CHEMISTRY
A EUROPEAN JOURNAL

Towards Supramolecular Fixation of NO_X Gases: Encapsulated Reagents for Nitrosation

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Abstract: The use of simple calix[4]arenes for chemical conversion of NO_2/N_2O_4 gases is demonstrated in solution and in the solid state. Upon reacting with these gases, calixarenes **1** encapsulate nitrosonium (NO^+) cations within their cavities with the formation of stable calixarene–NO^+ complexes **2**. These complexes act as encapsulated nitrosating reagents; cavity effects control their reactivity and selectivity. Complexes **2** were effectively used for nitrosation of secondary amides **5**, including chiral derivatives. Unique size–shape selectivity was observed, allowing for exclusive nitrosation of less crowded *N*-Me amides **5a–e** (up to 95% yields). Bulkier *N*-Alk (Alk > Me) substrates **5** did not react due to the hindered approach to the encapsulated NO^+ reagents. Robust, silica gel based calixarene material **3** was prepared, which reversibly traps NO_2/N_2O_4 with the formation of NO^+-storing silica gel **4**. With material **4**, similar size–shape selectivity was observed for nitrosation. The *N*-Me–*N*-nitroso derivatives **6d,e** were obtained with ~30% yields, while bulkier amides were nitrosated with much lower yields (<8%). Enantiomerically pure encapsulating reagent **2d** was tested for nitrosation of racemic amide **5t**, showing modest but reproducible stereoselectivity and ~15% *ee*. Given high affinity to NO^+ species, which can be generated by a number of NO_X gases, these supramolecular reagents and materials may be useful for NO_X entrapment and separation in the environment and biomedical areas.

Keywords: calixarenes · molecular recognition · nitrogen oxides · structure–activity relationships · supramolecular chemistry

Introduction

NO_X gases are nitrogen oxides, that is, NO, NO_2, N_2O_3 ($NO{\cdot}NO_2$), N_2O_4 ($NO_2{\cdot}NO_2$), and N_2O_5.[1] These are toxic atmospheric pollutants, originating in large quantities from fuel combustion and large-scale industrial processes. NO_X gases are involved in the formation of ground-level ozone. They form toxic chemicals and acid rains in the atmosphere and also participate in global warming. NO_X are active in various nitrosation processes with biomolecules and tissues, causing cancers and other diseases.[2] Extensive NO_X circulation in the atmosphere, industry, and agriculture necessitates the development of novel methods for their conversion and utilization. We apply supramolecular chemistry for sensing and fixation of environmentally important gases,[3] and we specifically target NO_2/N_2O_4. Thus, we recently discovered that simple caged compounds, calix[4]arenes, reversibly interact with NO_2/N_2O_4 and entrap reactive nitrosonium cations (NO^+) within their cavities.[4]

In this paper, we explore the unique opportunity to use such caged NO^+ complexes as nitrosating reagents for organic synthesis (Figure 1). These are conceptually novel, *encapsulated reagents*. We will show how to convert NO_2/N_2O_4

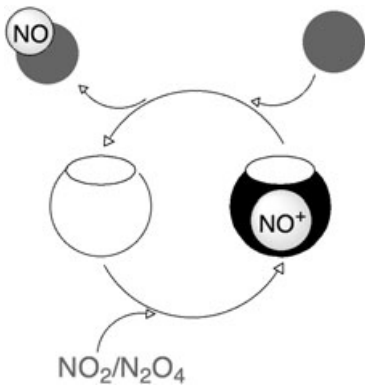

Figure 1. Supramolecular fixation of NO_X gases: encapsulated reagents for nitrosation.

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DOI: 10.1002/chem.200400939

gases into highly stable and selective nitrosating reagents and how to use them in synthesis. We will also report on the preparation of solid-supported encapsulated reagents for nitrosation. Finally, we will describe supramolecular properties of encapsulated reagents, which are responsible for their unique selectivity.[5]

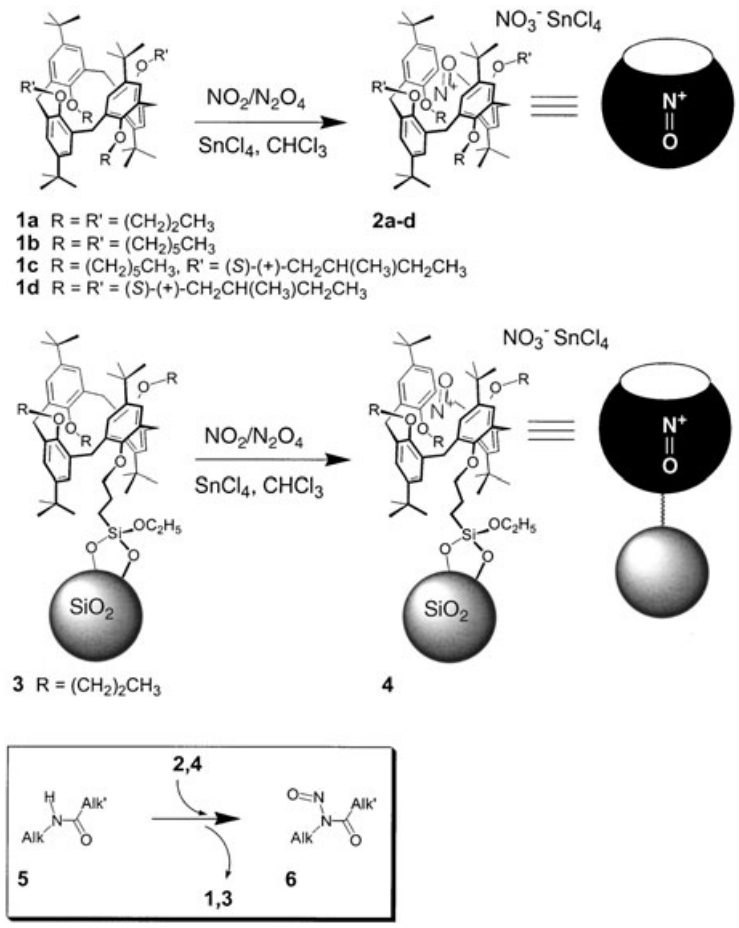
Results and Discussion

In organic chemistry, nitrosation holds a special place. Alkylnitrites, nitrosoamines/amides, and nitrosothiols are used in medicine as NO-releasing drugs.[6] In synthetic methodology, −N=O is an important activating group, allowing for elegant transformations of amides to carboxylic acids and their derivatives.[7] In addition, nitrosation mimics interactions between biological tissues and NO_X gases, especially NO, N_2O_3, and NO_2/N_2O_4, which generate mutagenic nitrosoamines/peptides and also nitrosate and deaminate DNA.[2]

We recently reported that simple tetra-*O*-alkylcalixarenes, for example, **1a**,**b**, react with NO_2/N_2O_4 and entrap highly reactive NO^+ species within their cavities (Scheme 1).[4] NO^+ is generated from N_2O_4, which is the dimer of NO_2 and known to disproportionate to $NO^+NO_3^-$.[8] Stable calixarene–nitrosonium complexes **2a**,**b** were quantitatively isolated and fully characterized. The process is reversible. Addition of H_2O or alcohols resulted in dissociation of **2a**,**b** and complete recovery of "empty" calixarenes **1a**,**b**.

