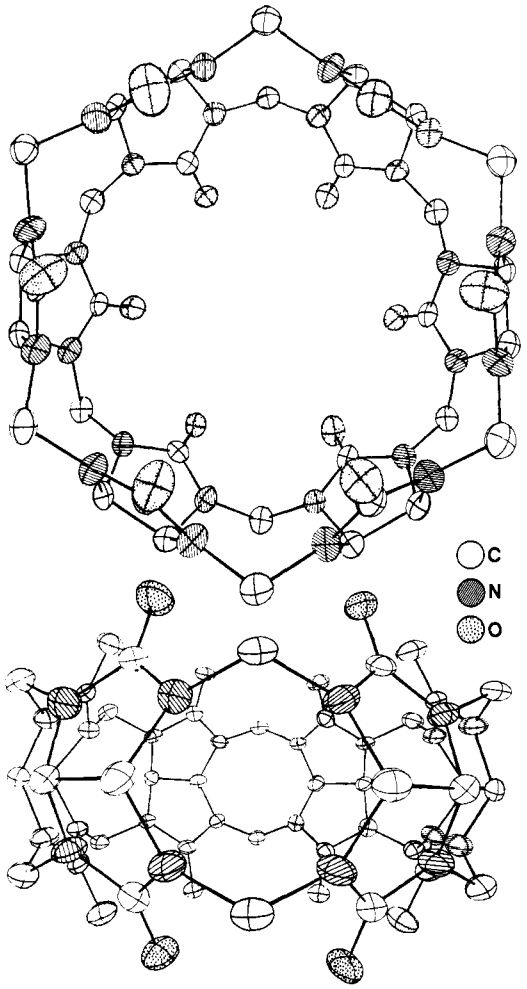

Figure 1. Top and edge-on view (ORTEP) of crystallographic structure of **2** (hydrogen atoms deleted).

occupied by a free H_2O molecule, which is part of a hydrogen-bonded chain of three aquo units threading through the interior of **2**.

A remarkable chemical aspect of the structure **2** (Figure 1) is that all of its 19 rings are held together entirely by aminal linkages, formed of the constituents formaldehyde, glyoxal, and urea. Regarding its preparation, little can be said at present other than that **2** appears to be the product of an acid-induced, thermodynamically controlled rearrangement of an initially formed macromolecular condensation product of **1** and formaldehyde. Aside from its enigmatic spontaneous synthesis, the most captivating feature of **2** is the presence of an internal cavity of approximately 5.5-Å diameter within the relatively rigid macrocyclic structure, to which access is provided by 4-Å diameter portals situated among the carbonyl groups. We have obtained NMR evidence pertinent to this feature of the structure. Apparently the interior of **2** comprises a magnetic shielding region, for the proton resonances of sterically unencumbered aliphatic amines undergo upfield shifts of 0.6–1.0 ppm in the presence of 1 molar equiv of **2** in acid solution. We suggest that this is indicative of formation of a molecular inclusion complex wherein the cationic head of the alkylammonium ion associates with the negative ends of the carbonyl dipoles of **2** and in which the hydrocarbon tail extends into the core of the cage structure. The stoichiometry of this complexation (1:1) is conveniently measurable by NMR integration. The specificity of binding appears quite remarkable. For example, cyclopentanemethylamine is held quite tightly ($K_d \sim 10^{-6}$ M at 40 °C in aqueous formic acid solution), but cyclohexanemethylamine evidently is excluded from the internal cavity of **2** by its size. A comprehensive survey of the host–guest chemistry of **2** will be reported subsequently.

We propose the trivial name cucurbituril for **2**.[4]

Acknowledgment. We thank K. L. Loening (Chemical Abstracts Service) and W. H. Pirkle (University of Illinois at Urbana-Champaign) for nomenclature assistance, K. L. Rinehart (University of Illinois at Urbana-Champaign) for mass spectral data, and J. M. Williams of the Argonne National Laboratory, where some of the crystallographic calculations were performed.

Supplementary Material Available: A listing of atomic and thermal parameters for **2**·calcium bisulfate (2 pages). Ordering information is given on any current masthead page.

