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Highly Selective Monomethylation of Primary Amines Through Host−Guest Product Sequestration

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Secondary amines are an important class of organic compounds whose synthesis is one of the most studied in organic chemistry. N-monomethylated amines, in particular, are present in a broad range of biologically active compounds, and they are widely utilized as intermediates in the preparation of pharmaceuticals and dyes.[1] Traditional methods for direct N-methylation of primary amines are still problematic despite the use of catalysts,[2] solid bases,[3] and nonconventional methylating agents.[4,5] Harsh reaction conditions, poor yields, and low selectivity are the major limitations.[1c] To control reaction output, supramolecular protection constitutes a possible alternative to catalysis or to the introduction of hindered protecting groups. To date, supramolecular structures have been used as catalysts, promoters, and nanovessels to direct reactivity, regioselectivity, and chemoselectivity of organic reactions.[6] A still unexplored approach to reaction control involves the sequestration of the desired product to avoid subsequent unwanted reactions. Herein, we report the exclusive N-monomethylation of primary amines through specific sequestration of the intermediate product by a suitable host, therefore avoiding further methylation in situ.[7]

The receptor chosen for this purpose is a tetraphosphonate cavitand **Tiiii**,[8] which exhibits extremely high affinity for N-methylammonium salts, forming 1:1 complexes with K_{ass} values exceeding 10^9 M^{-1} in chlorinated solvents. The peculiar affinity of **Tiiii** cavitand toward methylalkylammoniun ions[8a] is due to a synergistic combination of three interaction modes: (i) a multiple ion−dipole interaction between the inward facing P═O groups and the positively charged methylammonium moiety, (ii) directional H-bonding involving two adjacent P═O groups,[8b] and (iii) CH_3-π interaction between the acidic methyl group and the π-basic cavity (green, magenta lines, and blue arrow, Figure 1c).[8d]

According to this approach, the product distribution in the N-methylation reaction of primary amines is controlled by the relative stability of the corresponding cavitand-methylammonium complexes. To verify this hypothesis, the reaction of *n*-butylamine with an excess of methyl iodide was monitored in the presence of stoichiometric amounts of three different cavitands[9] that form complexes of increasing stability with monomethylammonium salts (Scheme 1). **MeCav** stands at the lower end of complexation ability, as it binds the guest only through CH_3-π interaction (blue arrow, Figure 1a).[10] Tetrathiophosponate **TSiiii** cavitand occupies an intermediate position: in addition to CH_3-π interaction, it offers the guest weak H-bonding and ion−dipole interactions (blue arrow and green line, Figure 1b).[11] The substitution of weakly polarized P═S moieties with highly polarized P═O units further increases ion−dipole and hydrogen bonding interactions, making **Tiiii** cavitand the best sequestrating agent.

Table 1 resumes the outcome of the N-methylation reaction in the presence of the three sequestrating agents, compared with the control reaction. In all three cases, there is a clear bias toward the monomethylated product. This bias is limited for **MeCav**, moderate for **TSiiii**, and complete for **Tiiii**, in line with the relative complexation strength of the three cavitands.

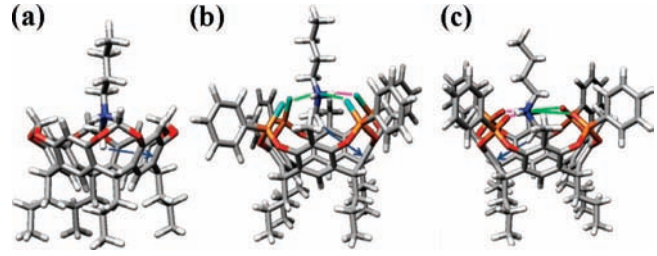

Figure 1. Spartan minimized structures of cavitand-butylmethylammonium complexes. The different interaction modes are evidenced: CH-π (blue arrow), ion-dipole (green line), and H-bond (magenta line).

Qualified as the best sequestrating agent, the **Tiiii** cavitand was next used to extend the monomethylation protocol to other primary amines. Table 2 reports the results obtained with aliphatic (entries 1−4), cycloaliphatic (entry 5), and aromatic amines[12] (entry 6). Three different procedures, summarized in Supporting Information, Scheme S1, were employed to determine the yields.

In all cases, the monomethylated product was the only compound detected, thus eliminating the need for tedious purification procedures to recover it in its pure form (procedure 1, Supporting Information). The **Tiiii** cavitand has been reused without appreciable loss of activity.

