(H)(OMe) (**11**) is reproducibly formed. The photoreaction of **1** with ethanol in xenon likewise gives Cp*(PMe₃)Ir(H)(OEt) (**12**),[20] although in this case significant amounts of other, unidentified products were sometimes observed.[21] The abrupt change in reactivity between ethanol and isopropyl alcohol is remarkable.

In summary, liquid xenon is a useful inert solvent for photochemically induced C–H oxidative addition reactions. Work is continuing aimed at examining the C–H insertion reactions of other substrates that cannot be liquified easily, using liquid xenon in fast kinetics experiments, and determining the cause of the dramatic substrate and solvent effects summarized above in the reactions of **1** with alcohols.

Registry No. 1, 80146-01-6; **2**, 80145-83-1; **3**, 88548-54-3; **4**, 121618-77-7; **5**, 121618-78-8; **6**, 121618-79-9; **8**, 121618-80-2; **9**, 114326-78-2; **10** (isomer 1), 121701-52-8; **10** (isomer 2), 121618-81-3; **11**, 121618-82-4; **12**, 121618-83-5; CH₄, 74-82-8; *t*-BuOH, 75-65-0; *i*-PrOH, 67-63-0; CH₃OH, 67-56-1; EtOH, 64-17-5; xenon, 7440-63-3; cyclohexane, 110-82-7; adamantane, 281-23-2; cubane, 277-10-1; naphthalene, 91-20-3.

Supplementary Material Available: Spectroscopic data for complexes **4**, **5**, **6/7/8**, and **11** (2 pages). Ordering information is given on any current masthead page.

(20) The ethoxy hydride **12** has been previously prepared in our group. Cf.: Newman, L. J. Ph.D. Dissertation, University of California, Berkeley, 1986. For the analogous triphenylphosphine-substituted complex, see: Newman, L. J.; Bergman, R. G. *J. Am. Chem. Soc.* **1985**, *107*, 5314–5315.

(21) We have recently discovered that complex **11** can be independently synthesized by treating Cp*(PMe₃)IrCl₂ (Isobe, K.; Bailey, P. M.; Maitlis, P. M. *J. Chem. Soc., Dalton Trans.* **1981**, 2003–2008) with sodium methoxide in tetrahydrofuran.

A New Synthesis of β-Lactams through Stereoselective Oxidative Coupling of the Dianions of Acyclic Amides

Takeo Kawabata, Kenzo Sumi, and Tamejiro Hiyama*

Sagami Chemical Research Center
*4-4-1 Nishiohnuma, Sagamihara, Kanagawa 229, Japan*

In view of steadily expanding chemotherapy with β-lactam antibiotics of a wide variety of structures,[1] development of a conceptually novel synthetic method is still of great importance.[2] We report herein that an intramolecular oxidative coupling reaction[3] of the dianions generated from acyclic amides affords

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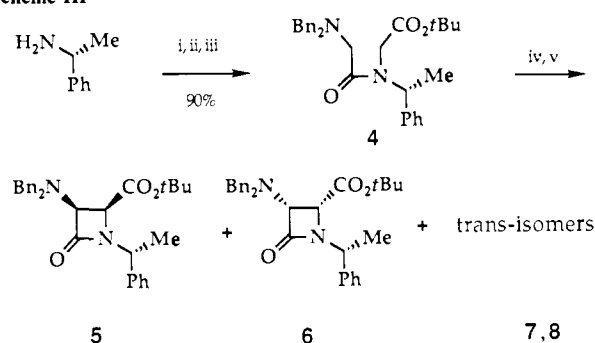
Scheme I
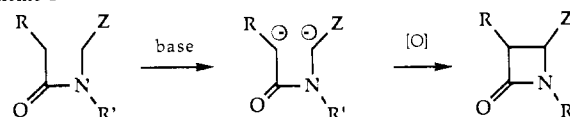
Scheme IIa
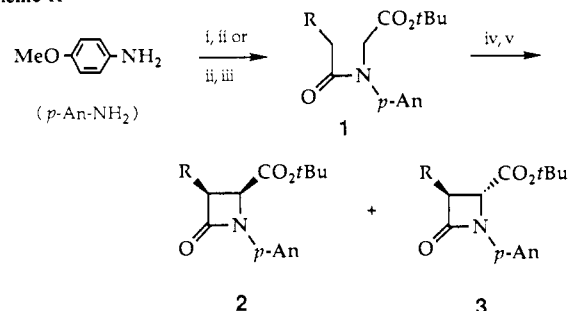
a: R = H, b: R = Et, c: R = MeO, d: R = Bn₂N

a (i) BrCH₂CO₂-*t*-Bu, NEt₃; (ii) RCH₂COCl, NEt₃; (iii) BrCH₂CO₂-*t*-Bu, NaOH; (iv) RLi additive (see the footnote of Table I), THF, −78 °C; (v) Cu(OAc)₂, Cu(OCOPh)₂, or NIS, −70 to −95 °C.

