# 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 shows 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 indicate that 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: The intercomponent hydrogen bonding *activates* the nitrone groups to electrochemical reduction, a one electron reduction of the rotaxane being stablized by a remarkable 400 mV (8.1 kcal $mol^{-1}$) with respect to the same process in the thread; encapsulation, however, *protects* the same functional groups from chemical reduction with an external reagent (and slows down electron transfer to and from the electroactive groups in cyclicvoltammetry 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 $C=N^{+}(R)\text{-}O^{-}$ although the $C^{-}\text{-}N^{+}(R)=O$ 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 as 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 compared to 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]; potentially useful for NLO applications and in controlling molecular orientation), they offer a simple route to stable radicals *via* a one electron electrochemical reduction[12] or conjugate addition to C=N followed by oxidation,[13] and the $N^{+}\text{-}O^{-}$ motif is a powerful hydrogen bond acceptor.[14]

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] By tuning structural rigidity and preorganization effects yields as high as 97 % for [2]rotaxanes incorporating amide threads have been reported.[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 the template assembly of building blocks about the thread to form the macrocycle is most often used to construct such rotaxanes.[15] These five component "clipping" 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 which brings the reactive end groups close together leading to rapid cyclization of **1** about the axle.[16a,16b,16i,17] The key factors determining the efficiency of rotaxane formation in such reactions are:

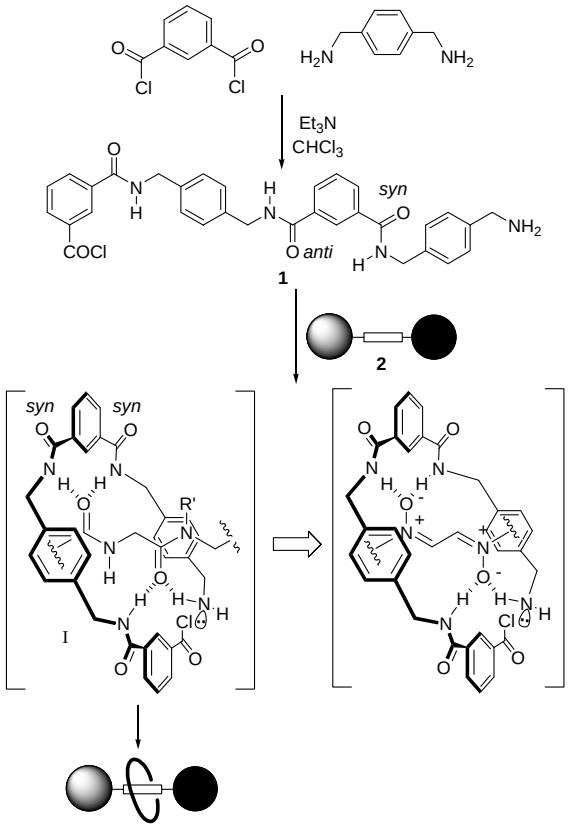
(i) the spatial arrangement of hydrogen bonding sites on the thread (ideally chosen such that a low energy conformation of the macrocycle-precursor **1** can bind in a multidentate manner to the thread as shown in **I**, Scheme 1).[16a,16b]

(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 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 consequence of the mechanically interlocked architecture on the chemistry of nitrones.

