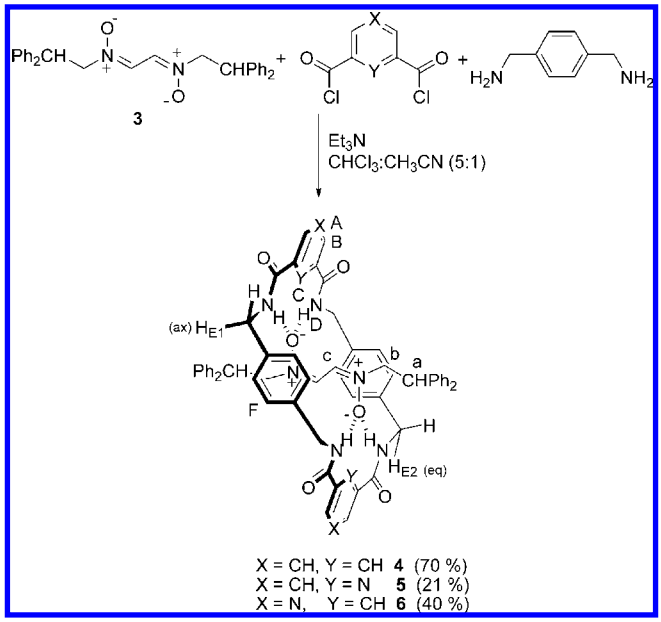
Scheme 2. Synthesis of Bisnitrone [2]Rotaxanes **4**−**6**



units (which have significant oxocarbon anion character), and esters.[16−19] However, the hydrogen-bond basicity of these carbonyl-based functionalities can be exceeded by other groups with significant ionic or mesomeric character, such as S^+-O^-, P^+-O^-, and N^+-O^-.[26] Accordingly, we decided to determine the effectiveness of employing nitrones as a hydrogen-bonding template for rotaxane formation and in turn investigate the effects of the mechanically interlocked architecture on the chemistry of nitrones.

Results and Discussion

Synthesis. The bisnitrone thread **3**, which features the two oxygen atoms at a separation and relative orientation similar to those of the amide carbonyls in a dipeptide, was prepared in three steps from diphenylacetaldehyde (see the Supporting Information). Solutions containing 6.0 molar equiv of isophthaloyl dichloride and 6.6 molar equiv of *p*-xylylenediamine were slowly added to **3** in a stirred anhydrous solution of 5:1 $CHCl_3/CH_3CN$ (Scheme 2). After the addition was complete, no unconsumed thread **3** could be detected in the reaction mixture by thin-layer chromatography. Filtration and purification by flash chromatography on silica gel ($CHCl_3$/MeOH as eluent) yielded the bisnitrone [2]rotaxane **4** in 70% yield.[16e] Under analogous conditions, replacing isophthaloyl dichloride with 2,6- or 3,5-pyridinedioyl dichloride afforded the corresponding [2]rotaxanes **5** and **6** in 21 and 40% yield, respectively.

X-ray Crystallography. The solid-state structures of the three bisnitrone rotaxanes were determined by X-ray crystallography (Figures 1−3). Suitable single crystals were obtained in each case by slow diffusion of water vapor into solutions of the rotaxanes in *N*,*N*-dimethylformamide (DMF). Despite the close similarities in the structural formulas of the rotaxanes and the similar conditions of crystal growth, significant differences in the solid-state structures are apparent. The hydrogen-bonding motifs and relative positions of the components in the solid-

