Chemistry of Cage-Shaped Polyquinane Derivatives. The Reaction of 14-Iodohexacyclo[6.6.$0^{2,6}$.$0^{3,13}$.$0^{4,11}$.$0^{5,9}$]tetradecan-10-one in Basic Solution

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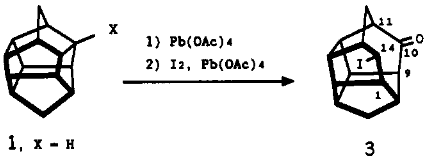
Reactions of the titled compound (**3**) in basic solutions are examined. Deprotonation at −40 °C proceeds at the C(11) position of **3**, followed by an intermolecular nucleophilic displacement to yield the condensation product **4** with a cage substituent at C(11). Elevating the reaction temperature to 0 °C results in the second deprotonation at C(9), followed by a rearrangement along with iodine transposition leading to the isomeric product **5**. The mechanisms of the reactions are discussed with the aid of theoretical calculations.

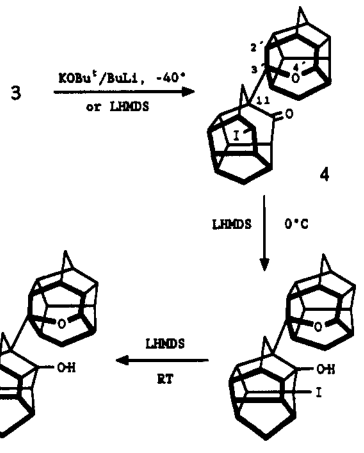
Introduction

The cage compound, heptacyclo[6.6.$0^{2,6}$.$0^{3,13}$.$0^{4,11}$.$0^{5,9}$.$0^{10,14}$]tetradecane (HCTD, **1**), can be synthesized readily according to a recently published procedure.[1] The structure of this compound consists of eight five-membered rings; therefore, it belongs to the family of polyquinanes. By virture of its easy preparation, compound **1** may serve as a starting material for the preparation of other polyquinane derivatives such as the iodo ketone **3**.[2] Subsequent deprotonation of **3** at an appropriate α-carbonyl position provides a way to further functionalize this compound. In this regard the chemical behavior of **3** under strongly basic conditions is examined.



1, X = H
2, X = OH

3



4

6

5

Results

In a typical experiment, compound **3** was treated with potassium *tert*-butoxide and *n*-butyllithium in THF at −40 °C for 30 min and a major product **4** was produced in 85% yield. In the downfield region of the ^{13}C NMR spectrum of the product an absorption at δ 228.2 indicates the presence of a carbonyl group. In the ^{1}H NMR spectrum a complicated pattern is shown in the region of δ 1.5–3.5 in addition to two lower-field absorptions at δ 4.13 and 4.21. In MS the parent peak appears at m/z 524 and the base peak at m/z 397 ($M^+ - I$). The structure of the product was solved by means of X-ray crystallography, and an ORTEP drawing is shown in Figure 1. Compound **4** contains two of the cage skeletons connected at C(11) and C(3′) positions. The formation of **4** must have proceeded through an initial nucleophilic attack by the anion of **3** to the carbonyl carbon of another **3**. The resulting oxide then underwent an intramolecular substitution to form an oxa bridge across the ring.

Compound **4** can also be obtained in a similar process using LHMDS as base at −78 °C in THF. However, if the reaction is not terminated at the optimal production of **4** but allowed to warm up gradually to 0 °C and to stay for a few hours, a complete conversion of **4** to a secondary product is observed. The new product **5** may be purified as colorless crystals. Prolonged reaction at room temperature induces further transformation of **5** to a third compound **6**. The structures assigned to both **5** and **6** are based on their spectroscopic characteristics.

Compound **5** is an isomer of **4** as indicated by its MS. An iodine is present as shown by the mass difference between the parent peak (m/z 524) and the base peak (m/z 397). In the IR spectrum a strong absorption appears at 3394 cm^{-1} for a hydroxy group, but no absorption corresponding to carbonyl group is observed. This information leads to a structure containing two cage molecules in which an iodo substituent is present at an unknown position.