***Scheme 1.*** Hydrogen bonding modes of dipeptide and *bis*-nitrone templates for rotaxane synthesis.

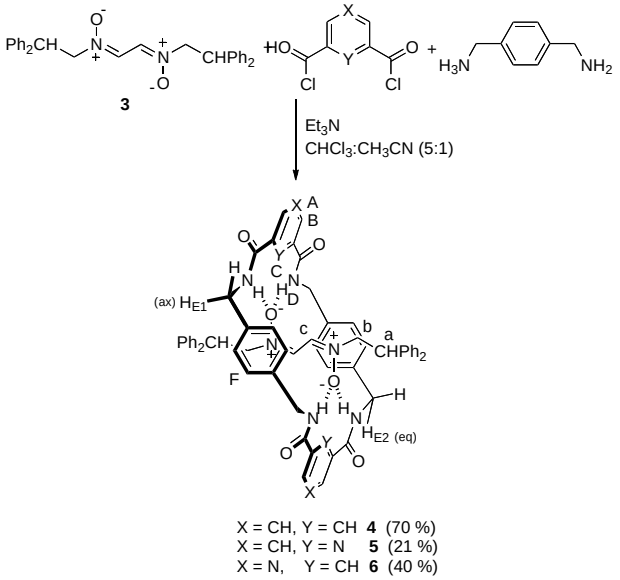



## Results and Discussion

### Synthesis

A *bis*-nitrone thread, **3**, featuring the two oxygen atoms at a similar separation and relative orientation to the amide carbonyls in a dipeptide, was prepared in three steps from diphenylacetaldehyde (see Supporting Information). Solutions of 6.0 molar equivalents of isophthaloyl dichloride and 6.6 molar equivalents of *p*-xylylenediamine were slowly added to **3** in a stirred anhydrous solution of $CHCl_3$ and $CH_3CN$ (5:1) (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 *bis*-nitrone [2]rotaxane **4** in 70 % yield.[16e] Under analogous conditions, replacing isophthaloyl dichloride with either 2,6- or 3,5-pyridinedioyl dichloride, the corresponding [2]rotaxanes **5** and **6** were obtained in 21 % and 40 % yields, respectively.

***Scheme 2.*** Synthesis of *bis*-nitrone [2]rotaxanes **4**-**6**.




## X-Ray Crystallography

The structures of each of the *bis*-nitrone rotaxanes in the solid state 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 DMF. Despite the close similarities between the structural formulae of the rotaxanes and the similar conditions of crystal growth, significant differences are apparent in the solid state structures. The hydrogen bonding motifs and relative positions of the components in the solid 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 to the nitrone oxygen atoms. The isophthalamide macrocycle-based rotaxane, **4** (Figure 1), adopts a different structure in the solid state from the other two rotaxanes, maximizing intermolecular amide-amide hydrogen bonds at the expense of the bifurcated intramolecular amide-nitrone hydrogen bonds. Presumably this is 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, the polarization caused by each interaction making the other stronger[27]; the structural changes that the hydrogen bonding motif brings about may increase van der Waals or π-π 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 considerably distorted in **4**).

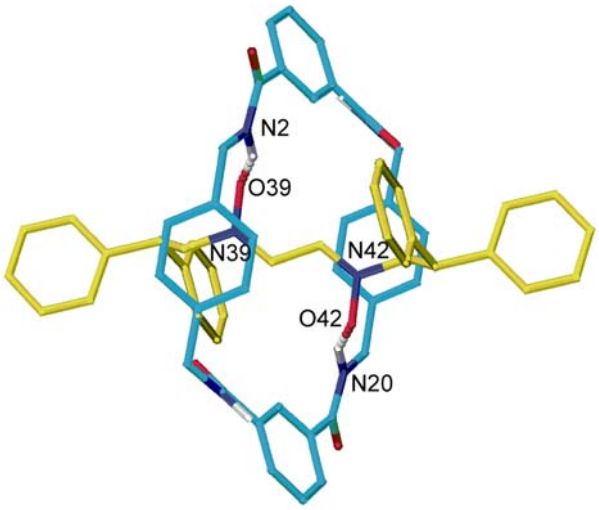



***Figure 1.*** X-Ray crystal structure of nitrone [2]rotaxane **4**. Selected bond lengths [Å]: N39-O39 = N42-O42 1.30. Distance between hydrogen bond acceptor groups [Å]: O39-O42 4.87. Intramolecular hydrogen bond lengths [Å]: O42-HN20 2.92, O39-HN2 2.92. Intramolecular hydrogen bond angles [°] N2-H-O39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

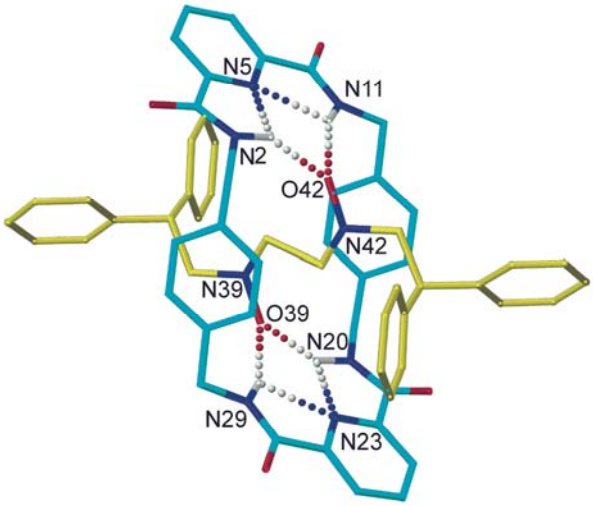



***Figure 2.*** X-Ray crystal structure of endopyridyl-macrocycle nitrone [2]rotaxane **5**. Selected bond lengths [Å]: N39-O39 = N42-O42 1.35. Hydrogen bond lengths [Å]: O42-HN2 = O42-HN11= O39-HN29 = O39-HN20 2.11, N5-HN2 = N23-HN20 2.39, N5-HN11= N23-HN29 2.33. Hydrogen bond angles [°]: O42-H-N2 = 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.