Scheme IIIa

a (i) BrCH₂CO₂-*t*-Bu, NEt₃; (ii) BrCH₂COBr, NEt₃; (iii) Bn₂NH, NEt₃; (iv) *n*-BuLi, TMEDA; (v) NIS or Cu(OAc)₂.

β-lactams in synthetically useful yields (Scheme I). The stereochemical course of the ring closure is controllable by proper choice of the oxidant. Furthermore, asymmetric synthesis of β-lactams is achieved by introducing a chiral auxiliary attached to the amide nitrogen.

The starting materials **1** are readily prepared by alkylation of *p*-anisidine with *tert*-butyl bromoacetate followed by acylation or vice versa as summarized in Scheme II. The overall yields fall in the range 68–93%. Dienolate formation of **1** was achieved quantitatively by treatment with slightly more than 2 equiv of butyllithium in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) or *tert*-butyllithium alone in tetrahydrofuran (THF) at −78 °C. The dianions thus formed exist as such at low temperatures. The yields of the dianion formation were estimated to be >90% by deuteration with CD₃CO₂D and CD₃OD followed by MS and ¹H NMR spectrometry. The dianions were then treated with *N*-iodosuccinimide (NIS) or Cu(II) carboxylates[4]

(3) Four-membered carbocyclic ring formation through an oxidative coupling reaction has been reported though in 15–37% yields. (a) Whitesides, G. M.; SanFilippo, J., Jr.; Casey, C. P.; Panek, E. J. *J. Am. Chem. Soc.* **1967**, *89*, 5302. (b) Kobayashi, Y.; Taguchi, T.; Morikawa, T.; Tokuno, E.; Sekiguchi, S. *Chem. Pharm. Bull.* **1980**, *28*, 262. (c) Minami, T.; Okada, Y.; Nomura, R.; Hirota, S.; Nagahara, Y.; Fukuyama, K. *Chem. Lett.* **1986**, 613. (d) Babler, J. H.; Sarussi, S. J. *J. Org. Chem.* **1987**, *52*, 3462.

(4) The oxidative coupling of enolates has been best carried out with Cu(OTf)₂ or CuCl₂, but Cu(OAc)₂ or Cu(OBz)₂ turned out to be suitable for the present reaction. (a) Maryanoff, C. A.; Maryanoff, B. E.; Tang, R.; Mislow, K. *J. Am. Chem. Soc.* **1973**, *95*, 5839. (b) Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 2567. (c) Ito, Y.; Konoike, T.; Harada, T.; Saegusa, T. *J. Am. Chem. Soc.* **1977**, *99*, 1487. (d) Kobayashi, Y.; Taguchi, T.; Tokuno, E. *Tetrahedron Lett.* **1977**, 3741.

Table I. Synthesis of β-Lactams **2** and **3** by Oxidative Coupling of Dianions Derived from **1**

| R	1	base[a]	additive[b]	oxidant[c] (mol equiv)	yield,[d] (%)	2:3
H	1a	*n*-BuLi	DABCO	Cu(OAc)$_2$ (3.0)	40	
H		*t*-BuLi	PPh$_4$Br	NIS (1.3)	39	
Et	1b	*t*-BuLi		Cu(OCOPh)$_2$ (2.5)	40	3:2
Et		*t*-BuLi	PPh$_4$Br	NIS (1.3)	51	10:0
MeO	1c	*t*-BuLi	PPh$_4$Br	Cu(OAc)$_2$ (2.5)	43	1:2
MeO		*t*-BuLi	PPh$_4$Br	NIS (1.3)	78	12:1
Bn$_2$N	1d	*t*-BuLi	PPh$_4$Br	Cu(OAc)$_2$ (2.5)	77	1:2
Bn$_2$N		*t*-BuLi	PPh$_4$Br	NIS (1.3)	48	7:1

[a] Dienolates were generated with 2.2 mol equiv of the base listed (−78 °C for 30 min to 1 h). [b] DABCO (2.2 mol equiv) was added prior to the addition of butyllithium. PPh$_4$Br (2.2 mol equiv) was added after the addition of *tert*-butyllithium. [c] Oxidation with Cu(II) or NIS was performed at −78 °C or at −95 to −70 °C, respectively. [d] Combined yield of **2** and **3**.

to achieve the C–C bond formation (Scheme II). Furthermore, the presence of tetraphenylphosphonium bromide slightly improved the yields of the oxidative coupling.[5] Representative results are summarized in Table I. It should be noted that NIS gave cis β-lactam highly selectively irrespective of the substituent R, whereas Cu(II) was effective for nonselective or slightly trans-directive ring closure.[5] For example, treatment of the dianion derived from **1c** with NIS gave a 12:1 mixture of **2c** and **3c**, whereas copper(II) acetate afforded a 1:2 mixture.

