Synlett G. L. Nixon et al. Letter

Tripodal Tris-*N*-oxides: Synthesis and Hydrogen Bonding Capabilities

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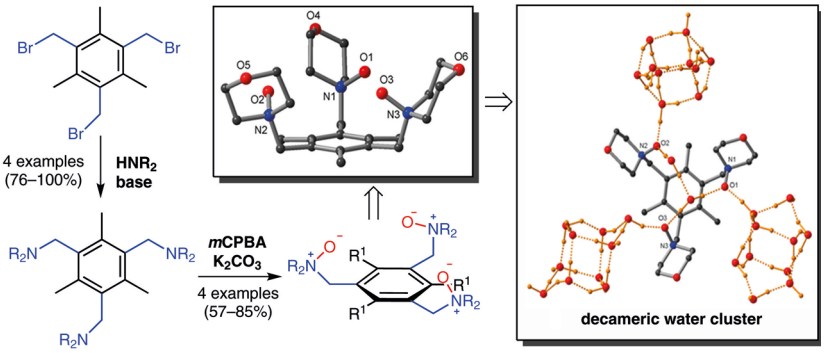
Dedicated with respect to Professor Steve Ley FRS, mentor and friend, on the occasion of his 70th birthday



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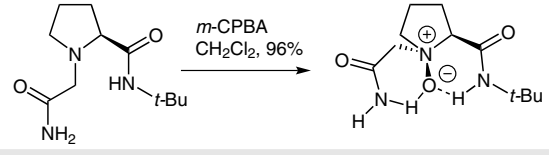
Abstract A number of tripodal tris-*N*-oxide receptors were synthesized and their hydrogen-bonding capabilities were investigated. Particular success was seen with both the benzene- and mesitylene-linked trismorpholine *N*-oxide receptors, which exhibited significant hydrogen bonding to both water and urea, as well as the inclusion of a rare decameric water cluster, as demonstrated by X-ray crystallography.

Key words tripodal receptors, amine oxides, hydrogen bonding, crystal structure, water clusters

Recently, there has been great interest in the area of synthetic hydrogen-bonding receptors that are capable of binding to small organic molecules or to metal cations.[1] This interest is due to the potential pharmaceutical applications of such compounds. Small molecules such as carbohydrates, ureas, or metal cations are involved in numerous biological processes in the body, such as inflammation, infection, and intercellular communication. Consequently, synthetic receptors might be useful as biomimetics or as prodrugs that transport active drugs to their sites of action and are subsequently cleaved to release the active molecule. Another potential application of hydrogen-bonding receptors is their use as scavengers to bind unwanted materials in chemical or biological systems.[2]

The hydrogen-bonding capabilities of *N*-oxides are well documented.[3] Recently, *N*-oxides have been reported as the first class of chemical reagents capable of stabilizing aldehyde hydrates (which are important but highly unstable transient intermediates in biological and synthetic oxidations to give carboxylic acids). This stabilizing affect has been attributed to hydrogen bonding.[4] Other examples of involving complexation of *N*-oxides to sulfonamides, phenols, or 2-amino-3-hydroxypyridium ions have also been described in the literature.[5] The stabilization of proteins by trimethylamine *N*-oxide and the ability of this compound to counteract the effects of urea have recently been demonstrated.[6] Commercially, 4-methylmorpholine *N*-oxide has been used as a solvent in spinning of cellulose fibers, and *N*-oxides can be used to dissolve a wide range of natural and synthetic polymers.[7] Despite this interest and potential there are only a few examples of hydrogen-bonding receptors for small organic molecules in organic solvents and none that work in an aqueous environment, so progress in this area would be significant.[8]