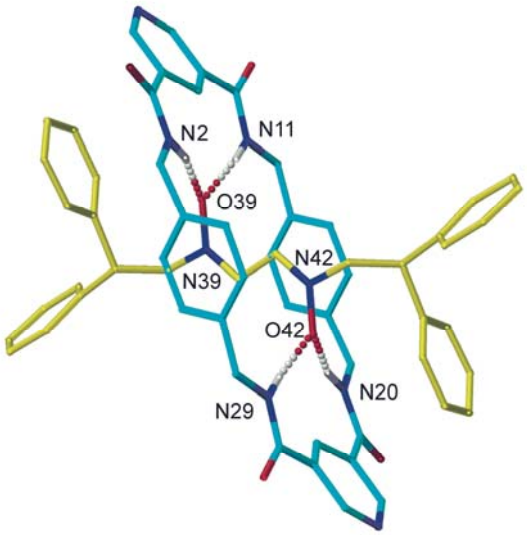



***Figure 3.*** X-ray crystal structure of exopyridyl-macrocycle nitrone [2]rotaxane **6**. Selected bond lengths [Å]: N39-O39 = N42-O42 1.30. Hydrogen bond lengths [Å]: O39-HN2 = O42-HN20 2.31, O39-HN11= O42-HN29 2.03. Hydrogen bond angles [°]: O39-H-N2 = O42-H-N20 127.4, O39-H-N11= O42-H-N29 114.2.

Double bifurcated hydrogen bonding to the nitrone groups in the rotaxanes might be expected to increase the contribution of the $C=N^{+}(R)\text{-}O^{-}$ canonical form relative to the $C^{-}\text{-}N^{+}(R)=O$ form compared to simple nitrones. This is indeed what is seen in the crystal structures of **5** and **6**, manifested in the lengthening of the N-O bonds (in the case of **5**, to the longest reported to date for a nitrone system): 1.30 Å (**4** and **6**) and **5**: 1.35 Å (**5**), *cf.* 1.28 Å[28] in $4\text{-Cl-}C_6H_4CH=N^{+}(Me)\text{-}O^{-}$; and shortening of the C=N bonds: 1.31 Å (**4**), 1.26 Å (**5**) and 1.28 Å (**6**), *cf.* 1.31 Å[28] in $4\text{-Cl-}C_6H_4CH=N^{+}(Me)\text{-}O^{-}$. 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 non-symmetrical hydrogen bond acceptor rotaxanes).

**Dynamic $^{1}$H NMR Spectroscopy**

Unlike the solid state, in nonpolar solvents the isolated rotaxanes can only adopt intramolecular hydrogen bonding patterns to lower their energy and the most stable co-conformations in each case will therefore involve two sets of bifurcated hydrogen bonds similar to the solid state structures of **5** and **6**. In $C_2D_2Cl_4$ at room temperature, the $^{1}$H NMR spectra of all three *bis*-nitrone rotaxanes are relatively simple. The isophthalamide **4** and exopyridyl **6** rotaxane macrocycles spin rapidly on the NMR timescale, however rotation of the endopyridyl macrocycle in rotaxane **5** is slow under the same

conditions. The resolution of the $H_E$ protons into two non-interconverting magnetically distinct environments can only arise from pirouetting of the macrocycle being slow on the NMR timescale (a 180° rotation of the macrocycle, accompanied by a chair-chair flip, maps the $H_{E1}$ protons onto $H_{E2}$, 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 $H_{E2}$ is the equatorial site.

