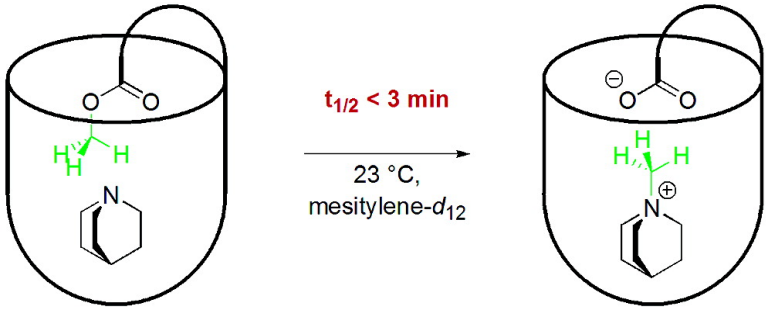
Communication

Reactivity and Molecular Recognition: Amine Methylation by an Introverted Ester

Byron W. Purse, Pablo Ballester, and Julius Rebek

J. Am. Chem. Soc., **2003**, 125 (48), 14682-14683• DOI: 10.1021/ja036595q • Publication Date (Web): 08 November 2003



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 8 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 11/08/2003

Reactivity and Molecular Recognition: Amine Methylation by an Introverted Ester

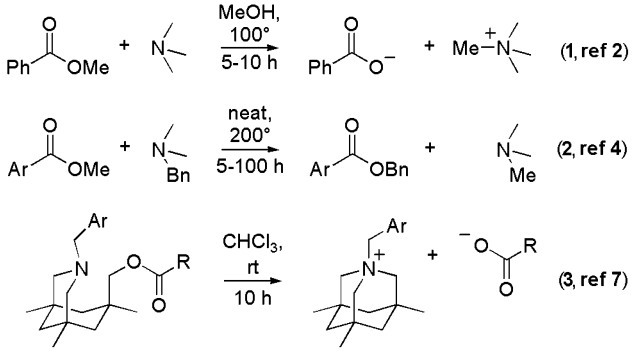
Byron W. Purse, Pablo Ballester, and Julius Rebek, Jr.*

The Skaggs Institute for Chemical Biology and Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Rd, La Jolla, California, 92037

Received June 10, 2003; E-mail: jrebek@scripps.edu

One goal of research in supramolecular chemistry is the investigation of reactivity of guests in the inner space of host molecules. Here we describe a host with an inwardly directed methyl ester and its reaction with a series of tertiary amine guests. A sizable rate acceleration of the methyl transfer reaction is observed; it can be understood as a phenomenon of molecular recognition.

The alkylation of amines by esters is more than 100 years old. Although the reaction stayed out of the mainstream of organic chemistry, its investigators did not: Willstätter,[1] Hammett (eq 1),[2] Newman,[3] Eliel (eq 2),[4] Joullié,[5] and Zaugg[5] had, at various times, studied the process. The reaction appeared, unintentionally and in an intramolecular context, in our laboratories as well (eq 3).[7] The reaction is sluggish given a typical tertiary amine and methyl ester, taking hours to days, even at temperatures above 100 °C. There are understood exceptions: Joullié reports that methyl trihaloacetates react within minutes, and the intramolecular case mentioned above (eq 3) has a half-life of hours at ambient temperature.



The introverted acid cavitand **1a** (Figure 1) features a unique arrangement of functionality.[8] The carboxyl group is directed into a cavity that more or less surrounds small amines. These guests fill appropriate amounts of space within the binding site and provide basic complements to the carboxylic acid. Accordingly, high binding affinities are seen. With suitable amines, the inversion dynamics at nitrogen are profoundly affected by complexation.[9]

Treatment of **1a** with an ethereal solution of diazomethane yields quantitatively introverted methyl ester cavitand **1b** in less than 3 min at ambient temperature. In an attempt to observe the NMR spectrum of the complex of quinuclidine with **1b** (Figure 2) in mesitylene-d_{12}, we were instead presented with the spectrum of *N*-methylquinuclidinium and **1c** as soon as the mixture could be placed in the spectrometer. The identity of this complex was established by comparison to an authentic sample of *N*-methylquinuclidinium tetrafluoroborate and the sodium salt of **1c** (Figure S3 in Supporting Information). In further confirmation of this result, *N*-methylquinuclidinium and **1a** could be clearly identified by ESI-MS. No reaction is observed in chloroform or other small solvents which compete to occupy **1b**.