(4) The proper (current Chemical Abstracts index) name for **2** is dodecahydro-1*H*,4*H*,14*H*,17*H*-2,16:3,15-dimethano-5*H*,6*H*,7*H*,8*H*,9*H*,10*H*,11*H*,12*H*,13*H*,18*H*,19*H*,20*H*,21*H*,22*H*,23*H*,24*H*,25*H*,26*H*-2,3,4a,5a,6a,7a,8a,9a,10a,11a,12a,13a,15,16,17a,18a,19a,20a,21a,22a,23a-,24a,25a,26a-tetracosaazabispentaleno[1‴,6‴:5″,6″,7″]cycloocta-[1″,2″,3″:3′,4′]pentaleno(1′,6′:5,6,7)cycloocta(1,2,3-*gh*:1′,2′,3′-*g′h′*)cyclooocta(1,2,3-*cd*:5,6,7-*c′d′*)dipentalene-1,4,6,8,10,12,14,17,19,21,23,25-dodecone. The trivial name cucurbituril is proposed because of a general resemblance of **2** to a gourd or pumpkin (family Cucurbitaceae), and by devolution from the similarly named (and shaped) component of the early chemists' alembic.

Successive Beckmann Rearrangement–Alkylation Sequence by Organoaluminum Reagents. A Simple Route to *dl*-Pumiliotoxin C

Kazunobu Hattori, Yasushi Matsumura, Tohru Miyazaki, Keiji Maruoka, and Hisashi Yamamoto*

Department of Applied Chemistry
Nagoya University, Chikusa, Nagoya 464, Japan

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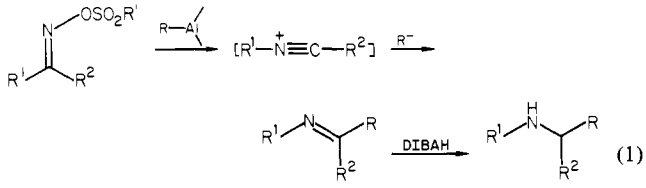
Undoubtedly, the Beckmann rearrangement is the best known and most thoroughly investigated of all azomethine rearrangements because of sustained interest in its mechanism, its application to synthesis, and the industrial interest in it as a step in the manufacture of synthetic polyamides.[1] We wish to disclose that facile alkylation at the intermediary iminocarbonium ion of Beckmann rearrangement is accessible by organoaluminum reagents.[2] The overall transformation is illustrated in eq 1.



(1)

Treatment of a wide variety of oxime sulfonates with several equivalents of alkylaluminum reagents in methylene chloride resulted in formation of the imines, which were directly reduced with excess diisobutylaluminum hydride (DIBAH) to give the corresponding amines (eq 1). This new synthetic approach provides a simple route to many substances hitherto accessible only by lengthy or complicated syntheses.[3] The examples cited in Table I illustrate the preparation of alkylated amines using indicated aluminum reagents and reaction conditions. Several aspects are quite noteworthy. First, a high regioselectivity is seen for rear-

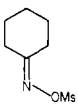
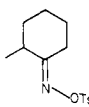
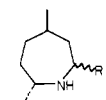
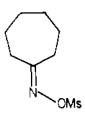
(1) For reviews, see: Blatt, A. H. *Chem. Rev.* **1933**, *12*, 215. Jones, B. *Chem. Rev.* **1944**, *35*, 335. Moller, F. *Methoden Org. Chem. (Houben-Weyl), 4th Ed.* **1957**, *11*, 892. Donaruma, L. G.; Heldt, W. Z. *Org. React. (N.Y.)* **1960**, *11*, 1. Beckwith, A. L. J. In "The Chemistry of Amides"; Zabicky, J., Ed.; Interscience: New York, 1970; p 131. McCarty, C. G. In "Chemistry of the Carbon-Nitrogen Double Bond"; Patai, S., Ed.; Wiley-Interscience: New York, 1970; p 408.