Asymmetric synthesis of β-lactams is carried out by using commercially available optically active 1-phenylethylamine as a chiral auxiliary.[6] The starting material amide **4** was prepared from (R)-(+)-1-phenylethylamine in 90% overall yield through a sequence of alkylation, acylation, and substitution reactions (Scheme III). The dianion of **4** was generated by treatment with butyllithium at −78 °C for 1 h in the presence of N,N,N′,N′-tetramethylethylenediamine (TMEDA). Oxidation of the dianion with NIS at −95 to −70 °C afforded a cis β-lactam **5** with high enantio- and diastereoselectivity: the ratio of the four possible products **5**, **6**, **7**, and **8** was 90:5:3:2 in 58% total yield.[7] Chromatographic separation allowed us to isolate the major product **5** in pure form, [α]^{20}$_D$ +41.3° (c 1.53, CHCl$_3$). On the other hand,

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(5) The stereochemical outcome observed might be explained as follows. The dilithium enolate of **1** is reasonably assumed to have an intramolecularly chelated form **i**. Iodonium cation would attack the enolate moiety from the

i
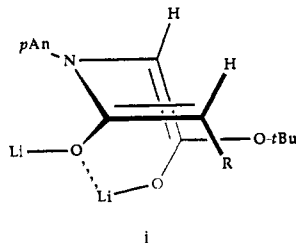
outside direction of **i**. Subsequent ring closure by intramolecular nucleophilic substitution would proceed spontaneously without C–C bond rotation to give rise to cis β-lactam. On the other hand, oxidation with Cu(II) should proceed through a single-electron-transfer mechanism to produce a biradical intermediate responsible for the nonselective or trans selective ring closure. Addition of Ph$_4$PBr improved the yield up to 10%. The salt might have removed the nonbridging lithium ion to activate the chelated dienolate **i**. The relative configuration of C(3) and C(4) was determined by $J_{3,4}$ = 5–7 Hz for the cis isomer and 1–3 Hz for the trans isomer.

(6) Asymmetric synthesis of β-lactams by use of a chiral auxiliary: (a) Ojima, I.; Suga, S.; Abe, R. *Chem. Lett.* **1980**, 853. (b) Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1985**, 26, 3783. Evans, D. A.; Sjogren, E. B. *Ibid.* **1986**, 27, 3119, 4961. (c) Hsiao, C.-N.; Ashburn, S. P.; Miller, M. J. *Tetrahedron Lett.* **1985**, 26, 4855. (d) Hart, D. J.; Lee, C.-S.; Pirkle, W. H.; Hyon, M. H.; Tsipouras, A. *J. Am. Chem. Soc.* **1986**, 108, 6054. (e) Sato, M.; Katagiri, N.; Muto, M.; Haneda, T.; Kaneko, C. *Tetrahedron Lett.* **1986**, 27, 6091. (f) Nagao, Y.; Kumagai, T.; Tamai, S.; Abe, T.; Kuramoto, Y.; Taga, T.; Aoyagi, S.; Nagase, Y.; Ochiai, M.; Inoue, Y.; Fujita, E. *J. Am. Chem. Soc.* **1986**, 108, 4673. (g) Shibasaki, M.; Ishida, Y.; Iwasaki, G.; Iimori, T. *J. Org. Chem.* **1987**, 52, 3488. (h) Fuentes, L. M.; Shinkai, I.; Salzmann, T. N. *J. Am. Chem. Soc.* **1986**, 108, 4675. (i) Baldwin, S. W.; Aubé, J. *Tetrahedron Lett.* **1987**, 28, 179.

(7) Four molar equivalents of butyllithium and 3.2 mol equiv of NIS were used. Use of 2.2 mol equiv of the base and 1.3 mol equiv of NIS resulted in a decrease of the yield to 22%. In the absence of TMEDA, the ratio of **5:6** was 4:1.