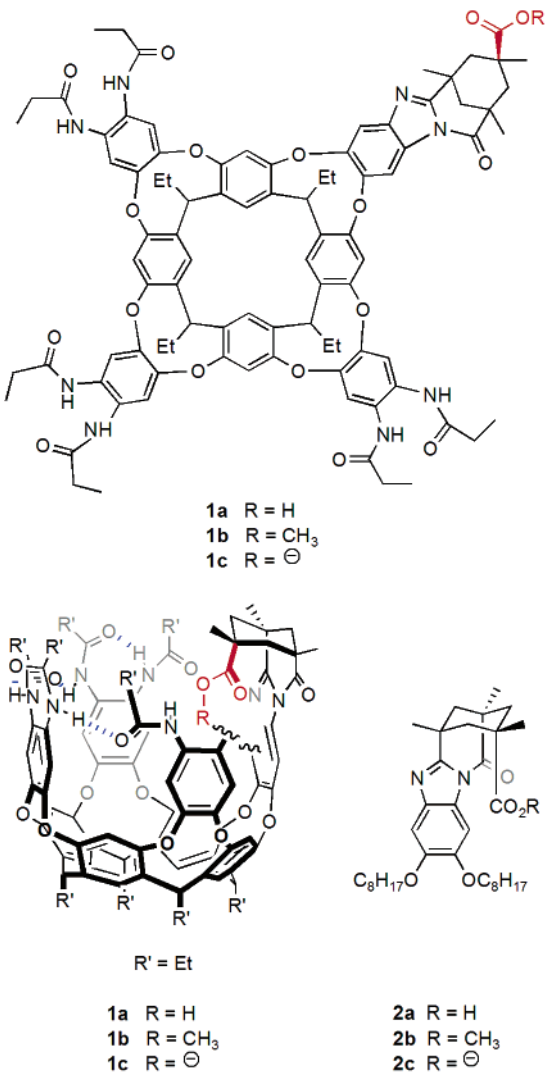


Figure 1. Introverted acid cavitand **1a**, control acid **2a**, and their derivatives.

We treated **1b** with a series of tertiary amines under ambient conditions (Table 1). Striking differences in reactivity were observed. Competitive binding experiments carried out by NMR at 240 K revealed that the reactivity of the amine is weakly correlated with its suitability for complex formation. For example, 2-(dimethylamino)ethanol (an amine whose quarternization yields choline) has a 3-fold higher binding constant than DABCO, although DABCO is at least 400-fold more reactive. The complex of DABCO with **1b** is predisposed to reach the transition state of the methyl transfer reaction. DABCO binds in an orientation analogous to that of quinuclidine (Figure 2), positioning a tertiary amine in near ideal alignment for rectilinear attack on the methyl

10.1021/ja036595q CCC: $25.00

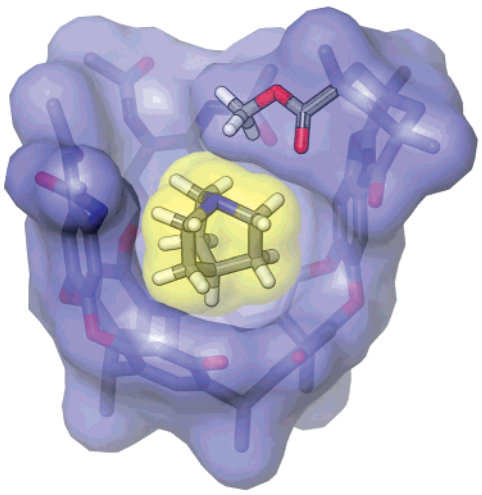


Figure 2. AMBER-minimized model of the complex of quinuclidine with **1b**. Ethyl groups have been shown as methyl groups, and one cavity wall has been removed for clarity.

Table 1. Reaction of Methyl Ester Cavitand **1b** with Tertiary Amines[a]

$$\mathbf{1b} + R_3N \xrightarrow[\text{mesitylene-}d_{12}]{} R_3N{-}CH_3^{+}\ \ \mathbf{1c}^{-}\ \ \text{complex}$$

amine	K_{rel}[b]	$k/M^{-1}\,s^{-1}$	$t_{1/2}$
quinuclidine	*c*	>0.4	<3 min
DABCO	1.0	>0.4	<3 min
trimethylamine	*d*	0.05(1)	26(4) min
N-methylpiperidine	0.3	0.004(2)	5(2) h
2-(dimethylamino)ethanol	3	$9(2) \times 10^{-4}$	25(5) h
triethylamine	<0.02	$5(3) \times 10^{-4}$	2(1) d
pyridine	0.6	*e*	*e*
N-methylmorpholine	1	*e*	*e*
(*S*)-(−)nicotine	*f*	*e*	*e*
N,*N*-diisopropylethylamine	*f*	*e*	*e*
2-(diisopropylamino)ethyl benzoate	*f*	*e*	*e*

[a] All reactions were carried out in an NMR tube using **1b** (1.3 μmol) and amine (5.7 μmol) in mesitylene-d_{12} (600 μL) at ambient temperature. [b] Relative association constants of amines to **1b** prior to reaction. See Supporting Information. [c] Too reactive to determine K_{rel}. [d] Too volatile to accurately determine K_{rel}. [e] No reaction detected in ^{1}H spectrum at 10 days. [f] Not bound by **1b**.

group. The smaller and less structurally rigid 2-(dimethylamino)-ethanol does not possess these binding constraints.