In this project, we tested the ability of encapsulated NO^+ to act as a nitrosating reagent. Specifically, we prepared complexes **2a**–**d** and also silica gel based material **4** and used them in reactions with variety of secondary amides **5**, including chiral derivatives (Scheme 1). These reactions led to *N*-nitrosoamides **6** and exhibited unique selectivity, which is attributed to supramolecular encapsulation effects. In further synthetic applications, *N*-nitrosoamides can be readily converted to carboxylic acids and their derivatives.[7]

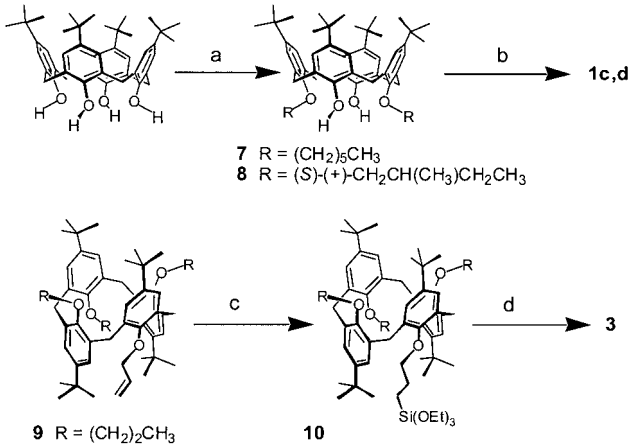
Encapsulated reagents are closely related to "molecule-within-molecule" complexes,[9] especially those which *reversibly* hold and release their guests. For such complexes stabilization of reactive species within the interiors,[10] unusual chemical reactivity in the inner phase,[11] and catalysis[12] have been demonstrated. More recently, it was shown that controlled release of reactants from a self-assembling capsule might lead to autocatalysis.[13] Unusual regioselectivities with encapsulated substrates were also observed.[14] We define encapsulated reagents as reactive species, entrapped within the cavity/cage, that can be released to the reaction mixture under subtle control. Temperature, solvent polarity, and the substrate–cavity size–shape complementarity are the critical factors responsible for the reaction progress. As a consequence, encapsulated reagents may influence the reaction kinetics and selectivity, modify a portion of a molecule without protecting other reactive sites, and control the direction/orientation of the approach of one molecule reacts with another.



Scheme 1. Calixarene based encapsulating reagents for nitrosation: preparation, immobilization on a solid support, and reactions.

Synthesis: Calix[4]arenes in their 1,3-alternate conformation (see for example, **1**) are ideally preorganized to complex NO^+. They possess a cylindrical, π-electron-rich inner tunnel, defined by two cofacial pairs of phenol rings, which are oriented orthogonal along the cavity axis. According to numerous X-ray studies, this tunnel is ~5 Å in diameter.[15] Calix[4]arenes **1a**,**b** were re-synthesized through the two-

step O-alkylation of the parent tetrahidroxycalix[4]arene with *n*-propyl- and *n*-hexylbromide, respectively, using successively K_2CO_3 and then Cs_2CO_3 in boiling MeCN.[16,17] The second alkylation converts the conformation to the 1,3-alternate derivative. Preparation of chiral calixarenes **1c**,**d** is similar (Scheme 2). 1,3-Dialkylated derivatives **7** and **8** were



Scheme 2. a) *n*-HexBr, K_2CO_3, MeCN, reflux, 60% for **7** and 1-bromo-2-(*S*)-(+)-methylbutane, K_2CO_3, MeCN, reflux, 50% for **8**; b) *n*-HexBr, Cs_2CO_3, MeCN, reflux, 42% for **7** and 1-bromo-2-(*S*)-(+)-methylbutane, Cs_2CO_3, MeCN, reflux, 15% for **8**; c) Karstedt cat, $HSi(OEt)_3$, toluene, reflux, 40%; d) activated silica gel (150 Å porosity), CH_2Cl_2, RT, 48 h, 10% loading.

prepared by treatment of the parent calix[4]arene was alkylated with *n*-hexyl bromide or enantiomerically pure 1-bromo-2-(*S*)-(+)-methylbutane, respectively, using K_2CO_3 in boiling MeCN. The alkylation of **7** and **8** with 1-bromo-2-(*S*)-(+)-methylbutane and Cs_2CO_3 in boiling MeCN lead to the formation of the 1,3-alternate conformation.

The synthesis of solid-supported calixarene material **3** begins with recently elaborated derivative **9**.[18] This already possesses a 1,3-alternate conformation and is also functionalized with a terminal allyl group. The allyl double bond in **9** was hydrosilylated under the standard conditions ($HSi(OEt)_3$, Karstedt catalyst, toluene, 90°C)[19,20] to afford calixarene **10** in 40% yield (Scheme 2). Compound **10** then reacted with silica gel (150 Å porosity, Aldrich), which was pre-activated with hot 18% aqueous HCl, to form material **3**. Finally, a variety of secondary amides **5** were prepared. For this, standard textbook protocols were effectively used, which involve the corresponding acid chlorides and amines.

Conversion of NO_2/N_2O_4 into encapsulated nitrosating reagents: Currently used nitrosating agents are HNO_2 (or $NaNO_2/H_2SO_4$), NOCl, N_2O_3, NO_2/N_2O_4, NO/O_2, NO/air, and $NO^+BF_4^-$ and other nitrosonium salts.[6,7] They are the source of nitrosonium ion NO^+, which is an aggressive electrophile and is typically not selective. Nitrosonium complexes **2b–d** were quantitatively prepared upon bubbling NO_2/N_2O_4 through a solution of calix[4]arenes **1b–d** in $CHCl_3$ in the presence of Lewis acid $SnCl_4$, followed by precipitation with dry hexanes. Lewis acids stabilize arene–NO^+ complexes,[8,21] which otherwise rather quickly undergo nitrosation and, further, nitration and/or oxidation.