The spectroscopic features of **6** are somewhat similar to those of **5**. A hydroxy group is present as shown by the strong absorption at 3409 cm^{-1} in the IR spectrum and the broad ^{1}H signal at δ 5.33 in the NMR spectrum. It produces 26 separable absorptions in the ^{13}C NMR spectrum including four secondary, 19 tertiary, and three quaternary carbons. Compound **6** gives a very strong parent peak in the MS at m/z 398 (relative intensity, 100) confirming the lack of an iodine. It seems that **6** is the dehalogenated hydrocarbon of **5**.

The structure of **5** was solved by means of X-ray diffraction analysis. Crystal parameters and the method of refinement are included in the supplementary material. An ORTEP drawing is shown in Figure 2. The two cages are connected in the same way as they are in **4**. The most interesting structural feature of **5** is the position of the iodine which is found at C(9) of the original **4**. The migration of the iodine atom cannot occur in a single step since a deprotonation at C(9) must happen prior to the ring closure.

Discussion

The acidity of the α-hydrogens (H(9) and H(11)) of **3** is quite weak since the corresponding enolate cannot adopt

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[1] (a) Chow, T. J., Chow, Y.-S., Liu L.-K. *J. Am. Chem. Soc.* **1987**, *109*, 797. (b) Chow, T. J.; Feng, J.-j.; Shih, H.-J.; Wu, T.-K.; Tseng, L.-H.; Wang, C.-Y.; Yu, C. *J. Chin. Chem. Soc.* **1988**, *35*, 291. (c) Marchand, A. P.; Earlywine, A. D. *J. Org. Chem.* **1984**, *49*, 1660.

[2] Chow, T. J.; Wu, T.-K. *J. Org. Chem.* **1988**, *53*, 1102.

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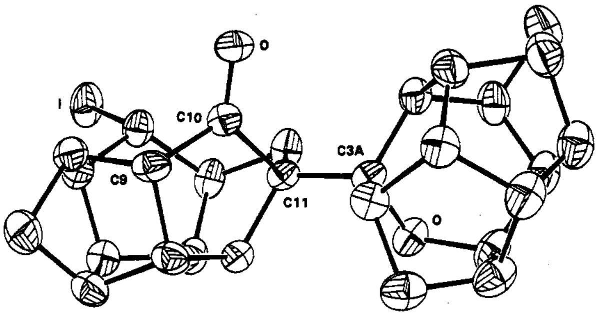


Figure 1. ORTEP drawing for the structure of **4**. Hydrogen atoms are omitted for clarity.

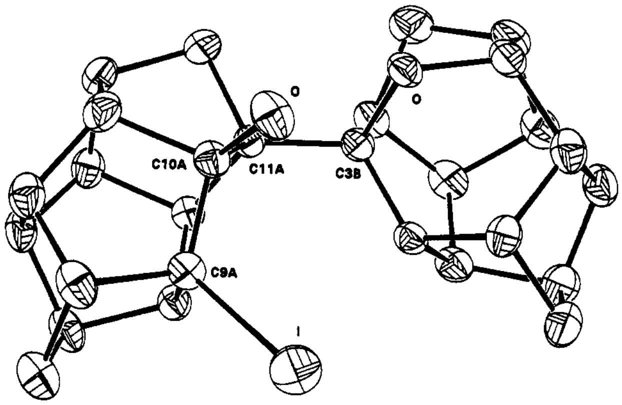


Figure 2. ORTEP drawing for the structure of **5**. Hydrogen atoms are omitted for clarity.

Table I. MNDO Calculated Net Atomic Charges, Heats of Formation (kcal/mol), and Deprotonation Enthalpies for Compound 3 and Its Anions

	3	anion C(9)	anion C(11)
heat of formation	−14.38	−14.85	−13.87
deprotonation enthalpy[a]		366.7	367.7
atomic charge			
C(10)	+0.24	+0.34	+0.32
O(16)	−0.27	−0.46	−0.48
C(9)	−0.077	−0.64	
C(11)	−0.080		−0.61

[a] The deprotonation enthalpy (kcal/mol) is calculated according to the equation of $\Delta H_f(H^+) + \Delta H_f(\text{anion}) - \Delta H_f(3)$, assuming $\Delta H_f(H^+) = 367.2$ kcal/mol.[4]

Table II. Semiempirical Calculated Heat of Formation of the Cage Compounds and Their Corresponding Anions (kcal/mol)

