Convergent Functional Groups: Intramolecular Acyl Transfer through a 34-Membered Ring

Christian M. Rojas‡ and Julius Rebek, Jr.*

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

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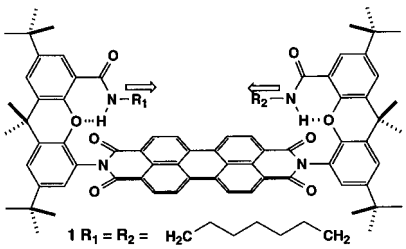
The synthesis of macrocyclic compounds is often aided by the rigidity of the platform on which the reactive components are attached and their initial "direction". For example, the spectacularly successful catenane syntheses of Sauvage[1] and Stoddart[2] owe much to the intermolecular forces that gather the components and position their electrophilic and nucleophilic sites in favorable directions. These are also factors in the use of a cyclic porphyrin trimer to catalyze an acyl transfer reaction as reported by Sanders.[3] Nowhere is this directionality more pronounced than with convergent functional groups (Scheme 1).[4] When inwardly directed groups are capable of reaction, high yields result, as shown by the smooth macrocyclization that leads to **1** from the appropriate diamine and diacid chloride.[4c] We describe here an intramolecular transfer of an acyl group from oxygen to nitrogen in this context. The reaction proceeds with high efficiency despite the 34-membered ring formed as an intermediate.[5,6]

A perylene based cleft, derived from the C-shaped diacid **2**,[4c] provided the appropriate scaffold for this reaction. Specifically, the isolated mixed anhydride **3**[7] was used to acylate a BOC-protected ethylenediamine unit as indicated in Scheme 2, and the remaining acid function was used to acylate the aniline derivative **5**. Deprotection of the phenol followed by acylation and removal of the BOC group (HCl, dry dioxane) gave the amine, which was stored as its hydrochloride salt **9**.

When this material was neutralized in a degassed $CDCl_3$ solution containing triethylamine (2 equiv) smooth O → N acyl transfer occurred, providing acetamide **10** (Scheme 3) in isolated yields of 70−80% for the two-step BOC removal, acyl transfer sequence.[8] Under these conditions, we detected no byproducts or intermediates from intermolecular processes using ^{1}H NMR (600 MHz) or, with ^{13}C-acetyl labeled material, the ^{13}C NMR (151 MHz) to follow the reaction. Even so, monitoring the kinetics of the acyl transfer in $CDCl_3$ by ^{1}H NMR (600 MHz), we noted some change in the first-order rate constants with concentration of substrate and base. Thus, using 2 equivs of added Et_3N we measured $k = 4.5 \times 10^{-6}$ s^{-1} at 2.7 mM and $k = 9.7 \times 10^{-6}$ s^{-1} at 26 mM.

Scheme 1



It is likely that triethylamine was acting as an external base in the rate determining step of the acyl transfer process.[9,10] When we conducted the reaction in pyridine-d_5 to maintain a constant concentration of external base, the rate of acyl transfer was unchanged over a concentration range from 3.8 to 38 mM.[11]

The first-order kinetics observed in both solvent systems and the failure to detect the (independently synthesized) bis-acetate **11** in the reaction mixture argue against an intermolecular course for the reaction. A bimolecular reaction with such ensconced components is unlikely, but we prepared the two lumbering half-cleft species, the nucleophile **15** and the electrophile **18**, as a realistic model for the bimolecular reaction.

These were prepared from amino acid **12**[4c] as outlined in Scheme 4, but under the conditions of the intramolecular acyl transfer (13 mM in each half cleft, $CDCl_3$, 2 equiv of Et_3N, 23 ± 1 °C),[12] we observed less than 5% formation of the (independently prepared and characterized) acetamide **19** after 15 days, along with slow decomposition of amine **15**. Another control experiment established that acetamide **19** was stable under these conditions. Since the half-life of the intramolecular reaction under these conditions is about 22 h, the value for the effective molarity[13] may be estimated as 3 M.[14] This is comparable with Kemp's results with thiol capture (EM ca. 5 M in a 12-membered-ring acyl transfer),[5a] and Sanders' results (E. M. ca. 2 in a 28-membered-ring acyl transfer). Precedents for a 34-membered-ring intermediate are unknown to us. At the suggestion of a reviewer, streamlined reaction partners were prepared.[14] The rate of their bimolecular O to N acyl transfer ($CDCl_3$, 2 equiv of Et_3N,

* To whom correspondence should be addressed.
‡ Present address: Department of Chemistry, Barnard College, 3009 Broadway, New York, NY 10027.