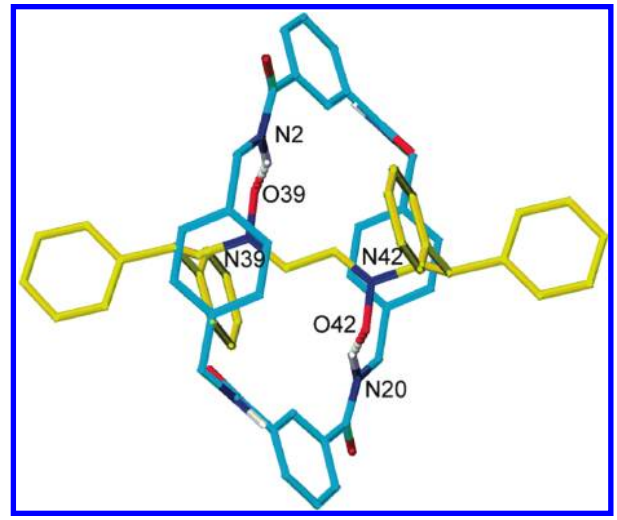


Figure 1. X-ray crystal structure of nitrone [2]rotaxane **4**. Selected bond lengths (Å): N39−O39 = N42−O42, 1.30. Distance between hydrogen-bond-acceptor groups (Å): O39−O42, 4.87. Intramolecular hydrogen-bond lengths (Å): O42−HN20, 2.92; O39−HN2, 2.92. Intramolecular hydrogen-bond angles (deg): N2−H−O39 = N20−H−O42, 173.3.

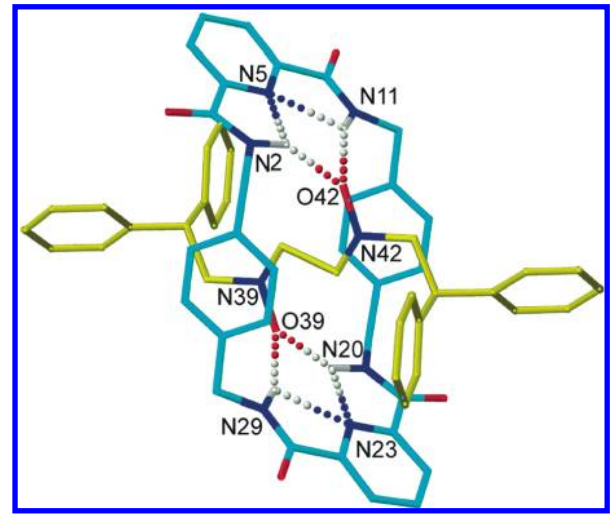


Figure 2. X-ray crystal structure of endopyridyl macrocycle nitrone [2]rotaxane **5**. Selected bond lengths (Å): N39−O39 = N42−O42, 1.35. Hydrogen-bond lengths (Å): O42−HN2 = O42−HN11 = O39-HN29 = O39−HN20, 2.11; N5−HN2 = N23−HN20, 2.39; N5−HN11 = N23−HN29, 2.33. Hydrogen-bond angles (deg): O42−H−N2 = O39−H−N20, 149.1; O42−H−N11 = O39−H−N29, 156.9, N5−H−N2 = N23−H−N20, 101.4, N5−H−N11 = N23−H−N29, 100.5.

state structures of rotaxanes **5** (Figure 2) and **6** (Figure 3) are essentially as predicted by design, with two sets of bifurcated hydrogen bonds between the 1,3-diamide groups of the macrocycle and the nitrone oxygen atoms. The isophthalamide macrocycle-based rotaxane **4** (Figure 1) adopts a different solid-state structure than the other two rotaxanes, maximizing intermolecular amide−amide hydrogen bonds at the expense of the bifurcated intramolecular amide−nitrone hydrogen bonds. This is presumably a result of the interplay between a number of factors: the intermolecular amide−amide hydrogen bonds formed in **4** are all strong (short, linear, and to regions of high electron density, i.e., amide carbonyl lone pairs); each amide hydrogen-bond donor to a nitrone group also acts as a hydrogen-bond acceptor, with the polarization caused by each interaction making the other stronger;[27] and the structural changes that the hydrogen-bonding motif brings about may increase van der