MNDO	H_f	MNDO	H_f
4[a]	17.28	8[b]	−9.11
5[a]	32.80	9[b]	4.05
7[b]	−14.73	10[c]	35.20

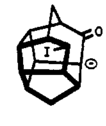
[a] Calculated using the crystal coordinates of all non-hydrogen atoms and allowing the hydrogen atoms to refine. [b] Geometry fully optimized. [c] The O–I distance is fixed at 1.956 Å.

a planar geometry. Semiempirical (MNDO)[3] calculations for the two possible α-anions indicate that delocalization of the atomic charge from carbon to oxygen is quite low. The calculated charge densities are listed in Table I. The anion deprotonated at C(11) spreads a little more of its negative charge onto oxygen (−0.48 e) than does the anion deprotonated at C(9) (−0.46 e). The gas-phase deprotonation enthalpies are estimated to be 366.7 kcal/mol at C(9) and 367.7 kcal/mol at C(11).[4] The difference in enthalpies can be ascribed to the relative strains in the corresponding anions.[5] The strains on the α-carbons can be estimated by the force-field calculation (MM2)[6] which shows that the bending energies around C(9) (1.27 kcal) are 0.55 kcal higher than that around C(11) (0.72 kcal). These calculations indicate that the deprotonation at C(9) is slightly favored over C(11), but only by a marginal difference (<1 kcal/mol).

The structures of **4** and **5** confirm the feasibility of deprotonation at both sites of C(9) and C(11). Since the thermodynamic parameters mentioned above cannot properly reflect the chemical behavior in solution, and also because LHMDS is known to act as a kinetic base, the observed sequence of deprotonations does not correspond exactly with the predicted order.

Model Study for the Transformation of 4 to 5. The mechanism for the conversion from **4** to **5** is not apparent since it might involve multiple steps. Deprotonation at C(9) must have proceeded before the ring closure, otherwise the iodination at C(9) would not be possible. Subsequent ring closure between the iodo carbon and the carbonyl carbon produces **5**. However, in this sequence the migration of iodine from C(14) to C(9) is not yet clear.

A model analysis was performed on the anions **7** and **8** in order to acquire a general knowledge about the relative state of energy among structural isomers. The calculations were done for the anions in isolated states where the effects of solvent and counter cations are not taken into consideration. The enthalpy of conversion from **7** to **8** is estimated to be endothermic by 5.62 kcal/mol according to MNDO method (Table II). In the crystal structure of **4**, the iodo substituent is located on the exo side of the cage opening, so that the transposition of the iodine from C(14) (exo) of **4** (or **7**) to C(9) (exo) of **5** (or **8**) may not proceed readily through a unimolecular process.



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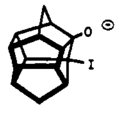

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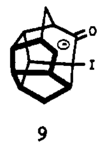

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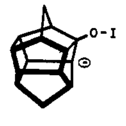

10

The migration of iodine may proceed either prior to or later than the ring closure. In the former case, anion **9** should present, otherwise the hypoiodo anion **10** may appear. The rearrangement of **7** to **10** can be viewed as the

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[3] (a) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899. (b) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4907.

[4] (a) Dewar, M. J. S.; Dieter, K. M. *J. Am. Chem. Soc.* **1986**, *108*, 8075 and references cited therein. (b) Kass, S. R. *J. Comput. Chem.* **1990**, *11*, 94. (c) Chandrasekhar, J.; Andrate, J. G.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1981**, *103*, 5609.

[5] Higher strain in the carbon increases its electronegativity and results in a larger J_{C-H} in NMR.[7] The J_{C-H} measured for the 10,14-dione[8] derivative of **3** are 139.9 Hz (28.0% s character) for C(9) and 136.8 Hz (27.4% s character) for C(11), which is consistent with the result of MM2. It is known that carbanions increase in stability with an increase in the amount of s character at the carbanionic carbon.[9]

[6] Burkert, U.; Allinger, N. L. *Molecular Mechanics* **1982**, ACS Monographs 177.

[7] (a) Wiberg, K. B.; Bader, R. F. W.; Lau, C. D. H. *J. Am. Chem. Soc.* **1987**, *109*, 1001. (b) Shoolery, J. N. *J. Chem. Phys.* **1959**, *31*, 1427.