Scheme IV^a
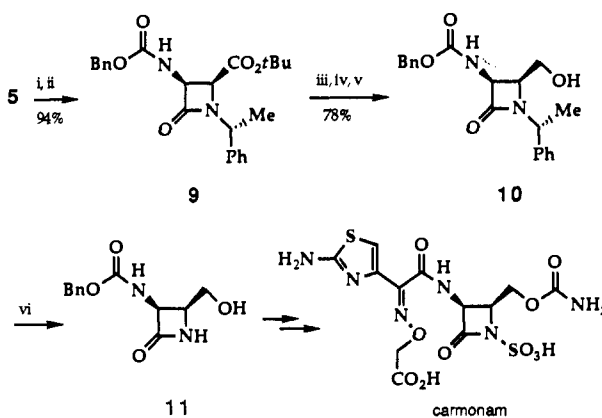
^{a}(i) 10% Pd–C, HCO$_2$NH$_4$; (ii) BnOCOCl, propylene oxide; (iii) CF$_3$COOH; (iv) CH$_2$N$_2$; (v) NaBH$_4$, THF–H$_2$O; (vi) (NH$_4$)$_2$S$_2$O$_8$.

the use of copper(II) acetate as the oxidant gave in a 63% yield a mixture **5–8** in a ratio of 35:17:32:16. Though nonselective, this method is particularly suitable for the preparation of all possible stereoisomers needed for biological testing,[8] since the isomers **5–8** are separable by preparative TLC or column chromatography. The absolute configuration of **5** was determined to be (3S,4S) by transformation into **11**, the key intermediate for the synthesis of a monobactam antibiotic carmonam[8,9] (Scheme IV). Catalytic hydrogenolysis[10] of **5** followed by benzyloxy-carbonylation gave **9** in 94% yield. Conversion of the *tert*-butyl ester to the methyl ester followed by reduction with sodium borohydride afforded alcohol **10**, mp 86–87 °C and [α]^{20}$_D$ −41.7° (c 0.99, CHCl$_3$) [lit.[11] mp 84.5–85.9 °C and [α]$_D$ −41° (c 0.82, CHCl$_3$)]. Removal of the chiral auxiliary ((NH$_4$)$_2$S$_2$O$_8$–K$_2$HPO$_4$–H$_2$O, 90 °C)[11] provided **11**, mp 129–130 °C and [α]^{20}$_D$ +8.7° (c 0.55, CHCl$_3$) [lit.[6b] mp 128.5–129.5 °C and [α]$_D$ +8.6° (c 0.9, CHCl$_3$); lit.[11] mp 127–128 °C and [α]$_D$ +9° (c 0.93, CHCl$_3$)]. The spectral data of **11** were identical with those reported [^{1}H NMR in DMSO-d_6 or acetone-d_6 and IR (KBr) or (CHCl$_3$)].[8,11] Thus, a highly stereoselective route to the synthesis of carmonam has been established starting from readily available (R)-1-phenylethylamine.

In conclusion, a new facile method for β-lactam ring formation is established through an unprecedented oxidative coupling of amide enolate using a novel oxidant NIS. This method provides us with optically active intermediates useful particularly for β-lactam antibiotics.

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(9) Compound **11** is also useful as a key synthetic intermediate for an orally absorbable antibiotic of the O-2-isocephem type. Mastalerz, H.; Menard, M.; Vinet, V.; Desiderio, J.; Fung-Tomc, J.; Kessler, R.; Tsai, Y. *J. Med. Chem.* **1988**, 31, 1190.

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Large Protonated Water Clusters H⁺(H₂O)ₙ (1 ≤ n > 60): The Production and Reactivity of Clathrate-like Structures under Thermal Conditions

Xiaolin Yang and A. W. Castleman, Jr.*

Department of Chemistry
The Pennsylvania State University
University Park, Pennsylvania 16802

The nature of gas-phase water clusters has been of long-standing interest, impacting on a number of areas including elucidating transitions from the gas to condensed state, determining the nature of hydrogen bonded liquids and ice, noting the influence of solvation on proton transfer, and studying important problems in the atmospheric sciences, for example. Although the structure and reactivities of small proton hydrates [H⁺·(H₂O)ₙ; $n \leq 10$] have been well explored[1-3] and large clusters up to $n = 22$ have been observed[4] under atmospheric pressure ionization, there has been little quantitative data to interpret particular features observed in larger clusters.[5,6] The focus of most work on special structures and magic numbers of large protonated water clusters has been based on supersonic beam and sputtering experiments[5-12] that have not been designed to elucidate the actual mechanisms of their production.