Complexes **2b–d** are stable, deeply colored solids. Similar to the previous studies,[4] they were characterized by UV-visible, FTIR, and ^{1}H NMR spectroscopy. The UV-visible spectra showed, in particular, a broad charge-transfer[22] band at $\lambda_{max} \sim 570$–590 nm. The FTIR spectra exhibited characteristic[23] arene–NO^+ stretching at $\nu \sim 1934\ cm^{-1}$. The ^{1}H NMR spectra showed new sets of the calixarene signals, different from the starting calixarenes **1** (Figure 2). For example, the aromatic CH protons of guest-free **1b** were seen as a singlet at $\delta = 6.95$ ppm. In nitrosonium complex **2b**, it was transformed into a singlet at $\delta = 7.02$ ppm. The methylene bridge CH_2 and the OCH_2 protons of **1b** were recorded as a singlet at $\delta = 3.73$ ppm and a triplet at $\delta = 3.38$ ppm, respectively. In complex **2b**, these exchanged places and were seen at $\delta = 3.60$ and 3.77 ppm, respectively.

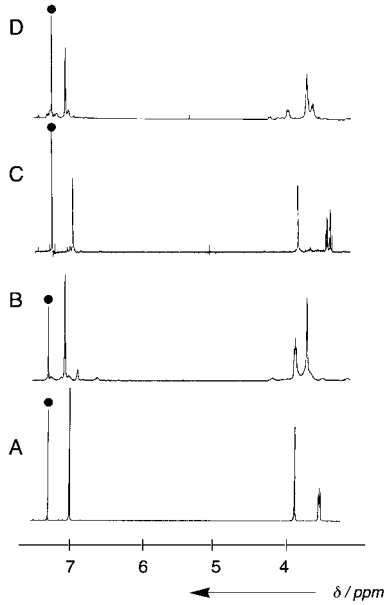


Figure 2. Portions of the ^{1}H NMR spectra (500 MHz, $CDCl_3$, 295 ± 1 K) of: A) Calix[4]arene **1b**. B) Calix[4]arene–nitrosonium complex **2b** prepared from **1b**, NO_2/N_2O_4, and $SnCl_4$. C) Calix[4]arene **1d**. D) Calix[4]-arene–nitrosonium complex **2d** prepared from **1d**, NO_2/N_2O_4, and $SnCl_4$. Mixtures of **1** and NO_2/N_2O_4 exhibit similar spectra, however nitration occurs within few hours. Addition of $NO^+SbF_6^-$ to calixarenes **1** results in analogous spectral changes. The residual $CHCl_3$ signals are marked •.

The aromatic protons of chiral calixarene **1d** were recorded as two 1:1 singlets at $\delta = 6.97$ and 6.95 ppm. In nitrosonium complex **2d**, they were observed as an apparent singlet at $\delta = 7.06$ ppm. The methylene bridge CH_2 protons of **1d** were recorded as an AB quartet centered at $\delta = 3.72$ ppm; in complex **2d**, it shifted upfield and appeared at $\delta =$ 3.62 ppm.

Independent sructural evidence for **2** came from the complexation experiments between calixarenes **1** and commercially available $NO^+SbF_6^-$ salt in $CDCl_3$. The corresponding

UV-visible, FTIR, and ^{1}H NMR complexation induced changes were identical with those of complexes **2** obtained from NO_2/N_2O_4.

Chemical properties of the encapsulated NO^+ are *different* from those in bulk solution and are evidently controlled by the calixarene cavity. Highly reactive NO^+ species are protected from the bulk environment. Indeed, complexes **2** are stable towards moisture and oxygen, and can be handled for hours without dry box and inert atmosphere. Such stability is remarkable.[23] On the other hand, they can be decomposed within seconds by addition of larger amounts of H_2O or alcohols, recovering free calixarenes **1**.

When added to secondary amides **5a–e,t** in freshly distilled $CHCl_3$ or CH_2Cl_2, compounds **2** smoothly reacted at room temperature, yielding 50–95% of corresponding *N*-nitrosoamides **6a–e,t**. Dark-colored solutions of **2** discharged upon reacting. In the ^{1}H NMR spectra of the reaction mixtures, signals for amides **5a–e,t** disappeared and novel, characteristic signals for *N*-nitrosoamides **6a–e,t** emerged. In the reaction between **2b** and **5b–e** for example, signals for the *N*-nitrosoproducts **6b–e** at δ ~3.1 ppm (a triplet for C(O)CH_2 and a singlet for N(NO)-CH_3) were clearly detected already after 30 min (Figure 3). Transformation of complex **2b** into free calixarene **1b** can also be easily followed. Most remarkable, however, is the selectivity.

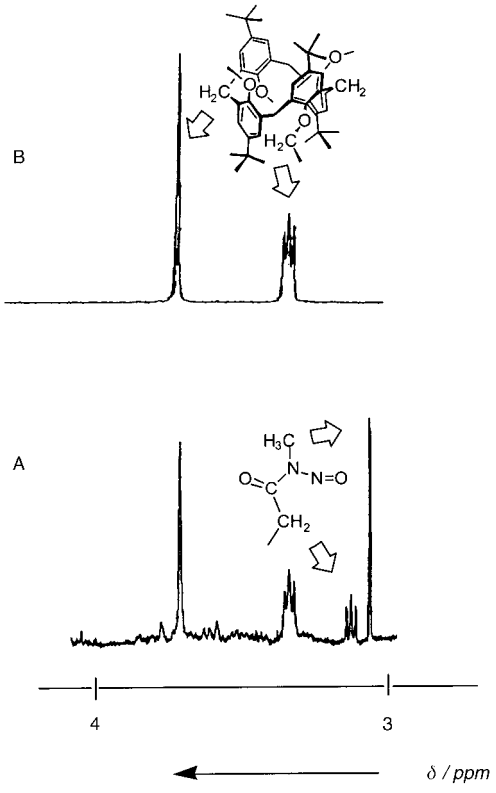


Figure 3. ^{1}H NMR analysis of nitrosation reactions (500 MHz, $CDCl_3$, 295 ± 1 K): A) Reaction mixture **1b+5c** after ~1 h. B) Guest-free calixarene **1b** for comparison. The signals for nitrosamide **6c** were assigned by comparison with the independently prepared sample.

Size–shape selectivity: In reaction of reagents **2b,d** with a variety of amides **5a–t**, only those possessing *N*-CH_3 substituents were transformed to the corresponding *N*-nitrosoamides **6a–e,t**. No reaction occurred for substrates **5f–s** (Table 1). Accordingly, no color discharge was observed for these cases. Such delicate selectivity of *N*-nitrosation was quite unexpected and may be due to the steric effects. The unreacted subtrates were those possessing *N*-Alk groups bulkier than CH_3.