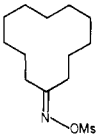
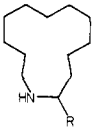
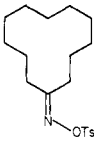
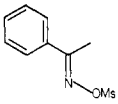
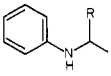
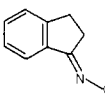
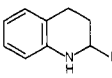
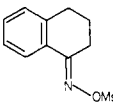
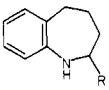
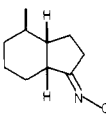
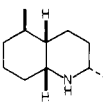
(2) For reviews of aluminum reagents, see: Yamamoto, H.; Nozaki, H. *Angew. Chem., Int. Ed. Engl.*, **1978**, *17*, 169.

(3) The conventional process for accomplishing this transformation consists of several steps, oxime → amide (Beckmann rearrangement) → imino ether (trialkyloxonium tetrafluoroborate) → imine (RLi or RMgX) → amine (reduction), and requires a considerably longer time for execution.

0002-7863/81/1503-7368$01.25/0

Table I. Synthesis of α-Alkylated Amines[a]

entry	starting material[b] (mp, °C)	method[c]	product[d]	R	yield,[e] %
1		A		*n*-Pr[h]	55
2	1 (75-77)	B	2	*n*-Pr[h]	58 (3)[r]
3		C		*n*-Pr[i]	62 (2)[s]
4		D	3	*n*-Pr[i]	23[t] (4)[s]
5		B		*n*-Pr[j,k]	70
6		C		*n*-Pr[j,k]	67
7		D		Me	70
8		D		Et	47
9		D		*n*-Pr	64
10		D		*i*-Bu	52
11	(43-45)	E		C≡C-Bu[l]	67
12		D		*n*-Pr[j]	48
13		F		Me[j]	57
14		G		H	82
15		D		*n*-Pr	68
	(38-40)				

entry	starting material[b] (mp, °C)	method[c]	product[d]	R	yield,[e] %
16		D		Me[m]	60
17		H		H	73
18		D		Me	56
19		E		C≡C-Ph	71
	(85-87)				
20		D		Me[n]	67
21		H		H	87
22		E		C≡C-Me	60
23		E		C≡C-Bu	83
24	(64-65)	E		C≡C-Ph[o]	67
25		H[f]		H	80
	(113-114)				
26		D[g]		*n*-Pr[p]	88
	(108-109)				
27		I		*n*-Pr	60
28		I		Me[q]	57
	9				