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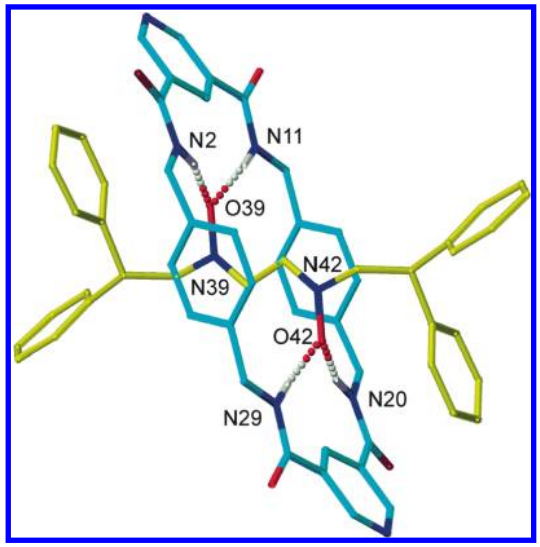

Figure 3. X-ray crystal structure of exopyridyl macrocycle nitrone [2]rotaxane **6**. Selected bond lengths (Å): N39−O39 = N42−O42, 1.30. Hydrogen-bond lengths (Å): O39−HN2 = O42−HN20, 2.31; O39−HN11 = O42−HN29, 2.03. Hydrogen-bond angles (deg): O39−H−N2 = O42−H−N20 127.4, O39−H−N11 = O42−H−N29, 114.2.

Waals or $\pi-\pi$ stacking interactions in the crystal packing (intercomponent stacking interactions between the N═C bonds of the thread and the xylylene rings of the macrocycle are apparent in all three rotaxane X-ray structures but are considerably distorted in **4**).

Double bifurcated hydrogen bonding to the nitrone groups in the rotaxanes might be expected to increase the contribution of the C═N^+(R)−O^- canonical form relative to that of the C^-−N^+(R)═O form in comparison with simple nitrones. This is indeed what is seen in the crystal structures of **5** and **6**, as manifested in the lengthening of the N−O bonds (in the case of **5**, to the longest reported to date for a nitrone system) to 1.30 Å in **4** and **6** and 1.35 Å in **5** [cf. 1.28 Å[28] in 4-ClC_6H_4CH═N^+(Me)−O^-] and shortening of the C═N bonds to 1.31 Å in **4**, 1.26 Å in **5**, and 1.28 Å in **6** [cf. 1.31 Å[28] in 4-ClC_6H_4CH═N^+(Me)−O^-]. The significant increase in the polarization of the N−O bond by double hydrogen bonding could prove useful for the design of high-dipole-moment systems (e.g., with nonsymmetrical hydrogen-bond-acceptor rotaxanes).

Dynamic ^{1}H NMR Spectroscopy. In nonpolar solvents, unlike the situation in the solid state, the isolated rotaxanes can only adopt intramolecular hydrogen-bonding patterns to lower their energy, so the most stable coconformations in each case involve two sets of bifurcated hydrogen bonds similar to those in the solid-state structures of **5** and **6**. In $C_2D_2Cl_4$ at room temperature, the ^{1}H NMR spectra of all three bisnitrone rotaxanes are relatively simple. The isophthalamide (in **4**) and exopyridyl (in **6**) rotaxane macrocycles spin rapidly on the NMR time scale, but rotation of the endopyridyl macrocycle in rotaxane **5** is slow under the same conditions. The resolution of the H_E protons into two noninterconverting magnetically distinct environments can arise only if pirouetting of the macrocycle is slow on the NMR time scale (a 180° rotation of the macrocycle accompanied by a chair−chair flip maps the H_{E1} protons onto the H_{E2} protons; Figure 4). The different amide couplings to the H_{E1} and H_{E2} protons (see Figure 4c) also confirm the chair conformation of the macrocycle in solution and indicate that H_{E2} is the equatorial site.