Table 1. Nitrosation of secondary amides **5a–t** with encapsulated reagents **2** and **4**. Yields of *N*-nitrosoamides **6a–t**.[a]

Entry	Reaction	Alk	Alk′	Yield [%]
1	**2b+5a**	CH_3	C_2H_5	50
2	**2b+5b**	CH_3	$(CH_2)_2CH_3$	68
3	**2b+5c**	CH_3	$(CH_2)_3CH_3$	53
4	**2b+5d**	CH_3	$(CH_2)_4CH_3$	95
5	**4+5d**	CH_3	$(CH_2)_4CH_3$	22
6	**2b+5e**	CH_3	$(CH_2)_6CH_3$	63
7	**4+5e**	CH_3	$(CH_2)_6CH_3$	30
8	**2b+5f**	CH_3	$C(CH_3)_3$	[b]
9	**2b+5g**	C_2H_5	C_2H_5	[b]
10	**2b+5h**	C_2H_5	$(CH_2)_2CH_3$	[b]
11	**2b+5i**	C_2H_5	$(CH_2)_3CH_3$	[b]
12	**2b+5j**	C_2H_5	$(CH_2)_4CH_3$	[b]
13	**4+5j**	C_2H_5	$(CH_2)_4CH_3$	5
14	**4+5k**	C_2H_5	$(CH_2)_6CH_3$	4
15	**2b+5l**	$(CH_2)_2CH_3$	C_2H_5	[b]
16	**2b+5m**	$(CH_2)_2CH_3$	$(CH_2)_2CH_3$	[b]
17	**2b+5n**	$(CH_2)_2CH_3$	$(CH_2)_3CH_3$	[b]
18	**2b+5o**	$(CH_2)_2CH_3$	$(CH_2)_4CH_3$	[b]
19	**4+5o**	$(CH_2)_2CH_3$	$(CH_2)_4CH_3$	8
20	**2b+5p**	$CH(CH_3)_2$	$(CH_2)_3CH_3$	[b]
21	**4+5q**	$(CH_2)_2CH_3$	$(CH_2)_6CH_3$	4
22	**2b+5r**	$C(CH_3)_3$	$C(CH_3)_3$	[b]
23	**2b+5s**	CH_2Ph	$(CH_2)_3CH_3$	[b]
24	**2c+5t**	CH_3	$CH_2CH(CH_3)CH_2CH_3$	80[c]
25	**2d+5t**	CH_3	$CH_2CH(CH_3)CH_2CH_3$	60[d]

[a] Determined by ^{1}H NMR spectroscopy and averaged after at least two independent runs. [b] Not detectable by ^{1}H NMR spectroscopy. [c] Yield ~50% after column chromatography. [d] Yield ~40% after column chromatography.

In the currently accepted mechanism,[24,25] nitrosation of secondary amides incorporates an electrophilic attack of NO^+ on the nucleophilic carbonyl oxygen of the substrate, yielding the corresponding *O*-nitroso species (Figure 4, top). Rapid deprotonation, rotation around the C–O bond, and the *cis–trans* inversion through the nitrogen results in the intermediate, in which both the nitrogen lone pair and the –N=O group are properly oriented for the isomerization to the *N*-nitrosoamide.

Dimensions and shapes of the amide Alk and Alk′ become much more crucial when encapsulated reagents **2** are employed. The substrate **5** approaches the cavity **2** facing it with the carbonyl oxygen atom (Figure 4, bottom). One scenario places the *N*-Alk alkyl group in a close proximity to the two *t*Bu and two alkoxy groups of the calixarene. For larger Alk, this could be sterically unfavorable, so

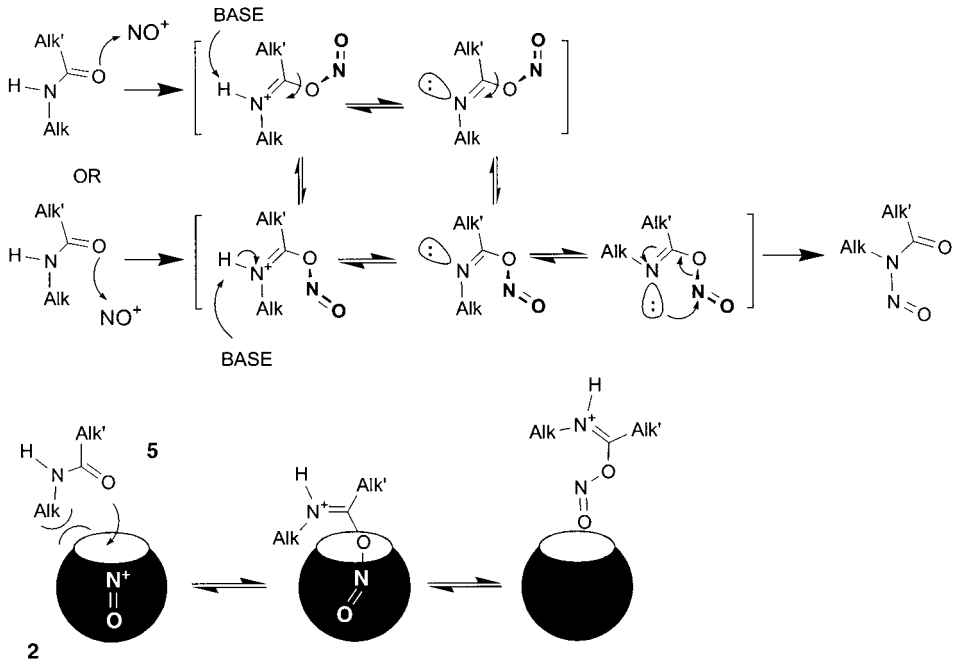


Figure 4. Top: currently accepted mechanism of *N*-nitrosation of secondary amides/peptides.[24,25] Bottom: proposed mechanism of nitrosation with encapsulated calixarene based reagents.

that the substrate C=O and the encapsulated NO^+ would not reach each other. The C(O)Alk′ alkyl group of substrates **5** is apparently positioned farther away from the calixarene substituents and does not significantly interfere, except in the case with bulky amide **5f** (Table 1).

Once formed, the *O*-nitroso intermediate leaves the interior and, as expected, further collapses in bulk solution (Figure 4, top). Due to the extremely strong binding of NO^+ by the calixarene ($K_{assoc} > 10^8\,M^{-1}$),[4,22] the rate-limiting formation of the O-nitrosation intermediates should take place within the cavity, *prior* to the NO^+ dissociation. Otherwise, all reactions should proceed with the similar rate, and no selectivity should be observed. Currently used nitrosating agents such as HNO_2, NOCl, N_2O_3, NO_2/N_2O_4, NO/O_2, NO/air, and nitrosonium salts are typically not selective.[26] This once again emphasizes the role of supramolecular effects in encapsulating nitrosating reagents.