[a] Reaction performed on a 1-2-mmol scale. [b] Oxime mesylates were prepared by reaction of oximes in CH_2Cl_2 containing a 50% molar excess of Et_3N with a 10% molar excess of mesyl chloride at −20 °C for 30 min. Recrystallization of the crude mesylate from ether-hexane or ether-CH_2Cl_2 gave the pure oxime mesylate as white crystals in 75-85% yields. Oxime tosylates can be obtained as described for the preparation of 9 (see text) in 80-95% yields. [c] Unless specified, a 1 M hexane solution of organoaluminum reagent was used. Method A: Treatment with *n*-Pr_3Al (2 equiv, a 2 M toluene solution) in $ClCH_2CH_2Cl$ at 80 °C for 15 min or *n*-Pr_3Al (3 equiv, a 2 M toluene solution) in $ClCH_2CH_2Cl$ at 25 °C for 30 min and then reduction with DIBAH (1.5 equiv) at 0 °C for 1 h. Method B: Treatment with *n*-Pr_3Al (2 equiv) in CH_2Cl_2 at 40 °C for 15 min followed by DIBAH (1.5 equiv) at 0 °C for 1 h. Method C: Treatment with *n*-Pr_3Al (3 equiv) in hexane at −78 °C for 5 min and at 0 °C for 1 h and then reduction with DIBAH (1.5 equiv) at 0 °C for 1 h. Method D: See the experimental procedure in text. Method E: Addition of oxime sulfonate to $Et_2AlC{\equiv}CR'$ (2-3 equiv, prepared from Et_2AlCl and $LiC{\equiv}CR'$ in ether at 0 °C for 30 min) at −78 °C for 5 min and stirring at 0-25 °C for 1-3 h and then reduction with DIBAH (1.5 equiv) at 0 °C for 1 h. Method F: Treatment of menthone oxime with *n*-BuLi (1.05 equiv) followed by MsCl (1.05 equiv) in toluene at 0-25 °C for 1 h and then Me_3Al (3 equiv) at −20 °C for 1-3 h and at 0 °C for 1 h, and finally reduction with DIBAH (3 equiv) at 0 °C for 1 h. Method G: Treatment of menthone oxime with *n*-butyllithium (1.05 equiv) followed by MsCl or TsCl (1.05 equiv) in ether at 0 °C and reduction with DIBAH (3 equiv) at 0 °C for 1 h. Method H: Reaction with DIBAH (3.5 equiv) in CH_2Cl_2 at −78 °C for 5 min and at 0 °C for 1 h. Method I: Treatment with R_3Al (3 equiv) in CH_2Cl_2 at 25 °C for 30 min and reduction with DIBAH (4 equiv) at 25 °C for 1 h. [d] All new compounds have been fully characterized by IR and ^1H NMR spectroscopies and satisfactory elemental analyses have been obtained. [e] Isolated yield. [f] Stirring was continued for 5 h. [g] Rearrangement was completed at 0 °C for 1 h and at 25 °C for 2 h. [h] ^1H NMR ($CDCl_3$) δ 2.87-3.31 (1 H, m, NCH), 2.22-2.87 (2 H, m, NCH_2). [i] ^1H NMR ($CDCl_3$) δ 2.77-3.21 (1 H, m, NCH), 2.38-2.70 (2 H, t, NCH_2). [j] Ca. 1:1 mixture of cis and trans isomers. [k] ^1H NMR ($CDCl_3$) δ 2.25-2.80 (2 H, m, NCH), 1.03 (3 H, d, J = 6 Hz, CH_3), 0.90 (3 H, br t, CH_3). [l] ^1H NMR ($CDCl_3$) δ 3.43-3.87 (1 H, m, NCH), 2.63-3.13 (2 H, m, NCH_2), 0.90 (3 H, br t, CH_3). [m] ^1H NMR ($CDCl_3$) δ 2.41-2.83 (3 H, m, NCH and NCH_2), 1.02 (3 H, t, J = 6 Hz, CH_3). [n] ^1H NMR ($CDCl_3$) δ 6.43-7.38 (5 H, m, Ar-H), 3.61 (1 H, t of q, J = 6 Hz, NCH), 1.22 (3 H, d, J = 6 Hz, CH_3). [o] ^1H NMR (CCl_4) δ 6.45-7.42 (10 H, m, Ar-H), 4.34 (1 H, q, J = 6.5 Hz, NCH), 3.53 (1 H, br s, NH), 1.55 (3 H, d, J = 6.5 Hz, CH_3). [p] ^1H NMR (CCl_4) δ 6.40-7.10 (5 H, m, Ar-H), 3.23 (1 H, br s, NH), 2.50-2.97 (3 H, m, NCH and $PhCH_2$), 0.94 (3 H, br t, CH_3). [q] ^1H NMR ($CDCl_3$) δ 2.62-3.32 (2 H, m, NCH), 1.01 (3 H, d, J = 6 Hz, CH_3), 0.97 (3 H, d, J = 6 Hz, CH_3); MS, *m/z* (relative intensity) 167 ($C_{11}H_{21}N_2^+$, 22), 152 (44), 135 (24), 124 (100); mp of hydrochloride 204-206 °C (*i*-PrOH-ether). [r] Yield of 3. [s] Yield of **2**. [t] Piperidine was formed as the major product.

rangement–alkylation site (entry 5, 6, 12, 13, 14, 20–28). Thus, the regioselectivity of the reaction follows the general rule of Beckmann rearrangement, and preferential migration of the group anti to the oxime sulfonate was observed.[1,4] In the case of cyclopentanone oxime tosylate (**1**), a mixture of the unrearranged amine **3** and piperidine was obtained in addition to a small amount (4%) of the desired **2** (entry 4).[5] Moreover, using hexane as the reaction solvent, the amine **3** was produced in 62% yield. Surprisingly, switching the initial temperature from −78 to 40–80 °C enhances the normal rearranged product **2** at the expense of

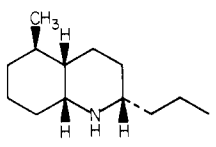
(4) An alternate mechanism which involves the initial alkylation of carbon–nitrogen double bond followed by rearrangement to the imine may not be likely because of the observed regioselectivity of the reaction. For such tetrahedral models for Beckmann rearrangement, see: Krow, G. R.; Szczepanski, S. *Tetrahedron Lett.* **1980**, *21*, 4593.