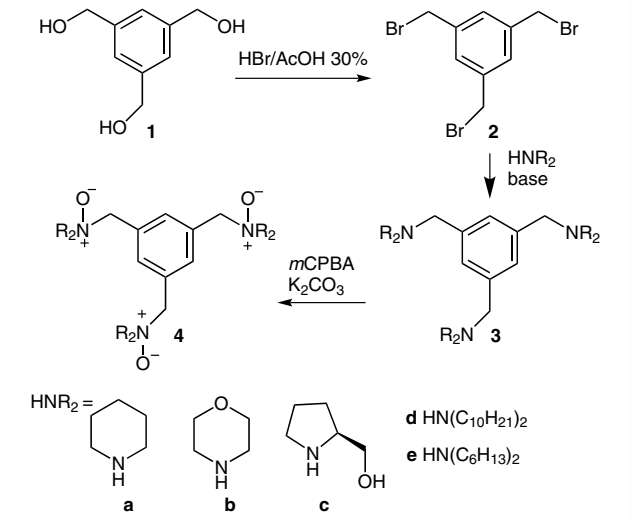
Previous work by our group has shown that *N*-substituted proline derivatives that possess a hydrogen-bond donor group in a carboxylate side chain undergo highly diastereoselective oxidations to give stable *N*-oxides in which the *N*-oxide is hydrogen-bonded to the donor group(s) (Scheme 1).[9] These observations led to the development of a wide range of chiral proline-derived *N*-oxides for use in asymmetric synthesis.[10] The extensive hydration of these *N*-oxides combined with evidence from the literature indicated to us that similar compounds containing additional *N*-oxide moieties might bind small hydrogen-bond-donor compounds such as carbohydrates, amino acids, specific peptide sequences, ureas, or metal cations (see below).[11]



Scheme 1 A proline-derived stabilized *N*-oxide

To this end, the synthesis of a related tris-*N*-oxide compound was of great interest, as we surmised that a better binding cavity would be created if the three *N*-oxide moieties were on the same face of the aryl linker. It was also hypothesized that by varying the amine groups it might be possible to introduce chirality and, consequently, selectivity into the tripodal receptor. Although there are several reported examples of tripodal receptors, none contain an *N*-oxide moiety.[12] The effect of using a different aromatic core unit, such as mesitylene, was also considered as a means of introducing hindered rotation and securing the positioning of the *N*-oxide moieties. As most *N*-oxides are highly polar compounds, we were aware that the preparation of compounds possessing multiple *N*-oxides might present significant problems in isolation and purification.

Our route for the synthesis of the tripodal tris-*N*-oxides with a benzene linker (Scheme 2) began with the reduction of commercially available trimethyl benzene-1,3,5-tricarboxylate with lithium aluminum hydride to give the triol **1** in 80% yield.[12a]



Scheme 2 Synthesis of phenyl-linked tripodal tris-*N*-oxides **4a–e**

Triol **1** was then brominated by using 30% hydrogen bromide in acetic acid to give tribromide **2** in 78% yield.[8a] We then examined the displacement of the bromo groups with a number of secondary amines; potassium carbonate and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were both tested as bases in this step (Table 1).

DBU gave the highest yields, with the exception of triamine **3c**. The resulting tertiary amines **3a–e** were oxidized with *m*-chloroperbenzoic acid to give the corresponding tris-*N*-oxides **4a–e** in good yields; however, we encountered problems with **4a–c**, which were inseparable from *m*-chlorobenzoic acid, a byproduct of the reaction. The prolinol-derived tris-*N*-oxide **4c** was found by mass spectrometry to have bound to potassium from the potassium carbonate used in the oxidation reaction, demonstrating the capability of these compounds to bind to metal cations. Several other oxidants were tested, including hydrogen peroxide, *tert*-butyl hydroperoxide/vanadyl bis(acetylacetonate), urea–hydrogen peroxide/phthalic anhydride, and sodium perborate. These methods either failed or gave the desired product in an inseparable mixture with byproducts of the reaction. We therefore decided that *m*-chloroperbenzoic acid is the reagent of choice, because of its simple reaction conditions, tolerance of a wide range of functional groups, and simple workup procedure. We were unable to perform an X-ray crystallographic analysis of any of these compounds.