Solid-supported encapsulating reagents: For application in organic synthesis, reagents must be readily immobilizable on solid supports.[27] Among the main advantages of such immobilized, supported reagents are the ease of their separation from the reaction mixture and also their recycling. For the case in hand, the simplification of handling toxic/odorous NO_X gases is of particular importance. Although a wide variety of polymers is now commercially available, NO_2/N_2O_4 (and also other NO_X) react with many of them, causing destruction and aging.[28] As a free radical NO_2 readily attacks double bonds in polybutadienes, polyisoprenes and their copolymers, ester groups in poly(methyl)methacrylate, and also amide fragments in polyamides and polyurethanes. Furthermore, NO^+, generated from various NO_X, reacts with alkenes and other double-bond-containing structures. In these studies, we used silica gel as a solid support. It is robust and stable.

Commercial silica gel of higher porosity (150 Å, Aldrich) was activated with 18% refluxing HCl and then treated with calixarene siloxane **10** in CH_2Cl_2 to give material **3** (Scheme 2). The presence of calix[4]arene units in **3** was confirmed by the appearance of characteristic absorption bands in the IR spectrum (see Experimental Section). From the (thermogravimetric analysis) TGA and also CHN analyses, the calixarene loading of ~10% was estimated. Such rather modest number appeared to be reproducible, even when larger quantities of **10** were employed, and may be due to the steric bulkiness of the calixarene fragment.

The dark-blue nitrosonium-storing silica gel **4** was prepared upon bubbling NO_2/N_2O_4 through the suspension of **3** in CH_2Cl_2 for 5–10 s, followed by filtration and washing with

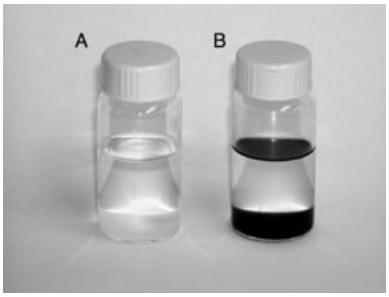


Figure 5. Silica gel supported material **3** (A) and nitrosating material **4** (B), prepared from **3** and NO_2/N_2O_4 in the CH_2Cl_2 suspension.

CH_2Cl_2 (see Figure 5). Material **4** is quite robust and does not change the color for several days. For nitrosation, it was suspended in dry CH_2Cl_2, an equimolar amount of amides **5** was then added, and the reaction mixture was stirred at room temperature for 24 h. The reaction's color disappeared, thus visually indicating the reaction progress. Material **3** was separated by simple filtration. Yields of nitrosamides **6** were determined by ^1H NMR spectroscopy, integrating signals of the product versus the starting compounds (Table 1).

The size-shape selectivity trend, observed for the solution experiments with complexes **2**, was clearly seen in this case as well. After at least three independent runs, the averaged

yields of *N*-Me nitrosoamides **6d**,**e** were established up to 30%, while bulkier *N*-Et **6j**,**k** and *N*-Pr derivatives **6o**,**q** formed in much smaller quantities ($\leq$8%). In control experiments, involving starting silica gel, no visible amounts of **6e** were seen, again emphasizing the role of calixarene cavity in the described reaction.

In future studies, the calixarene loading must be increased, so the yields can be further improved for selective nitrosations. Another important issue is the material stability and regeneration.[29] Multiple hydroxy groups in silica gels may react with the stabilizers, that is, Lewis acids, and also quench NO^+ reactive species. Partial nitration of the calixarene units in **3** may occur.[4] Stabilized calixarene silica gels for nitrosation will be our next targets. In the meantime we have noticed that the high affinity of **3** and its relatives to the nitrosonium species may be very useful for entrapment and utilization of NO_X gases in general, especially for synthetic and biomedical purposes.

Probing stereoselectivity: Chiral calixarenes **1c** and **d** were prepared, which posses 2-(*S*)-(+)-methylbutyl fragments attached to one or both calixarene rims, respectively (Scheme 1). Nitrosonium complexes **2c**,**d** were then generated from NO_2/N_2O_4, which may be considered as *chiral* encapsulating reagents. In the preliminary experiments, these complexes were used in reaction with a racemic secondary amide. Preference for one enantiomer of the amide over the other was expected, as the reaction takes place at the chiral calixarene rim.

When added to a solution of the racemic *N*-methylamide of 3-methylvaleric acid (*R*,*S*)-**5t** (~5–10 equiv excess) in freshly distilled CH_2Cl_2, complexes **2c**,**d** readily react. The dark-blue color disappeared in 1–2 h, yielding mixtures of (*R*)- and (*S*)-**6t** in 60–80% total yield (^{1}H NMR spectroscopy). The products were then purified by column chromatography. Initially, the Pirkle shift reagent, (−)-2,2,2-trifluoro-1-(9-anthryl)ethanol (Acros), was applied to determine the enantiomeric excess (further, *ee*). However, no reasonable separation of diastereomeric solvates was detected by ^{1}H NMR spectroscopy; this is, most probably, due to the insufficient intermolecular interactions. For assignment purposes, the mixture of *N*-nitrosoderivatives **6t** was then quantitatively decomposed back to amides **5t** upon treatment with trifluoroacetic acid (TFA) (RT, 14 h). In this case, addition of the Pirkle reagent to a solution of a mixture (*R*)- and (*S*)-**5t** in [D_6]benzene readily produced two sets of signals for diastereomeric complexes (Figure 6). These were used to determine the *ee* in nitrosation with **2c**,**d**.

While reaction between reagent **2c** and racemate **5t** did not result in chiral discrimination, modest but reproducible ~15% *ee* of (*S*)-*N*-nitrosoamide **6t** versus (*R*)-*N*-nitrosoamide **6t** was obtained (see Experimental Section for further details). Geometry of prereactive complexes **2c·5t** and **2d·5t** is, most probably, similar to the complex **2a**,**b·5** (see Figure 6C). In the proposed scenario, molecule **5t** approaches the cavity **2d** facing it with the carbonyl oxygen atom, thus placing the $C(O)CH_2CHEtMe$ group in close