(5) This "abnormal" product was produced only in the case of cyclopentanone oxime sulfonate.

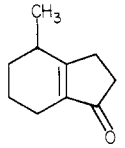
cyclopentylamine formation (entry 1 and 2). More significant is the coupling with aluminum alkynides (entry 11, 19, 22, 23, 24), and synthetically useful propargylic amino derivatives can be prepared in a single operation.

A representative procedure follows: Tri-*n*-propylaluminum (4 mmol, 4 mL of a 1 M hexane solution)[6] was added to a solution of cyclohexanone oxime methanesulfonate (2 mmol, 382 mg) in dry methylene chloride (10 mL) at −78 °C. After 5 min, the solution was warmed to 0 °C and stirred there for 1 h.[7] DIBAH (3 mmol, 3 mL of a 1 M hexane solution) was added at 0 °C, and the reaction mixture was stirred at 0 °C for 1 h. The reaction was terminated by dilution with methylene chloride (~20 mL) followed by successive treatment with sodium fluoride (28 mmol, 1.18 g) and water (21 mmol, 0.38 mL). Vigorous stirring of the resulting suspension was continued at 0 °C for 30 min. Filtration, washing with methylene chloride, and removal of solvent left a pale yellow liquid which was subjected to column chromatography on silica gel (isopropylamine–ether, 1:30) to give 2-propylazacycloheptane (**4**, 180 mg, 64% yield) as a colorless liquid.

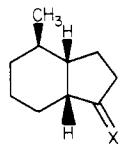
The efficiency of our new process is highlighted by the short synthesis of *dl*-pumiliotoxin C (**5**), one of a variety of alkaloids isolated from toxic skin secretions of neotropical frogs *Dendrobates pumilio* and *D. auratur*.[8] The synthesis of the key intermediate **7**[9] for the construction of the desired *cis*-decahydroquinoline is not possible by the obvious route, a direct hydrogenation of the readily available enone **6**,[10] since under the usual hydrogenation conditions, a stereochemical mixture of perhydroindanones was produced. Nonetheless **7** could be prepared in excellent yield from **6** under carefully chosen conditions.[11] Specifically, the selective



5



6



7, X = O
8, X = NOH
9, X = NOTs

hydrogenation was realized with reasonable stereoselectivity (~95%)[12] by using palladium black as a catalyst in dioxane in the presence of propionic acid (12 mol %) at 20 °C for 12 h and 1 atm of H_2. Reaction of **7** with hydroxylamine (NH_2OH·HCl–NaOAc) in methanol at 20 °C for 5 h produced, after one recrystallization from methanol–water, the oxime **8**,[13] mp 101–102 °C, in 84% overall yield from **6**. Treatment of the oxime **8** with *p*-toluenesulfonyl chloride (2 equiv)–pyridine at −20 °C for 1 h and at 0 °C for 5 h followed by trituration with excess cold water produced the oxime tosylate **9**[14] in 90–95% yield. Finally, with tri-*n*-propylaluminum–DIBAH (see Table I), the tosylate **9** was transformed into pumiliotoxin C (**5**) stereospecifically (>99% pure by GC assay) in 60% yield after column chromatography. The spectra of synthetic *dl*-**5** and natural pumiliotoxin C were identical.[15] Using the reaction conditions outlined above, *cis*-decahydroquinoline derivatives can now be prepared in substantial amount without any complex separations.

(6) We thank Nippon Aluminum Alkyls, Ltd., for generous gift samples of aluminum reagents.

(7) Any of double alkylation product, 2,2-dipropylazacycloheptane, was not detected from the reaction product. Thus, the alkylation of the resulting imine might be rather slow under these reaction conditions.

(8) Structure: Daly, J. W.; Tokuyama, T. Habemehl, G.; Karle, I. L.; Witkop, B. *Liebigs Ann. Chem.* **1969**, *729*, 198. Daly, J. W.; Witkop, B.; Tokuyama, T.; Nishikawa, T.; Karle, I. L. *Helv. Chim. Acta* **1977**, *60*, 1128. For synthesis (review), see: Inubushi, Y.; Ibuka, T. *Heterocycles* **1977**, *8*, 633 and references cited therein. See also: Overman, L. E.; Jessup, P. J. *J. Am. Chem. Soc.* **1978**, *100*, 5179 and references therein.