A comparison of *N*-methylpiperidine and *N*-methylmorpholine further supports this model. Although *N*-methylmorpholine is a better guest than *N*-methylpiperidine, it is not quaternized by **1b**. Low-temperature NMR experiments (^{1}H 1D and NOESY) showed that *N*-methylmorpholine is bound with the amine oriented toward the bottom of the cavity, and thus quaternization is precluded.

The reaction mechanism involves several steps: an unfolding of the vase-like conformation of **1b** shown in Figure 1, displacement of the resident solvent, complexation of the amine, and refolding. The unfolding process involves the breaking of the seam of three hydrogen bonds stabilizing the vase-like conformation; typical activation barriers for this unfolding process are approximately $\Delta G^{\ddagger} = 13$ kcal mol^{-1}.[9] Finally, a nucleophilic attack of the amine nitrogen on the methyl carbon leads directly to the product complex. The Eyring plot from a kinetic study of the reaction of **1b** with 2-(dimethylamino)ethanol yielded the activation parameters $\Delta H^{\ddagger} = 25.1 \pm 0.5$ kcal mol^{-1} and $\Delta S^{\ddagger} = 12 \pm 2$ cal mol^{-1} K^{-1} (see Supporting Information).[10]

Kemp's triacid derivative **2b**, outfitted with a sterically comparable wall, was prepared as a control. We were unable to observe quaternization of quinuclidine by **2b** even after heating at 100 °C. A sample of *N*-methylquinuclidinium tetrafluoroborate and Na**2c** in $CDCl_3$ (chosen in place of mesitylene-d_{12} for solubility) showed no formation of **2b**, confirming that this could not be attributed to a change in equilibrium.

What causes the rate acceleration? First, a high local concentration of nucleophile exists in the host. The volume of the cavity[11] is approximately 160 Å^3, and one molecule within this space is present at a concentration of 10 M. Second, the CH/π interactions between host and guest position the reacting centers on a trajectory ready for an S_N2 reaction. Third, after complex formation, there are no solvent molecules involved; instead, the aromatic surfaces of the cavity itself provide fixed solvation. Reorganization of solvent molecules is known to contribute to activation energies.[12] The reaction is known to be sensitive to solvent polarity with slower reactions in hydrocarbons and faster reactions in polar solvents. The rim of the cavitand resembles DMF as a solvent, while the depths of the cavitand are more like benzene in nature. The sum of these factors leads to a rate acceleration of greater than 2×10^4 fold.[13]

Acknowledgment. We are grateful to the Skaggs Institute for Research, the National Institutes of Health (GM 27932), and the Natural Sciences and Engineering Research Council of Canada for financial support. P.B. Thanks SEEyU (Spain) PR2001−0274 for partial financial support. B.W.P. is a Skaggs Predoctoral Fellow.

Supporting Information Available: Detailed experimental procedures, full synthetic procedures, characterization of new compounds, and kinetic study data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Willstätter, R. *Ber.* **1902**, *35*, 584. (b) Willstätter, R.; Kahn, W. *Ber.* **1902**, *35*, 2757.
(2) Hammett, L. P.; Pfluger, H. L. *J. Am. Chem. Soc.* **1933**, *55*, 4079.
(3) Newman, M. S.; Lloyd, H. A. *J. Am. Chem. Soc.* **1952**, *74*, 2672.
(4) Eliel, E. L.; Anderson, R. P. *J. Am. Chem. Soc.* **1952**, *74*, 547.
(5) Pierce, A. C.; Joullié, M. M. *J. Org. Chem.* **1962**, *27*, 3968.
(6) Zaugg, H. E.; Helgren, P. F.; Schaefer, A. D. *J. Org. Chem.* **1963**, *28*, 2617.
(7) Ballester, P.; Tadayoni, B. M.; Branda, N.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 3685.
(8) Renslo, A. R.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2000**, *39*, 3281.
(9) Wash, P. L.; Renslo, A. R.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2001**, *40*, 1221 and references therein.
(10) Zaugg reports the unaccountably low Arrhenius activation energy of 8 ± 1 kcal mol^{-1} for the reaction of pyrrolidine with methyl 2,3-dihydro-3-phenyl-3-benzofurancarboxylate; the reaction mixture (at molar concentration) must be heated at 90 °C for hours to reach completion.[6]
(11) Determined using the GRASP program. Nicholls, A.; Sharp, K.; Honig, B. *Proteins* **1991**, *11*, 281.
(12) See, for example: Regan, C. K.; Craig, S. L.; Brauman, J. I. *Science* **2002**, *295*, 2245.
(13) Eyring plot data for the reaction of 2-(dimethylamino)ethanol with **1b** was extrapolated to obtain a rate constant at 100 °C, the temperature for which Hammett reports the eq 1 rate constant. The ratio of these rate constants is approximately 400. Trimethylamine reacts >50 times faster than 2-(dimethylamino)ethanol, giving a total acceleration of $>2 \times 10^4$ fold. When comparing the reactions of **1b** and **2b** with quinuclidine, the acceleration is even greater.

JA036595Q