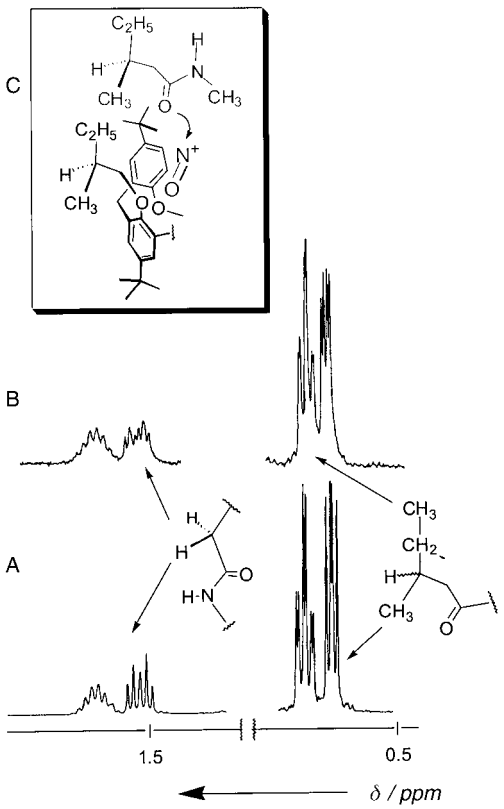


Figure 6. ^{1}H NMR analysis of nitrosation reactions between chiral complexes **2c**,**d** and racemic amide **5t**. For the enantiomeric excess (*ee*) determination, the obtained *N*-nitroso products (*R*)-**6t** and (*S*)-**6t** were quantitatively converted back to **5t** with TFA, and the stereoisomers distribution was analyzed with (−)-2,2,2-trifluoro-1-(9-anthryl)ethanol (Pirkle shift reagent) (500 MHz, [D_6]benzene, 295 ± 1 K): A) Mixture of amides (*R*)-**5t** and (*S*)-**5t**, obtained after the reaction with complex **2c**; no *ee* was detected. Identical spectrum was obtained for independently synthesized, racemic **5t** with the Pirkle reagent. B) Mixture of amides (*R*)-**5t** and (*S*)-**5t**, obtained after the reaction with **2d**; ~15% *ee* was detected, with the preference for the (*S*)-configuration. For details, see Experimental Section. C) Proposed intermediate for chiral reaction between complex **2d** and racemic amide **5t**.

proximity to the calixarene rims' chiral OCH_2C*HEtMe groups. Van der Waals contacts occur, and chiral discrimination results. In the case of calixarene **2c**, possessing one rim with a chiral OCH_2C*HEtMe fragment and the other with $O(CH_2)_5CH_3$ group, the substrate apparently chooses the latter, less hindered site. Consequently, no stereoselectivity is observed.

Despite being modest, the stereoselectivity offered by chiral nitrosating reagent **2d** is novel. Indeed, all currently employed sources of NO^+ are achiral. We are now working to improve the *ee* values. For this, further structural modification of calixarenes is needed; this includes placement of the chiral groups much closer to the reaction center.[30] In the future, thermal decomposition of enantiomerically enriched or pure *N*-nitrosamides could lead to chiral carboxylic acids and their derivatives. Exploratory, these features may help to design optically active NO donors.

Conclusions

Novel nitrosating reagents are now available that can be obtained upon fixation of NO_2/N_2O_4 with calix[4]arenes. These are encapsulated reagents, and their reactivity and selectivity is controlled by the host cavity. They are stable, mild, and size–shape selective. The first chiral nitrosating reagents are also in hand; this opens doors for stereoselective syntheses of various nitroso derivatives and their transformations. We are currently testing these encapsulated reagents in optimized syntheses of NO-releasing pharmaceuticals. For this, further synthetic modifications of the calix[4]arene cage is required and is currently in progress. Another attractive avenue is solid-supported encapsulating reagents, which greatly expand the scope of reactions. Given high affinity to nitrosonium species, generated by a number of NO_X gases, these supramolecular materials may be very useful for NO_X entrapment and separation in biomedical areas. Our findings clearly demonstrate that concepts and techniques of supramolecular chemistry can be applied for conversion of environmentally important gases.[3]

Experimental Section

General: Melting points were determined on a Mel-Temp apparatus (Laboratory Devices, Inc.) and are uncorrected. ^{1}H, ^{13}C NMR, and COSY spectra were recorded at 295±1°C on a JEOL Eclipse 500 MHz spectrometer. Chemical shifts were measured relative to residual nondeuterated solvent resonances. FTIR spectra were recorded on a Bruker Vector 22 FTIR spectrometer. ESI-MS spectra were obtained on a Finnigan LCQ Ion Trap apparatus. MALDI-TOF mass spectra were recorded on a delayed extraction MALDI-TOF mass spectrophotometer Voyager DE (Applied Biosystems). HRMS MALDI spectra were obtained on an Ion Spec Ultima FTMS. Elemental analysis was performed on a Perkin–Elmer 2400 CHN analyzer. For TGA, TA Instruments TGA 2050 instrument was used.

All experiments with moisture- and/or air-sensitive compounds were run under a dried nitrogen atmosphere. For column chromatography, silica gel 60 Å (Sorbent Technologies, Inc.; 200–425 mesh) was used. Parent tetrahydroxycalix[4]arene,[31] calixarene **1b**,[17] its complex **2b**,[17] and derivatized calixarenes **7**[32] and **9**[18] were prepared according to the published procedures. NO_2/N_2O_4 gas was generated from copper and concentrated HNO_3. Molecular modeling was performed using commercial MacroModel 7.1 with Amber* Force Field.

Caution 1: NO_2 has an irritating odor and is very toxic!

Caution 2: *N*-Nitrosoamides are carcinogens[2] and should be treated with extreme care!

General procedure for alklylation of 25,26,27,28-tetrahydroxycalix[4]arene—preparation of 1,3-alternates: An alkylbromide (0.03 mol) was added to a suspension of tetrahydroxycalix[4]arene (0.01 mol) and K_2CO_3 (4.2 g, 0.03 mol) in MeCN (200 mL), and the reaction mixture was refluxed under nitrogen for 48 h. The precipitate was filtered off, and the solution was evaporated to dryness. The residue was redissolved in CH_2Cl_2 (200 mL), and the solution was washed with water (3×150 mL) and dried over $MgSO_4$. After evaporation, the solid residue was treated with MeOH (200 mL) to yield the corresponding 5,27-bis(alkyloxy)-26,28-hydroxycalix[4]arene. An alkylbromide (0.04 mol) was added to a suspension of this compound (0.01 mol) and Cs_2CO_3 (50 g, 0.15 mol) in MeCN (300 mL), and the reaction mixture was refluxed under nitrogen for 48 h. After cooling, the precipitate was filtered off and treated with a mixture of water (100 mL) and CH_2Cl_2 (100 mL). The organic layer was separated, washed with water (2×100 mL), dried over $MgSO_4$, and evaporated.