[8] Chow, T. J.; Liu, L.-K.; Chao, Y.-S. *J. Chem. Soc., Chem. Commun.* **1985**, 700.

[9] March, J. *Advanced Organic Chemistry*, 3rd ed.; John Wiley & Sons: New York, 1985; p 154.

reverse of the ring opening during the conversion of **2** to **3**. The energy difference between **7** and **10** (in the gas phase) is estimated to be ca. 50 kcal/mol and that between **7** and **9** ca. 18–19 kcal/mol. The conversion of **10** to **8** is exothermic by ca. 44 kcal/mol and probably proceeds with no apparent energy barrier. When the initial structure of **10** (Table II) was put into the program AMPAC for a full geometry optimization, the migration of iodine atom from oxygen to C(9) proceeded automatically during the energy minimization process and **8** came out as the final structure.

It seems that in the conversion of **7** to **8**, the ring closure proceeds first, followed immediately by the transposition of iodine. The presence of an intermediate analogous to that of **9** cannot completely clarify the timing of the iodine migration. Prior to the formation of **9**, other types of intermediates such as bis-iodide or dianion could exist. The existence of a transient structure analogous to that of **10** requires that the high activation energy be reduced significantly by the polar medium in the solutions. Although this simple modeling study has provided some quantitative information for the rationalization of a sensible mechanism, the nature of the true intermediates and the actual sequence of events still need to be determined by further experimental work.

Experimental Section

^{1}H and ^{13}C NMR spectra were obtained at 200 and 500 MHz, respectively. Melting points are uncorrected. MM287 and AMPAC programs were obtained from QCPE, Indiana University.

11-(4′-Oxaheptacyclo[7.6.0.0$^{2',7'}$.0$^{3',14'}$.0$^{5',12'}$.0$^{6',10'}$.0$^{11',15'}$]pentadecan-3′-yl)-14-iodoheptacyclo[6.6.0.0^{2,6}.0^{3,13}.0^{4,11}.0^{5,9}]tetradecan-10-one (4). To a dry THF (80 mL) solution containing potassium *tert*-butoxide (250 mg) at −78 °C was injected through a syringe a solution of *n*-butyllithium (1.53 mL, 15% in *n*-hexane). The resulting solution was stirred for 30 min at −78 °C then was allowed to warm to −40 °C. To the light yellowish solution was added dropwise a THF solution (2.0 mL) containing **3** (84 mg, 0.26 mmol) and TMEDA (0.50 mL). The resulting solution was stirred at −40 °C for 30 min, during which time the reaction was examined regularly by TLC. At the end of 30 min all the starting material disappeared and a product of less polarity appeared. The reaction was quenched by the addition of distilled water. The organic products were extracted several times with ether and dried over anhydrous $MgSO_4$. Compound **4** was isolated by silica gel chromatography eluted with *n*-hexane/ethyl acetate (v/v = 9/1) to yield **4** as a white solid (56 mg, 0.11 mmol, 85%): mp 184.5–185.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.47–1.54 (m, 1 H), 1.67–1.76 (m, 5 H), 1.85–1.92 (m, 1 H), 2.30–2.90 (m, 15 H), 3.0 (m, 1 H), 3.10–3.20 (m, 2 H), 3.30–3.40 (m, 2 H), 4.10–4.25 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 33.05, 33.58, 37.14, 43.12, 44.50, 45.74, 45.84, 47.20, 47.77, 49.72, 50.12, 50.85, 51.57, 52.31, 52.79, 53.98, 54.50, 57.50, 57.71, 64.20, 64.99, 71.31, 76.90, 228.19; MS (70 eV) (rel. int.) 524 (M^+, 0.8), 397 ($M^+ - I$, 100), 369 (11), 351 (5.5), 303 (3.8), 285 (3.3); HRMS calcd M^+ 524.1213, found 524.1205. Anal. Calcd for $C_{28}H_{29}O_2I$: C, 64.12; H, 5.57. Found: C, 64.25; H, 5.68.