Spin polarization transfer by selective inversion recovery (SPT-SIR)[29] measurements on the resolved H_E resonances for the isophthalamide rotaxane **4** gave a value of 12.2 ± 0.1 kcal mol^{-1} for the energy barrier for macrocycle pirouetting at 271 K in $C_2D_2Cl_4$. Fumaric thread bisamide and bisester [2]rotaxanes having the same macrocycle and near-identical spacing and orientation of the hydrogen-bond-accepting groups have energy barriers for pirouetting of 11.4 ± 0.1 and 7.2 ± 0.4 kcal mol^{-1}, respectively, in chlorinated solvents at 298 K.[17] If it is assumed that the structures and mechanism of ring rotation in solution are similar for all of these rotaxanes, the differences in the energy barriers can largely be attributed to the difference in strength between the four intercomponent hydrogen bonds present in the three systems: an amide−nitrone [−CONH···$^-$O−N^+(R)═C−] hydrogen bond is ∼0.2 kcal mol^{-1} stronger than the corresponding amide−amide (−CONH···O═CNH−) hydrogen bond and ∼1.3 kcal mol^{-1} stronger than the analogous amide−ester (−CONH···O═CO−) interaction.

Chemical and Electrochemical Effects of Encapsulation. After the structures of the nitrone rotaxanes in both solution and the solid state had been established, investigations to probe the redox chemistry of the nitrone functional group within the rotaxane structure were undertaken. The threaded architecture proved to have significant influences on the chemical and electrochemical reduction of the nitrone functional group in contrasting ways.

The nitrone groups of thread **3** are quantitatively reduced to give bishydroxylamine **7** in 30 min by sodium borohydride in aqueous isopropanol under reflux (Scheme 1). However, no reaction was observed in the case of rotaxane **4** after refluxing under identical conditions for >12 h (Scheme 3). The macrocycle clearly provides a highly effective mechanical barrier to the reagent, and the intercomponent hydrogen bonding may also play an important role both by holding the macrocycle in position and by preventing boron coordination to the nitrone oxygen atoms. Although encapsulation within rotaxane architectures has previously been shown to stabilize reactive regions of a rotaxane axle,[30] most notably for chromophores[30c] or enzyme-degradable peptide sequences,[30e] this is one of the most dramatic examples of the effectiveness of a molecular sheath in protecting a functional group from a small chemical reagent.

The electrochemical behavior of the bisnitrone thread and rotaxane also differ significantly from one another. Figure 5 shows the cyclic voltammetry curves for 1.0 mM solutions of thread **3** and rotaxane **4** in DMF obtained at 298 K using a scan rate of 500 mV s^{-1}. In both cases, a reversible one-electron reduction peak corresponding to reduction of the nitrone groups was observed. The fact that only one electron is consumed in the reduction is indicative of effective conjugation between the two nitrone groups that leads to extensive delocalization of the