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(5) For examples of related acyl transfers in medium-sized rings, see: (a) Kemp, D. S.; Kerkman, D. J.; Leung, S.-L.; Hanson, G. *J. Org. Chem.* **1981**, *46*, 490. (b) Kemp, D. S.; Galakatos, N. G.; Bowen, B.; Tan, K. *J. Org. Chem.* **1986**, *51*, 1829.

(6) It appears that our present work encounters the largest ring-sized intermediate yet reported for an intramolecular acyl transfer. For examples of closures to 36-membered macrolides, see: (a) Kennedy, R. M.; Abiko, A.; Takemasa, T.; Okumoto, H.; Masamune, S. *Tetrahedron Lett.* **1988**, *29*, 451. (b) Nicolaou, K. C.; Daines, R. A.; Chakraborty, T. K.; Ogawa, Y. *J. Am. Chem. Soc.* **1988**, *110*, 4685. (c) Rychnovsky, S. D.; Khire, U. R.; Yang, G. *J. Am. Chem. Soc.* **1997**, *119*, 2058. (d) Rychnovsky, S. D.; Yang, G.; Hu, Y.; Khire, U. R. *J. Org. Chem.* **1997**, *62*, 3022. Review: Mandolini, L. *Adv. Phys. Org. Chem.* **1986**, *22*, 1.

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(8) It was important to use freshly distilled reagents and to maintain CO_2-free conditions to avoid the reversible formation of a carbamic acid intermediate from the liberated amine (see Supporting Information for complete experimental descriptions).

(9) For a related example, see: Neumann, H.; Shashoua, V. E.; Sheehan, J. C.; Rich, A. *Proc. Natl. Acad. Sci. U.S.A.* **1968**, *61*, 1207.

(10) For mechanistic descriptions of ester aminolysis, see: (a) Blackburn, G. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1968**, *90*, 2638. (b) Menger, F. M.; Smith, J. H. *Tetrahedron Lett.* **1970**, 4163. (c) Menger, F. M.; Smith, J. H. *J. Am. Chem. Soc.* **1972**, *94*, 3824.

(11) Six independent kinetic runs, two each at 3.8, 9.2, and 38 mM, agreed to within 10% of the mean value, 3.8×10^{-6} s^{-1}. For details of the kinetic analyses, including representative ^{1}H NMR traces and data plots, see the Supporting Information.

(12) At 12 mM **9** in $CDCl_3$ with 2 equiv of Et_3N added we measured the first-order rate constant $k = 8.7 \times 10^{-6}$ s^{-1} for the intramolecular acyl transfer.

(13) For a discussion of effective molarity, see: Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183.

(14) For details, see the Supporting Information.

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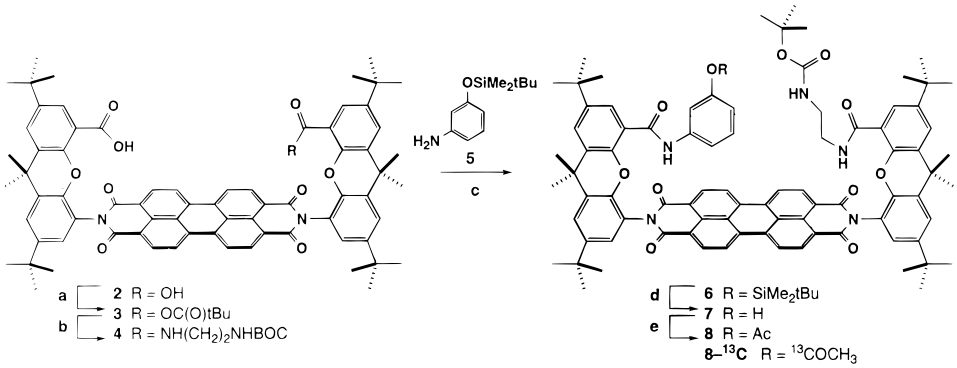
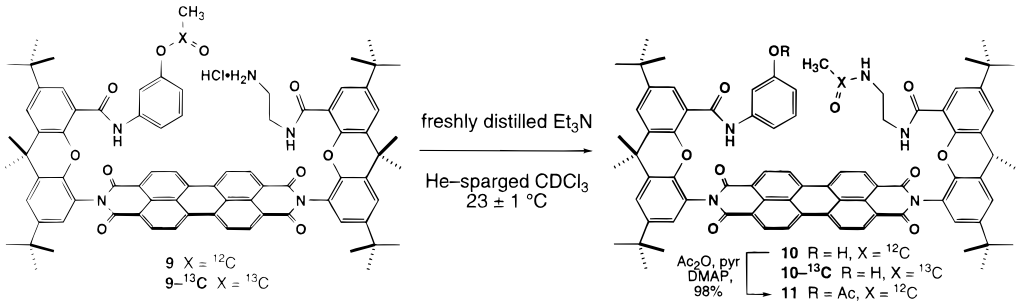
Scheme 2[a]