Table 1 Yields of Triamines **3a–e** and the Corresponding *N*-Oxides **4a–e**

Amine	Yield (%) of **3**		Yield (%) of **4**
	K_2CO_3	DBU	
a	72	81	>100[a]
b13	61	88	>100[a]
c	98	0	>100[a]
d	50	57	79
e	40	75	79

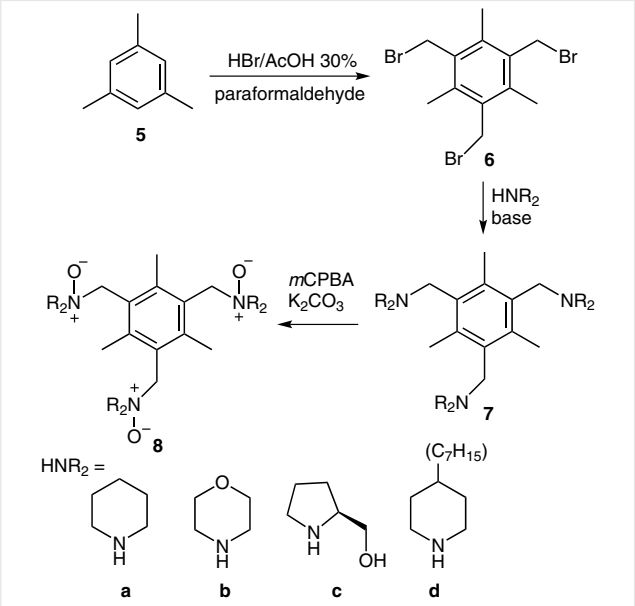
[a] The product was inseparable from 3-$ClC_6H_4CO_2H$.

Our synthetic route to tripodal tris-*N*-oxides with a mesitylene linker (Scheme 3) began with commercially available mesitylene (**5**), which was treated with paraformaldehyde and 30% hydrogen bromide in acetic acid to give tribromide **6** in 92% yield.[14] Substitution of the tribromide with three equivalents of the appropriate amine and three equivalents of a base gave the corresponding triamines **7a–d**. The amine required for the synthesis of **7d** was synthesized by using the route previously reported by Prasad et al.[15]

In the case of these mesitylene-linked compounds, potassium carbonate was the base of choice, giving much higher yields (Table 2). The oxidation step of the reaction was achieved by using *m*-chloroperbenzoic acid, giving compounds **8a–d**.

Table 2 Yields of Mesitylene-Linked Triamines **7a–d** and Their *N*-Oxides **8a–d**

Amine	Yield (%) of **7**		Yield (%) of **8**
	K_2CO_3	DBU	
a	100	–	78
b	86	33	85
c	96	–	79
d	76	–	57



Scheme 3 Synthesis of the mesityl-linked tripodal tris-*N*-oxides **8a–d**

We next attempted to grow crystals for X-ray structure analysis of both the benzene derivatives **4** and the mesitylene derivatives **8**, with the aim of studying the relative conformations of the *N*-oxide groups and their potential role as tripodal hydrogen-acceptors in supramolecular aggregates. Suitable crystals containing **4b** were obtained as co-crystals with urea (**4b**·3urea·3H_2O), whereas **8b** crystallized in the form of its heptahydrate (**8b**·7H_2O).[16]

The crystal structure of **4b**·3urea·3H_2O shows that all three *N*-oxide groups are axial with respect to the chair-shaped morpholine rings. The overall conformation of the three *N*-oxide groups with respect to the central C_6 ring is such that two of the *N*-oxide groups are situated on one face with one *N*-oxide group on the other face (Figure 1). All three *N*-oxides of **4b** are engaged in intermolecular hydrogen bonds with urea molecules, confirming the strong hydrogen-acceptor properties of the partially negative oxygen sites. One of the *N*-oxide groups forms a bifurcated hydrogen bond with two amino groups of urea, whereas the other two bind in a single fashion.