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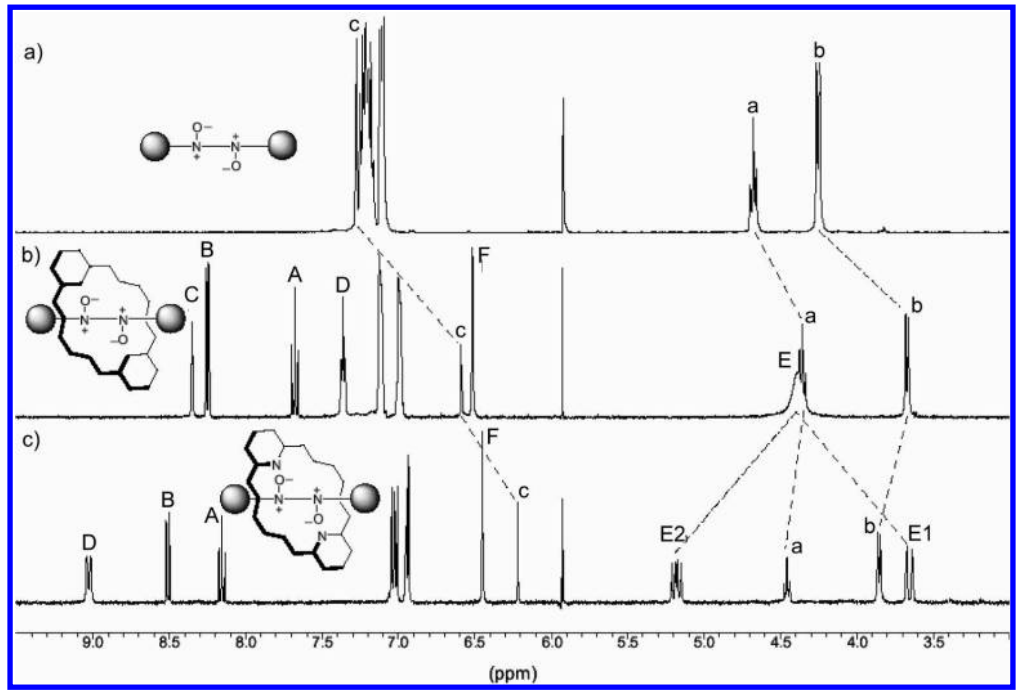
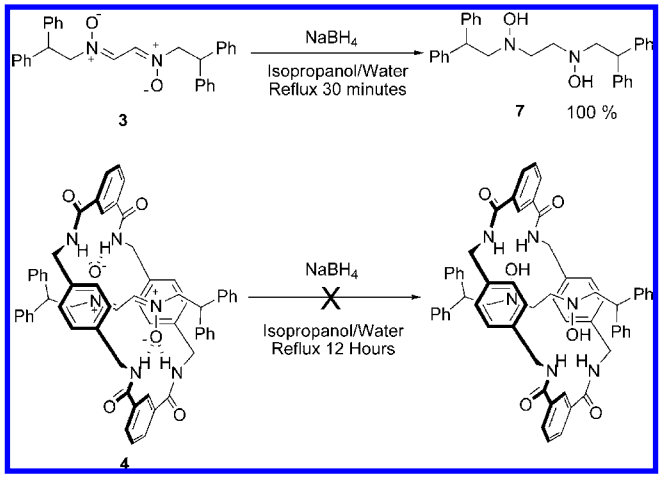


Figure 4. ^{1}H NMR spectra (400 MHz, $C_2D_2Cl_4$, 295 K) of (a) bisnitrone thread **3**, (b) isophthalamide [2]rotaxane **4**, and (c) endopyridyl rotaxane **5**. The assignments correspond to the lettering shown in Scheme 2.

Scheme 3. Chemical Reduction of Nitrone Thread **3** and Nitrone [2]Rotaxane **4**



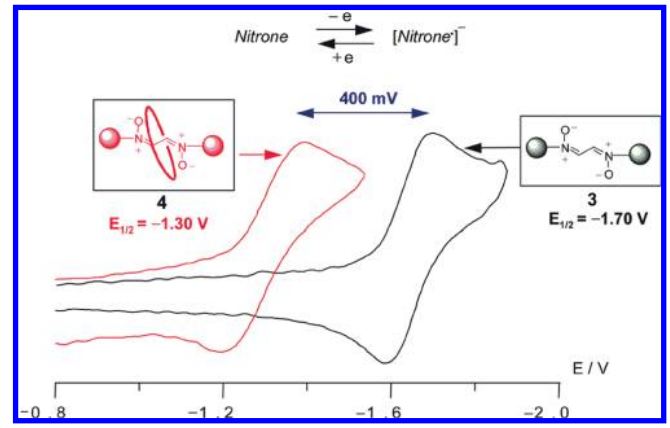


Figure 5. Cyclic voltammetry curves of 1.0 M **4** (red curve) and **3** (black curve) in 0.05 M tetraethylammonium tetrafluoroborate DMF solution at 298 K using a scan rate of 500 mV $s^{-1}$with a platinum ultramicroelectrode (125 μm) as the working electrode.

negative charge over both nitrone groups, in line with the reported voltammetric behavior of other bisnitrone derivatives in aprotic media.[12] Significantly, the reduction was anodically shifted by 400 mV for the rotaxane relative to the thread ($E_{1/2}$ = −1.70 V for **3** and −1.30 V for **4**). This effect can be attributed directly to the stabilizing effect of hydrogen bonding on the nitrone group.[31] Since the injected electron is expected to increase the negative charge on the nitrone oxygen atoms, hydrogen bonding is stronger in the reduced state than for the neutral nitrone, with the stabilization being ~8 kcal mol^{-1} on the basis of the 400 mV anodic shift.[31,32]