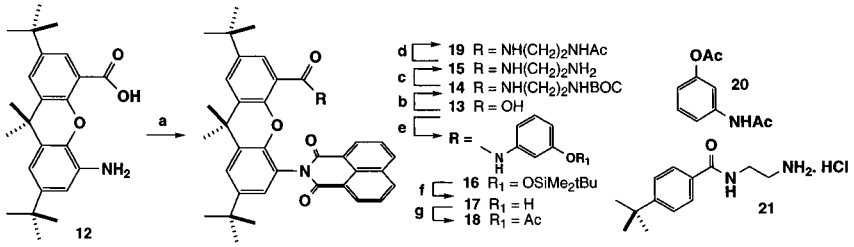


[a] (a) PivCl, pyr, CH_2Cl_2, 62%. (b) $H_2N(CH_2)_2NHBOC$, pyr, CH_2Cl_2, 88%. (c) i: $SOCl_2$, pyr, CH_2Cl_2. ii: **5**, pyr, CH_2Cl_2, 96%. (d) TBAF, THF, 96%. (e) Ac_2O or $H_3C^{13}COCl$, Pyr, DMAP (cat), 70−98%.

Scheme 3



Scheme 4[a]



[a] (a) 1,10-Naphthalic anhydride, $Zn(OAc)_2$ (cat), quinoline, 220 °C, 76%. (b) $H_2N(CH_2)_2NHBOC$, PyBOP, Et_3N, CH_2Cl_2, 89%. (c) HCl/dioxane or TFA/CH_2Cl_2, 85−90%, then Et_3N. (d) Ac_2O, Et_3N, DMAP (cat), 95%. (e) **5**, BOP-Cl, Et_3N, CH_2Cl_2, 69% (f) TBAF, THF, 75%. (g) Ac_2O, Pyr, DMAP (cat), 98%.

23 ± 1 °C) was 3.9×10^{-5} M^{-1} s^{-1}, corresponding to an EM for the case at hand of 0.22 M.

One might well ask: Why are these values not larger? Many cyclizations of 30 to 40-membered-ring sizes show EM values in the 10^{-3} to 10^{-1} range[6k] and would, at first glance, be related to the reactions here. But these processes, slow as they may be, are generally exocyclic, and i**ncrease** the number of molecules or ions. The transfer reaction is endocyclic and lacks this entropic advantage in the rate determining transition state. This may be a more common determinant of EM magnitude than is generally appreciated,[13] and we are working to test the notion using the cleft-shaped scaffolds.

We also examined some catalysts for the 34-membered acyl transfer.[15] The bifunctional 2-pyridone[15,16] (1.3 equiv) under the $CDCl_3/Et_3N$ conditions (13 mM in cleft, 2 equiv of Et_3N) accelerated the acyl transfer by a factor of 10 ($k = 9.6 \times 10^{-5}$ s^{-1}), while δ-valerolactam[15,17] (1.3 equiv) provided less than a 2-fold rate enhancement ($k = 1.3 \times 10^{-5}$ s^{-1}).[12,15] Using the trifluoroacetate (rather than the hydrochloride salt **9**) or any excess trifluoroacetate also increased the rate of acyl transfer.

In summary, the large and rigid molecular clefts here provide a framework on which to present reaction partners in a manner likely to resemble their bimolecular counterparts.[18] It should be possible to use this scaffold to hold acidic and basic functions in place, prevent them from collapsing on one another, but still provide sites for concerted catalysis on opposite sides of substrates held in between.

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Supporting Information Available: Experimental procedures, characterization data, and copies of ^1H NMR spectra for all new compounds, as well as representative plots of kinetic data (60 pages, print/PDF). See any current masthead page for ordering and Web access instructions.

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(15) For discussion of various catalysis for ester aminolysis, see: Su, C.-W.; Watson, J. W. *J. Am. Chem. Soc.* **1974**, *96*, 1854.
(16) Rony, P. R. *J. Am. Chem. Soc.* **1969**, *91*, 6090.
(17) For amide-catalyzed aminolysis of carboxylic acid derivatives, see: Titskii, G. D.; Litvinenko, L. M. *Zh. Obsch. Khim.* **1970**, *40*, 2680.
(18) For a rare but relevant example of a medum-ring endocyclic substitution see: Lok, R.; Coward, J. K. *Bioorg. Chem.*, **1976**, *5*, 169.