The X-ray crystal structure of **8b**·7H_2O also shows that the *N*-oxide groups adopt an axial position relative to the morpholine rings. However, in contrast to the benzene derivative in **4b**·3urea·3H_2O, all the *N*-oxide groups in **8b**·7H_2O are located on the same face of the central C_6 ring, resulting in a molecular symmetry that is close to C_3 (Figure 2). The three *N*-oxide groups form a coordination cavity that encapsulates a pair of water molecules. Each *N*-oxide group interacts with two water molecules; one is part of the encapsulated pair, the other is part of a decameric cage-like cluster of water molecules. The result is a three-dimensional supramolecular network in which every tris-*N*-oxide molecule is connected to three $(H_2O)_{10}$ clusters,[17c] which, in return, bind six tris-*N*-oxides. The decameric water cluster can be described as a polyhedral cage consisting of two four-membered- and four five-membered-ring systems, analogous to the C_{10} framework of the 1,4-bishomocubane water cluster. Decameric and dodecameric water cages that are part of molecular organic or metaloorganic crystals have been reported,[17] including one example that exhibits the same cage topology as our structure.[17a] Structural data for water clusters can provide useful models for the complex structures of liquid water and aggregates in the gas phase.[18]

The most striking difference between the crystal structures of the benzene derivative **4b** and the mesitylene derivative **8b** is the orientation of the three morpholine oxide groups with respect to the central C_6 ring. This all-*cis* configuration might be the result of a templating effect facilitated by hydrogen bonding to hydrogen donors, which forces all three *N*-oxide groups onto one side of the molecule. These are then locked into place as a result of the presence of the three methyl groups of the mesitylene ring, which in-

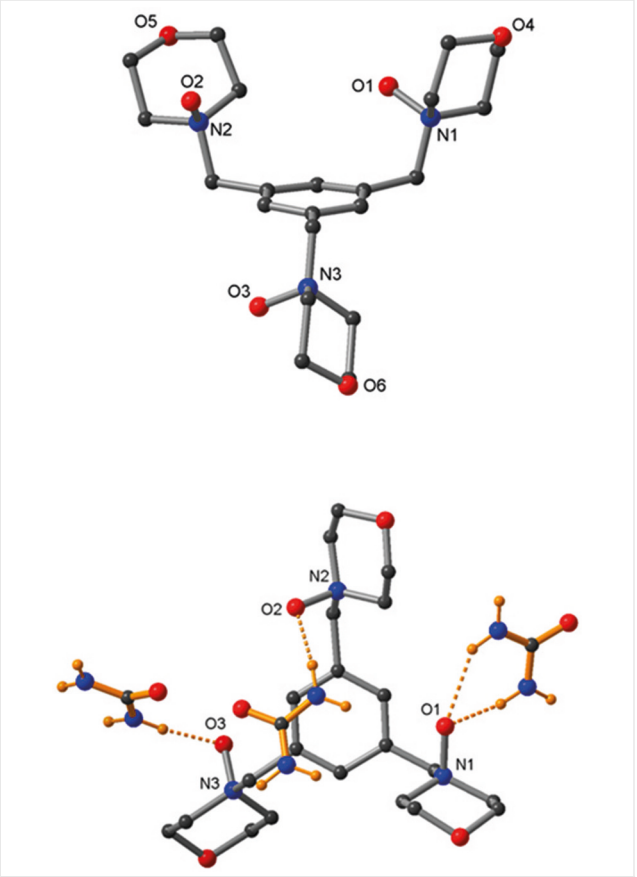


Figure 1 Crystal structure of **4**·3urea·3H_2O. Top: View of **4** showing the molecular confirmation. Bottom: Hydrogen-bonded aggregate of **4** and three urea molecules. The hydrogen atoms of the tris-*N*-oxide molecule have been omitted for clarity.