8-(4′-Oxaheptacyclo[7.6.0.0$^{2',7'}$.0$^{3',14'}$.0$^{5',12'}$.0$^{6',10'}$.0$^{11',15'}$]pentadecan-3′-yl)-14-iodoheptacyclo[6.6.0.0^{2,6}.0^{3,13}.0^{4,11}.0^{5,9}]tetradecanol (5). A solution of LHMDS was prepared by adding *n*-butyllithium (1.3 mL, 15% solution in *n*-hexane) to a solution of THF (25 mL) containing HMDS (0.4 mL) at 0 °C. This solution was cooled to −78 °C under N_2, and to it was added dropwise a solution of THF (5 mL) containing **3** (72 mg, 0.22 mmol) and HMPA (0.75 mL). The resulting mixture was stirred at −78 °C for 1 h, and compound **4** was isolated as previously described. If the solution was not quenched at this stage, but allowed to warm to −30 °C for 3 h, followed by 0 °C for 2 h, compound **5** was isolated as the only product. It was purified by silica gel chromatography eluted with hexane/ethyl acetate (v/v = 9/1) to form a white solid (52 mg, 0.10 mmol, 90% yield): mp 200.5–201.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.50–1.70 (m, 3 H), 1.85–1.95 (m, 3 H), 2.25–2.85 (m, 19 H), 2.95 (m, 1 H), 3.02 (m, 1 H), 4.35 (t, 1 H, J = 9 Hz), 5.06 (s, 1 H, OH); ^{13}C NMR ($CDCl_3$) δ 33.61 (t), 37.00 (d), 41.98 (t), 42.45 (t), 42.67 (t), 47.02 (d), 47.77 (d), 50.25 (d), 50.32 (d), 50.42 (d), 50.98 (d), 51.25 (d), 51.79 (d), 52.39 (d), 52.79 (d), 53.47 (d), 54.12 (d), 54.39 (d), 54.81 (d, 2 C), 62.53 (d), 62.72 (d), 64.17 (d), 66.90 (s), 68.89 (s), 76.90 (CHO), 85.85 (s), 98.20 (s); IR ($CHCl_3$) 3394 (OH), 3019, 2955 (s), 2868, 1215 (s) cm^{-1}; MS (70 eV) (rel. int.) 524 (M^+, 5.4), 397 (100), 379 (8.1), 369 (2.7), 351 (5.4), 313 (2.7), 287 (8.1). Anal. Calcd for $C_{28}H_{29}O_2I$: C, 64.12; H, 5.57. Found: C, 64.08; H, 5.63. A complete conversion of **5** to **6** was observed when the reaction was allowed to proceed overnight at room temperature. Compound **6**: mp 190–191 °C; ^{1}H NMR ($CDCl_3$) δ 1.54 (dt, J = 4, 11 Hz, 1 H), 1.73–1.90 (m, 6 H), 2.10 (m, 1 H), 2.32 –2.60 (m, 15 H), 2.65–2.75 (m, 5 H), 4.35 (t, J = 8.5 Hz, 1 H), 5.33 (br, OH); ^{13}C NMR ($CDCl_3$) δ 33.31 (t), 36.29 (d), 41.62 (t), 42.68 (t), 43.13 (t), 47.45 (d), 48.24 (d), 48.68 (d), 49.07 (d), 50.45 (d), 50.89 (d), 50.95 (d), 51.60 (d), 52.54 (d), 53.11 (d), 53.56 (d), 54.10 (d), 54.23 (d), 54.45 (d), 54.85 (d), 58.86 (d), 65.99 (d), 68.33 (s), 76.90 (d), 86.05 (s), 98.95 (s); IR ($CDCl_3$) 3409 (OH), 2960 (s), 2866, 1295, 1215 (s) cm^{-1}; MS (70 eV) (rel. int.) 398 (M^+, 100), 380 ($M^+ - H_2O$, 97), 362 (4.3), 352 (4.6), 314 (10), 299 (17), 286 (22), 275 (8.8).

Acknowledgment. This work was supported by the National Science Council of the Republic of China.

Registry No. **3**, 112533-30-9; **4**, 136804-82-5; **5**, 136804-83-6; **6**, 136804-84-7; **7**, 136804-85-8; **8**, 136804-86-9; **9**, 136804-87-0; **10**, 136804-88-1.

Supplementary Material Available: Tables of crystal information, atomic coordinates, thermal parameters, and bond lengths and angles of compounds **4** and **5** (20 pages). Ordering information is given on any current masthead page.