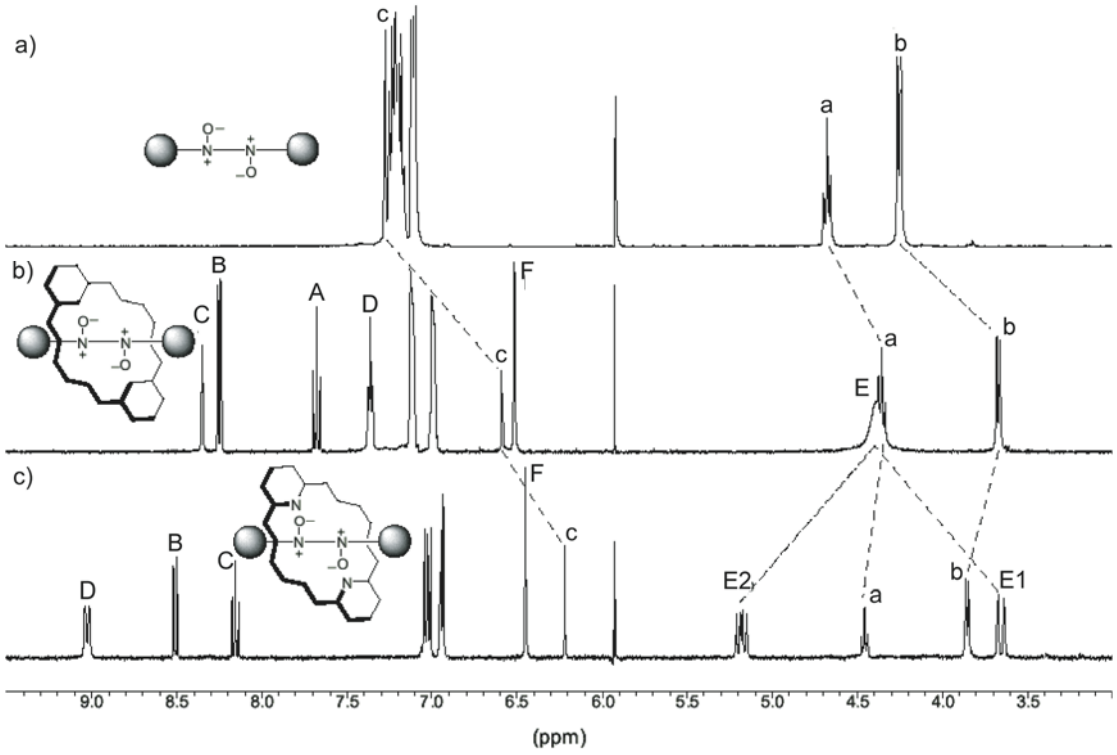



***Figure 4.*** $^1$H NMR spectra (400 MHz, $C_2D_2Cl_4$, 295 K) of (a) *bis*-nitrone thread **3**, (b) isophthalamide [2]rotaxane **4**, and (c) endopyridyl rotaxane **5**. The assignments correspond to the lettering shown in Scheme 2.

Spin polarisation transfer by selective inversion recovery (SPT-SIR)[29] measurements on the resolved $H_E$ resonances for the isophthalamide rotaxane **4** give an energy barrier for macrocycle pirouetting at 271 K in $C_2D_2Cl_4$ of 12.2 ± 0.1 kcal mol$^{-1}$. Fumaric thread *bis*-amide and *bis*-ester [2]rotaxanes, with the same macrocycle and near-identical spacing and orientation of 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] Assuming the structures and mechanism of ring rotation in solution is similar for all these rotaxanes, the differences in energy barriers can be largely attributed to the difference in strength between the four intercomponent hydrogen bonds present in the three systems, *i.e.* an amide-nitrone (-CONH$\cdots^-$O-N$^+$(R)=C-) hydrogen bond is ~0.2 kcal mol$^{-1}$

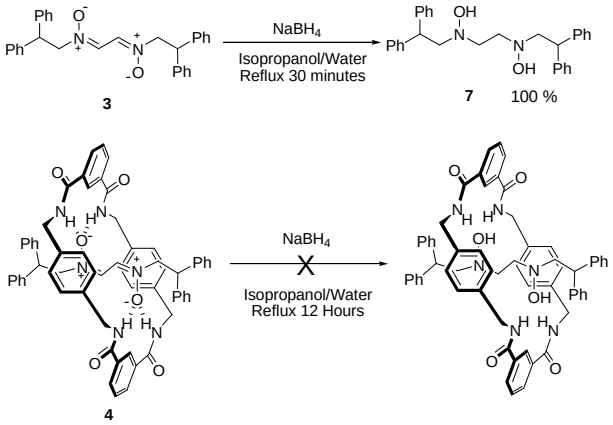
stronger than a corresponding amide-amide (-CONH···O=CNH-) one and ~1.3 kcal $mol^{-1}$ stronger than the analogous amide-ester (-CONH···O=CO-) interaction.