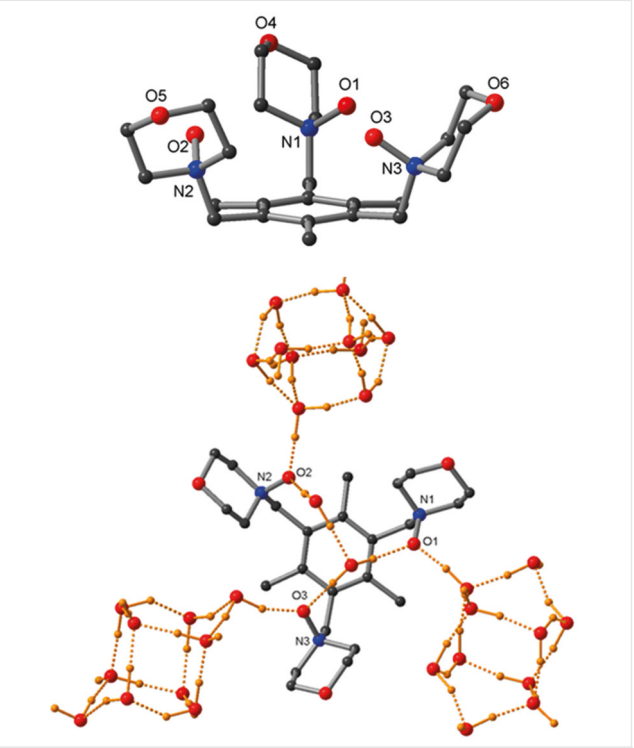


Figure 2 Crystal structure of **8**·7H_2O. Top: View of **8** showing the molecular conformation. Bottom: Part of the supramolecular structure, emphasizing the hydrogen-bond interactions of the tris-*N*-oxide, the encapsulated water pair, and the decameric water clusters. The hydrogen atoms of the tris-*N*-oxide molecule have been omitted for clarity.

hibit inner rotation of the C(ring)–C(H_2) bonds and thereby block the migration of morpholine oxide groups from one side of the molecule to the other. The all-*cis* configuration suggests interesting applications in host–guest chemistry, as it equips the molecule with a hydrophilic side that offers a tripodal cavity of strong hydrogen acceptors, whereas the opposite face has a hydrophobic character.

To conclude, we have demonstrated the ability of tripodal tris-*N*-oxides to hydrogen bond to water and urea. We have also demonstrated their potential to bind to metal cations. X-ray crystallography has shown that the orientation of the three morpholine *N*-oxide groups with respect to the central C6 ring can be manipulated by the use of a mesitylene core to provide a hydrophilic side that offers a tripodal cavity of strong H-acceptors, while the opposite face has a hydrophobic character. This provides a promising tool for further investigations in biological systems.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560533.

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(16) **Tris-*N*-oxides 4a–e and 8a–d; General Procedure**

*m*CPBA (2.20 mmol) was added to a stirred solution of triamine **3** or **7** (0.70 mmol) and K_2CO_3 (2.20 mmol) in CH_2Cl_2 (14 mL) under N_2 at –78 °C, and the reaction vessel was allowed to warm to r.t. After 48 h, the mixture was filtered, the residue was washed with CH_2Cl_2, and the solvent was removed in vacuo to give the desired compound.

4,4′,4″-[Benzene-1,3,5-triyltris(methylene)]tris(morpholine) 4,4′,4″-Trioxide (4b)