Separate ^{31}P NMR resonances are observed for the complexed and free **Tiiii** cavitand at 8.65 and 4.65 ppm, respectively, as the rates of guest exchange in and out the cavity are slow on the NMR

Scheme 1. Monomethylation Reaction of Primary Amines in the Presence of Cavitands as Sequestrating Agents

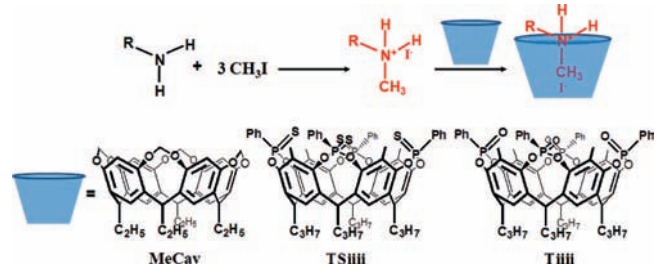

Table 1. Monomethylation Reaction of *n*-Butylamine Using Different Cavitands as Sequestrating Agents

entry	cavitand	yield[a] (%)
1	**Tiiii**	100
2	**TSiiii**	65
3	**MeCav**	45
4	control reaction	25

[a] GC yields using *n*-butanol as precursor of the internal standard (see SI for the procedure).

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Table 2. Amine Monomethylation in the Presence of **Tiiii** Cavitand as Sequestrating Agent

entry	amine	*T* (°C)	yield[a]	yield[b]	yield[c]
1	$C_2H_5NH_2$	25	62	75	96
2	$C_3H_7NH_2$	25	62	79	98
3	$C_4H_9NH_2$	25	62	87	100
4	$C_7H_{15}NH_2$	25	67	75	100
5	$C_6H_{11}NH_2$	45	72	64	97
6	$C_6H_5NH_2$	45	72	82	99

[a] Isolated yields of the crystallized monomethylated ammonium salts. [b] Isolated yields of the derivatized monomethylated products. [c] GC yields of derivatized monomethylated products. In all cases the yields are the average of three reaction runs.

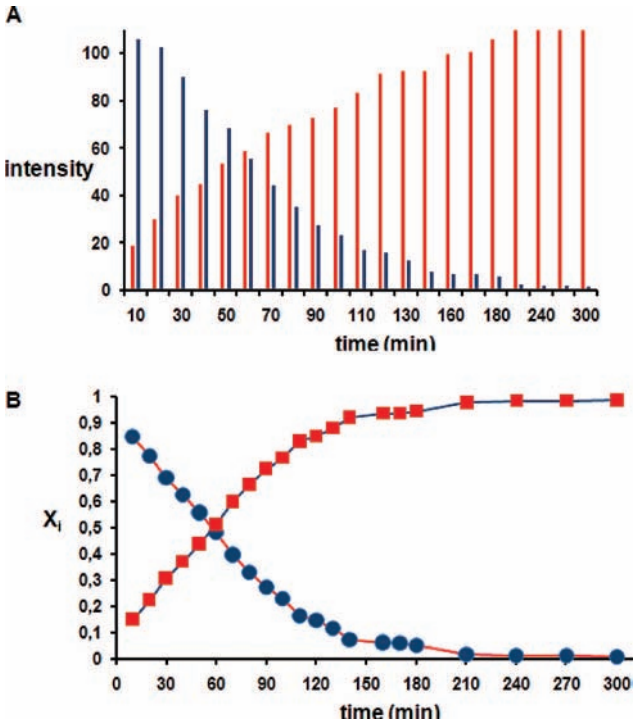

Figure 2. Formation of the **Tiiii**·*N*-methylheptylammonium complex monitored via ^{31}P NMR: (A) Sequence of the ^{31}P spectra taken at different times; (B) corresponding plot of the normalized areas X_i of the ^{31}P signals versus time. Blue peaks and circles = free **Tiiii**; red peaks and squares = **Tiiii**·*N*-methylheptylammonium complex.

time scale. As a result, the reaction can be monitored through both the disappearance of the free cavitand and the formation of the **Tiiii**·methylalkylammonium complex. At 0.035 M concentration, total conversion was achieved in 2 min for propylamine, 90 min for butylamine (Figures S6−S7), and 215 min for heptylamine (Figures 2 and S8).[13] As control experiment, the **Tiiii**·*N*,*N*-dimethylethylammonium complex was prepared (^{31}P resonance = 7.32 ppm in $CDCl_3/D_2O$) and exchanged with *N*-butylmethylammonium iodide. Complete replacement of the dimethylated guest with 1 equiv of the monomethylated one has been recorded via ^{31}P NMR (Figure S9), proving the exclusive formation and higher stability of the **Tiiii**·*N*-methylalkylammonium complexes in the reaction medium.

This conceptually novel procedure for the N-monomethylation of primary amines demonstrates that host−guest interactions can be successfully employed to impart unique selectivity to organic reactions, offering attractive alternatives to current synthetic protocols. High association constants and specific complexation modes are the two key properties that must be considered when choosing an effective sequestrating agent. Heterogeneization of the **Tiiii** receptor, either by grafting on surfaces[14] or by inclusion in sol−gel,[15] will further simplify the procedure.

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Supporting Information Available: Procedural and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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