5,11,17,23-Tetra-*tert*-butyl-25,27-bis(*n*-hexyloxy)-26,28-bis[(*S*)-(+)-2-methylbutyloxy]calix[4]arene, 1,3-alternate (1c): Yield 42%; m.p. 144°C; ^{1}H NMR ($CDCl_3$): δ=6.96, 6.94 (2×s, 8H), 3.75 (m, 8H), 3.35 (m, 4H), 3.26 (t, J=7.0 Hz, 4H), 1.53 (m, 2H), 1.28, 1.25 (2×s, 36H), 1.21 (m, 8H), 1.11 (m, 8H), 1.03 (d, J=5.0 Hz, 4H), 0.86 (t, J=7.0 Hz, 6H), 0.81 (t, J=7.5 Hz, 6H), 0.48 ppm (d, J=6.5 Hz, 6H); ^{13}C NMR ($CDCl_3$): δ= 155.6, 155.1, 143.2, 143.1, 133.3, 133.0, 132.8, 132.7, 126.4, 126.2, 126.1, 126.0, 76.8, 70.8, 39.3, 39.2, 34.9, 34.0, 33.9, 32.1, 31.8, 31.7, 29.1, 26.5, 25.7, 23.2, 17.3, 14.2, 11.3 ppm; MALDI-MS: m/z calcd for $C_{66}H_{100}O_4Na$: 979.7519; found: 979.7481 [M^++Na]; $[\alpha]_D$=3.92 (c=5.0 in $CHCl_3$).

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrakis[(S)-(+)-2-methylbutoxy]-calix[4]arene, 1,3-alternate (1d): Yield 15%; m.p. 252°C; ^{1}H NMR ($CDCl_3$): δ=6.97, 6.95 (2×s, 8H), 3.72 (ABq, 8H), 3.28 (2×dd, 8H), 1.64 (m, 4H), 1.26 (bs, 36H), 1.03 (d, J=5.0 Hz, 8H), 0.84 (t, J=8.0 Hz, 12H), 0.57 ppm (d, J=7.0 Hz, 12H); ^{13}C NMR ($CDCl_3$): δ=155.9, 142.6, 132.8, 132.6, 127.0, 126.9, 77.5, 34.9, 33.9, 31.7, 26.7, 17.3, 11.3 ppm; MALDI-MS: m/z calcd for $C_{64}H_{96}O_4Na$: 951.7235; found: 951.7235 [M^++Na]; $[\alpha]_D$=5.36 (c=2.7 in $CHCl_3$).

Calixarene siloxane (10): The Karstedt catalyst was added dropwise at 40°C under nitrogen to a solution of calixarene **9** (0.5 g, 0.61 mmol) in dry toluene (20 mL), and the mixture was stirred for 1 h, after which $SiH(OEt)_3$ was added dropwise and the resulting mixture was refluxed at 90°C for another 24 h. The solvent was evaporated, and the product **10** was purified by column chromatography. Yield 40%; ^{1}H NMR ($CDCl_3$): δ=6.98 (2×s, 2H), 6.95 (s, 2H), 6.93 (s, 4H), 3.8 (m, 8H), 3.75 (m, 6H), 3.36 (m, 6H), 3.24 (t, J=7.6 Hz, 3H), 1.47 (m, 2H), 1.26 (s, 18H), 1.24 (s, 18H), 1.21 (t, J=7.0 Hz, 9H), 1.14 (m, 4H), 0.98 (m, 2H), 0.67 (t, J= 7.5 Hz, 6H), 0.58 (t, J=7.5 Hz, 3H), 0.43 ppm (m, 2H); ^{13}C NMR ($CDCl_3$): δ=155.1, 154.9, 154.7, 143.5, 143.4, 143.1, 133.2, 133.0, 126.3, 125.9, 125.8, 73.6, 72.1, 71.7, 58.5, 58.4, 39.2, 39.0, 33.9, 31.7, 31.5, 30.4, 23.2, 22.7, 22.3, 18.4, 10.2, 10.1, 6.4 ppm; FTIR (KBr): $\tilde{\nu}$=2962, 2901, 2873, 2029, 1597, 1482, 1473, 1360, 1243, 1211, 1123 cm^{-1}; MS ESI TOF: m/z calcd for $C_{62}H_{94}O_7Si$: 979.6841; 979.6829 [M^++H].

Silica gel supported calixarene (3): The suspension of silica gel (150 Å) and 18% aq HCl was refluxed for 9 h, after which the mixture was filtered and washed with deionized water until pH ~4. Thus activated silica gel was dried under vacuum (0.1 mm Hg) at 100°C for 48 h. The mixture of calixarene **10** and the activated silica gel in CH_2Cl_2 was stirred at room temperature for 48 h and then filtered. The filtrate was washed successively with CH_2Cl_2, acetone, water, THF, and diethyl ether to afford silica gel supported material **3** as a white powder. FTIR (KBr): $\tilde{\nu}$=2965, 2357, 1633, 1470, 1106, 966, 801, 471 cm^{-1}; elemental analysis calcd (%) for 9.5% loading: C 7.82, H 0.94; found: C 7.49, H 1.34; TGA: 10% weight lost.

General procedure for the preparation of calixarene–nitrosonium complexes (2): NO_2/N_2O_4 gas was bubbled for 20 s through the solution of calixarene **1** (1×10^{-5} mol) and $SnCl_4$ (~2.5×10^{-5} mol) in dry $CHCl_3$ (1 mL). The solvent was evaporated under the steam of dry nitrogen. The dark-colored precipitate was redissolved in dry CH_2Cl_2 (1 mL) and used for further reactions. Yields 90–95%.

Complex ***2c***: ^{1}H NMR ($CDCl_3$): δ=7.06 (s, 4H), 7.02 (s, 4H), 3.75 (t, J= 8.0 Hz, 4H), 3.58 (m, 12H), 1.96 (m, 2H), 1.83 (m, 4H), 1.30 (m, 20H), 1.33 (s, 18H), 1.26 (s, 18H), 1.07 (d, J=5.0 Hz, 6H), 0.99 (t, J=7.0 Hz, 6H), 0.93 ppm (t, J=7.0 Hz, 6H); UV/Vis ($CDCl_3$): λ_{max}=580 nm; IR ($CDCl_3$): $\tilde{\nu}$=1934 cm^{-1} (NO^+).

Complex ***2d***: ^{1}H NMR ($CDCl_3$): δ=7.06 (s, 8H), 3.88 (m, 4H), 3.62 (ABq, 8H), 3.53 (2×br d, 4H), 1.96 (m, 4H), 1.83 (m, 4H), 1.28 (m, 20H), 1.33 (s, 18H), 1.23 (m, 40H), 1.07 (d, J=6.5 Hz, 12H), 0.99 ppm (t, J=7.0 Hz, 12H); UV/Vis ($CDCl_3$): λ_{max}=590 nm; IR ($CDCl_3$): $\tilde{\nu}$= 1934 cm^{-1} (NO^+).