Herein, we report the first observation of magic numbers for proton hydrates corresponding to $n = 21, 24, 26,$ and 28, produced and studied under thermal conditions, and also present the first information on trends in their reactivity with cluster size. The well-established fast-flow reactor technique,[13] equipped with a "poorman's" SIFT,[14] was used to produce large protonated water clusters containing more than 60 molecules and study their reactions with several molecules including acetonitrile, at well defined temperatures.

Figure 1 is a distribution spectrum of the protonated water clusters taken at $T \approx 120$ K, which clearly demonstrates that (1) a second envelope is formed, emerging with a cluster size about $n = 13$, and (2) a peak maximum appears with $n = 21$ with some weak maxima features at $n = 24, 26,$ and 28 (the maxima at $n = 24$ and 26 are present under most but not all conditions). It is important to note that the magic numbers similar to those observed in various beam and sputtering experiments[5-12] do not depend on the source conditions. Although the envelope was shifted, the prominence of the magic numbered clusters did not
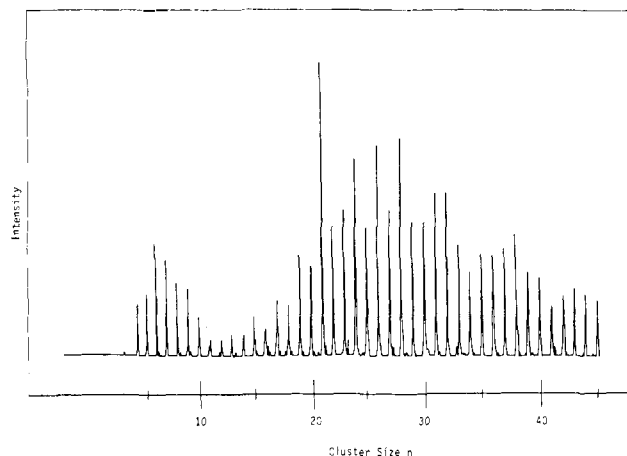

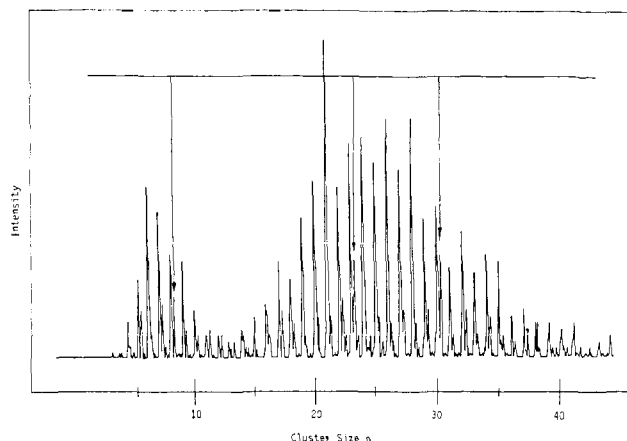**Figure 1.** Mass spectrum of protonated water clusters H⁺(H₂O)ₙ ($n = 4$–45) at 119 K flow tube temperature and 0.3 Torr He.

Figure 2. Product distribution of the reactions between protonated water clusters H⁺(H₂O)ₙ ($n = 4$–45) and acetonitrile at $T = 119$ K. The arrows point to the association products, e.g., H⁺(H₂O)₆·CH₃CN, H⁺(H₂O)₂₁·CH₃CN, and H⁺(H₂O)₂₈·CH₃CN.

vary with small changes in temperature and water vapor partial pressure.

Although small water clusters undergo proton transfer or replacement reactions with molecules that have higher gas-phase proton affinities (PA),[3,15] this possibility becomes less likely at larger sizes, and it can become endoergic at large sizes where solvation affects the relative proton affinities in the cluster complex. As seen in Figure 2, larger clusters simply undergo an association reaction with CH₃CN (PA = 188.4 compared to 166.5 kcal/mol for H₂O)[16] as is evident from the shift in the water cluster spectrum to a nearly identical distribution, but one containing a single attached CH₃CN molecule. The reaction rates at 119 K are very close to the calculated collisional rates obtained by using the Su–Chesnovich method[17] and show a slow decrease proportional to the inverse square root of reduced mass. Most importantly, they do not display any abrupt variations at the cluster sizes corresponding to the magic numbers and no dependence on pressure over the range 0.3–0.5 Torr.

Several important implications of our new findings include the following: (1) the magic number proton hydrates can be produced by association reactions and survive the more than 10⁵ collisions with helium during their 20-ms transient in the reactor, (2) simple addition of CH₃CN to these species does not display any abrupt variation with size in the vicinity of magic numbers, and (3) the CH₃CN directly attaches to larger water clusters. This strongly argues against the non-equilibrium growth kinetics being re-

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