(9) Compound **7**: IR (liquid film) 1740, 1462, 1450, 1416, 1380, 1160, 1115, 1061 cm^{-1}.

(10) The enone **6** may be prepared in molar scale from 2-methylcyclohexanone (Stobbe condensation followed by acid treatment). See: El-Abbady, A. M.; El-Ashry, M.; Doss, S. H. *Can. J. Chem.* **1969**, *47*, 1483.

(11) We thank Professor S. Nishimura for helpful discussions for this hydrogenation reaction.

(12) The ratio of 4β/4α isomer was determined by GC assay (10% Apiezon L on Neopak 1A, 150 °C): t_r of the 4β isomer = 5.46 min; t_r of the 4α isomer = 6.60 min.

(13) ^1H NMR ($CDCl_3$) δ 9.15 (1H, br s, OH), 2.26–2.86 (3 H, m, NCH and NCH_2), 0.94 (3 H, br s, CH_3).

(14) Mp 69–71 °C; ^1H NMR ($CDCl_3$) δ 7.18–8.00 (4 H, m, Ar-H), 2.33–2.90 (3 H, m, NCH and NCH_2), 2.43 (3 H, s, Ar-CH_3), 2.88 (3 H, br s, CH_3).

(15) *dl*-Pumiliotoxin C (**5**) hydrochloride: mp 241–243 °C (lit.[8] 243–244 °C). The ^1H NMR and IR spectra of the synthetic *dl*-**5** hydrochloride were identical in all respects with the reported ones.[8]

Oscillatory Behavior in Fluorescence Intensity from Irradiated Sodium Dodecyl Sulfate Micellar Solutions of Zinc Porphyrin

Shinji Tsuchiya,* Hiroyuki Kanai, and Manabu Senō

Institute of Industrial Science, University of Tokyo 7-22-1, Roppongi, Minato-Ku, Tokyo 106, Japan

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Chemical systems maintained far from equilibrium and having a feedback mechanism may show instabilities.[1] The role of light in inducing oscillations, multiple stationary states, and instabilities in chemical systems has been investigated by theoretical and experimental methods. For example, Ross et al. reported that the absorption of light, followed by a radiationless transition, offers the possibility of multiple steady states, damped oscillations, and instabilities,[2] and some investigators reported chaotic or periodic oscillations induced by light.[3] We wish to report our observation concerning unusual variation of fluorescence intensity of zinc protoporphyrin dimethyl ester in a sodium dodecyl sulfate (SDS) micellar system. Excitation of the fluorescence of zinc protoporphyrin in SDS micelles at 410 nm results in behavior giving rise to chaotic oscillations in emission intensity at 580 nm. Findings of this kind were reported for the chemical system dissolved in an organic solvent, which displayed temporal or spatial oscillations.[3,5] We consider it important to report the observation of fluctuations in fluorescence of zinc protoporphyrin in a micellar system, in contrast with the case of organic solutions.

The work was prompted by the desire to carry out fluorescence quenching experiments on zinc protoporphyrin in micelles. We found that excitation of an SDS solution of zinc protoporphyrin produces fluorescence which varies in time after an induction period and this variation of intensity disappears when organic quenchers are added to the micellar solutions.

Zinc protoporphyrin dimethyl ester was prepared from protohemin[4] and purified by silica gel column chromatography; the purity of this substance was confirmed by silica gel TLC and reversed-phase HPLC with an octadecylsilane-treated silica gel column. The SDS employed in this experiment was purified by Soxhlet extraction with hexane and recrystallization from water–acetone. The observation was made with a Hitachi MPF-2A fluorescence spectrometer which was equipped with a Haake D3 temperature-regulated cell holder, and the fluorescence spectra were normally recorded at 298 K. Zinc protoporphyrin was dissolved in only a small amount of methanol, and this methanol solution was added dropwise into a large amount of SDS solution. The sample cell was stoppered but not degassed.

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