Preparation of amides (5a–t): Amides **5a–t** were synthesized by the textbook procedure upon mixing equimolar amounts of the corresponding amines and acid chlorides in H_2O/EtOAc (1:1) in the presence of K_2CO_3, and purified by recrystallization from MeOH. No traces of the solvent were present in samples used for nitrosation (^{1}H NMR, $CDCl_3$). The

spectral data for amides **5a–s** were published in the supplementary materials in associated with reference [5] and elsewhere.[33–44,7h]

(*R*,*S*)-*N*-Methyl-(2-methyl)valeramide ((*R*,*S*)-5t): Yield = 50%; ^{1}H NMR ([D$_6$]benzene): δ = 5.6 (br s, 1H), 2.42 (d, J = 4.5 Hz, 3H), 1.96 (m, 1H), 1.82 (dd, J = 14.5 Hz, J = 6.0 Hz, 1H), 1.55 (dd, J = 14.5 Hz, J = 6.0 Hz, 1H), 1.3 (m, 1H), 1.1 (m, 1H), 0.87 (d, J = 7.0 Hz, 3H), 0.82 ppm (t, J = 7.5 Hz, 3H); ^{13}C NMR: δ = 173.8, 44.0, 32.3, 29.5, 26.2, 19.2, 11.4 ppm; EI-MS: m/z calcd for $C_7H_{17}NO$: 129.1; found: 129.0 [M^+].

(*S*)-3-Methylpentyl *N*-methyl amide ((*S*)-5t): The mixture of (*S*)-3-Methylpentanoic acid[45] (2 mL) and $SOCl_2$ (15 mL) was refluxed for 4 h. Excess $SOCl_2$ was evaporated in vacuum and the resulting acid chloride was redissolved in CH_2CL_2 (10 mL). This solution was added dropwise to the mixture of methylamine and Et_3N in CH_2CL_2 (10 mL) at ~0 °C. The resulting mixture was stirred at RT for 2 h, and then acidified with 10% aq HCl, washed with water (3 × 15 mL), dried over $MgSO_4$, and evaporated under reduced pressure. Yield 90%.

General nitrosation procedure with encapsulated reagents: Calixarene–nitrosonium complex **2** (1 equiv) was added to the solution of amide **5** (~5 equiv) in freshly distilled CH_2Cl_2 or $CHCl_3$, and the reaction mixture was stirred at RT for 2–3 h until bleaching. The solvent was evaporated, and the residue was analyzed by ^{1}H NMR spectroscopy and in some cases separated by preparative TLC, resulting in *N*-nitrosoamides as orange oils. All runs were performed at least in duplicate. The spectral data for the obtained *N*-nitroso compounds **6a–e,t** were identical with those independently obtained from **5a–e,t** and NO_2/N_2O_4 in $CHCl_3$ (> 95% yields) following the literature protocols.[46] *N*-nitrosamides **6f–s** cannot be obtained from **5f–s** and complexes **2**. These were prepared, for spectral comparison, by employing NO_2/N_2O_4 in $CHCl_3$. The spectral data for nitrosamides **6a–s** were published in the supplementary materials associated with reference [5] and elsewhere.[47–52,7h,26b]

Nitrosation with chiral reagents (2c,d): The standard nitrosation procedure was applied, after which the reaction mixture was evaporated under reduced pressure at RT. The residual oil was separated by column chromatography with hexanes/CH_2Cl_2 (2:1) for **2c+5t** and hexanes/C_6H_6 (3:1) for **2d+5t**. Fractions containing *N*-nitroso-(2-methyl)valeramides **6t** were collected and evaporated under reduced pressure at RT. The resulting oil was treated with TFA (20–25 mL) at RT for 14 h, after which the volatiles were evaporated to give pure *N*-methyl-(2-methyl)valeramides **5t** in 40–50% yield.

For identification purposes, amide **5t** was separately prepared in both the enantiomerically pure (*S*)-form and as a racemate. The ^{1}H NMR signals were assigned through COSY experiments. The optimal stoichiometry for the Pirkle reagent was established, which is ~6 equiv in [D$_6$]benzene. Particularly useful for the *ee* determination are the methylene C*H*$_2$C(O) signals and, to lesser extent, both methyl CH$_3$ groups of **5t**. In the absence of the shift reagent, the diastereotopic methylene C*H*$_2$C(O) protons exhibit two sets of doublets (J = 14.5 Hz) at δ = 1.82 and 1.55 ppm. Addition of the shift reagent to racemic **5t** splits the more downfield set into three doublets at δ = 1.55, 1.53 and 1.51 ppm in a 1:2:1 ratio. The intensity of the left and right doublets varies with respect to the enantiomeric ratio. In the ^{1}H NMR spectrum of amides **5t**, obtained after the reaction with **2c**, the diastereotopic methylene C*H*$_2$C(O) protons exhibited, in particular, three doublets at δ = 1.55, 1.53 and 1.51 ppm in exact 1:2:1 ratio. No chiral discrimination was seen. In the ^{1}H NMR spectrum of amides **5t**, obtained after the reaction of **2d**, the same *CH*$_2$C(O) protons exhibited the three doublets at in a ~0.85:2:1.15 ratio. The intensity of the right doublet, assigned to the (*S*)-enantiomer was higher and showed good reproducibility in at least three independent experiments.

*(R,S)-N-Methyl-N-nitroso-(2-methyl)valeramide ((R,S)-**6t**)*: ^{1}H NMR: δ = 3.16 (m, 1H), 3.10 (s, 3H), 3.0 (m, 1H), 2.07 (m, 1H), 1.43 (m, 1H), 1.30 (m, 1H), 0.98 (d, J = 8.0 Hz, 3H), 0.88 ppm (t, J = 8.0 Hz, 3H); ^{13}C NMR: δ = 177.2, 41.5, 32.1, 29.6, 25.7, 19.8, 11.3 ppm; EI-MS: m/z calcd for $C_7H_{14}N_2O_2$: 158.1; found: 158.1 [M^+].

Nitrosation procedure with silia gel supported reagent (4): The suspension of material **3** in dry CH_2Cl_2 NO_2/N_2O_4 was bubbled for ~10 s. The dark-blue colored solid was filtered off and washed with CH_2Cl_2 and suspended in CH_2Cl_2. The corresponding amide **5** (1:1) was added the mixture and stirred at room temperature for 20 h. After filtration, the solvent was evaporated and the residue was analyzed by ^{1}H NMR spectroscopy in $CDCl_3$.

Acknowledgements

Financial support is acknowledged from the Texas Advanced Technology Program (003656-0146-2003), NSF (CHE-0350958) and the Alfred P. Sloan Foundation.

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Received: September 13, 2004
Published online: January 26, 2005