White solid; yield: 201 mg (>100%). ^{1}H NMR (300 MHz, CD_3OD): δ = 7.89 (s, 3 H, 3Ar–H), 4.56 (s, 6 H, $3CH_2$), 4.18 (t, *J* = 11.7 Hz, 6 H, 6CH α and *syn* to N^+–O^-), 3.83 (d, *J* = 11.7 Hz, 6 H, 6CH α to O and *syn* to N^+–O^-), 3.63 (t, *J* = 11.7, 6 H, 6CH α to O and *anti* to N^+–O^-), 3.05 (d, *J* = 11.7, 6 H, 6CH α and *anti* to N^+–O^-). ^{13}C NMR (75 MHz, CD_3OD): δ = 138.7 (3 ring × C–CH_2), 129.1 (3 × ring C–H), 73.4 (6CH_2 α to O), 63.1 (3ArCH_2), 61.0 (6CH_2 α to N). MS (FAB): *m/z* = 424 (55) $[M + H]^+$, 322 (43) $[M + H]^+ - C_4H_8NO_2$, 220 (25) $[M + H]^+ -2[C_4H_8NO_2]$. HRMS: *m/z* $[M + H]^+$ calcd for $C_{21}H_{34}N_3O_6$: 424.24476; found: 424.24416.

Crystal data: $C_{21}H_{33}N_3O_6{\cdot}3CH_4N_2O{\cdot}3\ H_2O$: Stoe IPDS, *T* = 213 K, monoclinic, space group $P2_1/c$, *a* = 10.166(2) Å, *b* = 21.823(4) Å, *c* = 15.565(2) Å, β = 103.58(2)°, *V* = 3356.7(10) Å^3, $2\theta_{max}$ = 45°; 4097 unique reflections, *R*1 [$I > 2\sigma(I)$] 0.081, *wR*2 (all data) = 0.242. Crystals diffracted very weakly; therefore data were truncated at $2\theta_{max}$ = 45°; all three water molecules are disordered. Crystal data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html. **4b**·$3CH_4N_2O{\cdot}3H_2O$: CCDC 1439355.

4,4′,4″-[(2,4,6-Trimethylbenzene-1,3,5-triyl)tris(methylene)]tris(morpholine) 4,4′,4″-Trioxide (8b)

White solid; yield: 480 mg (85%); mp 128–130 °C. IR (nujol): 2924, (s, C–H), 1665 (s, C=C aryl), 1570 (s, C=C aryl), 1114 (s, C–N), 858 (s, N^+–O^-) cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD): δ = 2.85 (s, 9 H, $3CH_3$), 3.05 (s, 6 H, 3 × ring C–CH_2), 3.46 (m, 6 H, 6 *CH* α to O and *syn* to N^+–O^-), 3.66 (m, 6 H, 6 *CH* α to O and *anti* to N^+–O^-), 4.35 (m, 6 H, 6 *CH* α to N and *syn* to N^+–O^-), 4.81 (m, 6 H, 6 *CH* α to N and *anti* to N^+–O^-). ^{13}C NMR (75 MHz, CD_3OD): δ = 130.05 (3 × ring *C*–CH_2), 129.65 (3 × ring *C*–CH_3), 69.2 (3 × ring C–*C*H_2), 62.6 (6 *C*H_2 α to O), 61.4 (6 *C*H_2 α to N), 21.8 (3 *C*H_3). MS (ES,+ve): *m/z* (%) 488 (100) $[M + Na]^+$, 472 (35%) $[M + Na - O]^+$. HRMS: *m/z* $[M + Na]^+$ calcd for $C_{24}H_{40}N_3NaO_6$: 488.2723; found: 488.2752.

Crystal data: $C_{24}H_{39}N_3O_6{\cdot}7\ H_2O$: Bruker Smart Apex, *T* = 150 K, orthorhombic, space group *Pbca*, *a* = 17.8733(11) Å, *b* = 18.0114(11) Å, *c* = 18.6381(12) Å, *V* = 6000.0(6) Å^3, $2\theta_{max}$ = 55°; 7125 unique reflections, *R*1 [$I > 2\sigma(I)$] = 0.050, *wR*2 (all data) = 0.130. H-atoms on water molecules were refined by using restraints. Crystal data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html. **8b**·$7H_2O$: CCDC 1439354.

All other experimental procedures and characterization data can be found in the Supporting Information.

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