**Chemical and Electrochemical Effects of Encapsulation**

Having established the structures of the nitrone rotaxanes both in solution and in the solid state, investigations to probe the redox chemistry of the nitrone functional group within the rotaxane structure were undertaken. The threaded architecture proved to have a significant influence on the chemical and electrochemical reduction of the nitrone functional group in contrasting ways.

The nitrone groups of the thread **3** are quantitatively reduced to the *bis*-hydroxylamine **7** in 30 minutes 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 hours (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 through 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.

***Scheme 3.*** Chemical reduction of nitrone thread **3** and nitrone [2]rotaxane **4**.




The electrochemical behavior of the *bis*-nitrone thread and rotaxane also differ significantly from one another. Figure 5 shows the cyclic voltametry curves for 1.0 mM solutions of each of thread **3** and rotaxane **4** in DMF obtained at 298 K and 500 mV $s^{-1}$ scan rate. In both cases a one-electron reversible reduction peak is observed corresponding to reduction of the nitrone groups. The fact that only one electron is consumed in the reduction is indicative of effective conjugation between the two nitrone groups leading to an extensive delocalization of the negative charge over both nitrone groups in line with the reported voltammetric behavior of other *bis*-nitrone derivatives in aprotic media.[12] Significantly, the reduction is anodically shifted by 400 mV in the rotaxane with respect 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 onto the nitrone oxygen atoms, hydrogen bonding is stronger in the reduced state with respect to the neutral nitrone, the stabilization being ~8 kcal $mol^{-1}$ based on the 400 mV anodic shift.[31,32]

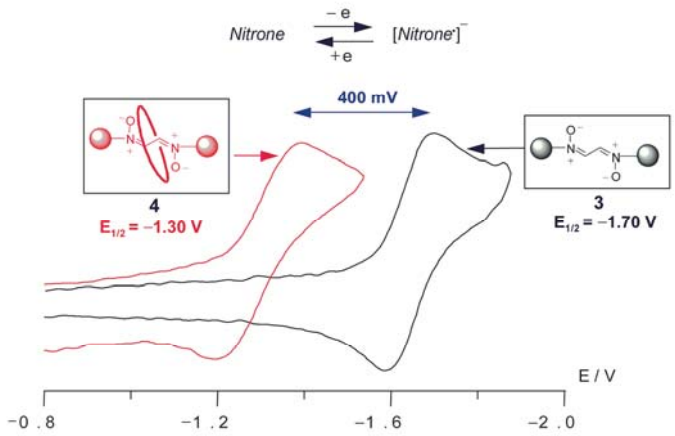



***Figure 5.*** Cyclic voltammetric curves of 1.0 M **4** (red curve) or **3** (black curve), 0.05 M tetraethylammonium tetrafluoroborate (TEATFB) DMF solution. T = 298 K, v = 500 mV $s^{-1}$, working electrode: platinum ultramicroelectrode (UME): 125 μm).

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 Supporting Information). Simulations of the CV curves for the thread and rotaxane based on the Butler-Volmer rate law provide a value for heterogeneous electron transfer standard (*i.e.* at E = E°) rate constant $k°_{et}$ = 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 α = 0.5, as expected for a reversible process. Rotaxane formation is therefore responsible for the lowering the standard rate constant by two-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** with respect to **3** by exp[-βd], 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 towards electrochemical reduction. Other properties of these rotaxanes 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 super-stable radicals.

## Experimental Section

**General method for the preparation of *bis*-nitrone [2]rotaxanes:** The *bis*-nitrone thread **3** and triethylamine were dissolved in 5:1 anhydrous $CHCl_3$:$CH_3CN$ and stirred vigorously whilst solutions of the amine in anhydrous $CHCl_3$ and the acid chloride in anhydrous $CHCl_3$ were added over 3 hours 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 % yields, respectively. See Supporting Information for further details.

## Acknowledgements

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## Supporting information available

Experimental procedures and spectroscopic data for nitrone [2]rotaxanes **4**, **5**, and **6**, full crystallographic data 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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