The kinetics of electron transfer are also affected by encapsulation within the rotaxane architecture.[33] The CV measurements showed that while the nitrone reduction is electrochemically reversible in thread **3**, in the nitrone rotaxane **4** the reduction is quasi-reversible (see the Supporting Information). Simulations of the CV curves for the thread and rotaxane

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based on the Butler−Volmer rate law provided the following values for the heterogeneous electron-transfer standard (i.e., at $E = E°$) rate constant: $k_{et}^{o} = 0.01$ cm s^{-1} for the rotaxane and 1 cm s^{-1} for the thread. Moreover, an α value of 0.3 was obtained for the rotaxane, while for the thread $\alpha = 0.5$, as expected for a reversible process. Rotaxane formation is therefore responsible for lowering the standard rate constant by 2 orders of magnitude. The macrocycle probably acts as an insulating sheath through which electron transfer to the redox center must take place by tunneling. In analogy to heterogeneous electron transfer to redox centers occurring through adsorbed blocking monolayers on electrodes[34] or to proteins,[35] the standard rate constant of the redox process should decrease in **4** relative to **3** by $\exp(-\beta d)$, where β is a parameter defined by the medium and d is the thickness of the insulating barrier.[35a]

Conclusions

The powerful hydrogen-bond-accepting properties of nitrones have been utilized in the synthesis of a series of [2]rotaxanes. Dynamic ^{1}H NMR experiments show that the amide−nitrone hydrogen bonds present in these systems are significantly stronger than analogous amide−ester and even amide−amide hydrogen-bonding interactions. The rotaxane architecture significantly alters the reduction and oxidation properties of the nitrone functional group, simultaneously shielding it from chemical reduction by external agents while activating it toward electrochemical reduction. Other properties of these rotaxanes, including the variation in the Kerr effect under an alternating electric field, which has been linked to the rate of pirouetting of the macrocycle about the thread,[16e] are currently under investigation. The hydrogen-bond-directed synthesis of nitrone rotaxanes is simple and, in the case of the isophthaloyl dichloride building block, high-yielding. The methodology provides an unusual functional addition to the diversity of templates available for assembling amide−macrocycle rotaxanes and could potentially lead to new generations of electrochemically driven molecular machines and superstable radicals.

Experimental Section

General Method for the Preparation of Bisnitrone [2]Rotaxanes. The bisnitrone thread **3** and triethylamine were dissolved in anhydrous 5:1 $CHCl_3/CH_3CN$ and stirred vigorously while solutions of the amine in anhydrous $CHCl_3$ and the acid chloride in anhydrous $CHCl_3$ were added over 3 h using motor-driven syringe pumps. The reaction mixture was filtered and the solvent removed under reduced pressure. The crude material was then subjected to column chromatography (silica gel, $CHCl_3$/MeOH as eluent) to give the pure [2]rotaxanes **4**, **5**, and **6** in 70, 21, and 40% yield, respectively. Further details are given in the Supporting Information.

Acknowledgment. This work was supported by the ERC Advanced Grant *WalkingMols* and the EPSRC. We thank the Deutsche Akademia der Naturforscher Leopoldina (BMBF LPD 9901/8-166) and Peter und Traudl Engelhorn-Stiftung for a postdoctoral fellowship to D.M.D. D.A.L. is an EPSRC Senior Research Fellow and holds a Royal Society−Wolfson Research Merit Award. F.P. acknowledges financial support from MIUR (PRIN 2008N7CYL5 and 20085M27SS) and the University of Bologna.

Supporting Information Available: Experimental procedures and spectroscopic data for nitrone [2]rotaxanes **4**, **5**, and **6**; full crystallographic data (CIF); and details of the electrochemical experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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