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Cation, Carbene, and Radical Centers in a [4.4.4.5]Fenestrane

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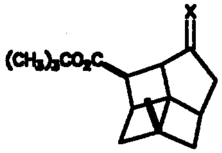
Abstract: Carbocation **2a**, formed on photolysis of iodide **3a** in methanol is captured by solvent to yield **4d** exclusively. Carbene **2b**, formed on photolysis of salt **1b** in methanol, also yields only **4d**. Radical **2c**, formed on photochemical initiation of reaction between **3a** and tributylstannane, abstracts hydrogen without rearrangement to give only **3c**. These reactions and relevant MNDO calculations are discussed.

Earlier investigations revealed a number of unusual thermal and photochemical reactions in the fenestrane keto ester **1a**, all of which reflected the relief of strain available on fragmentation of the [4.4.4.5]fenestrane skeleton.[1] These findings and appropriate MNDO calculations[2] that are noted below suggested that intermediates such as the related cation **2a**, carbene **2b**, and radical **2c** might also be susceptible to cleavage of the tetracyclic ring system. We have evaluated this possibility and found that these species are kinetically quite stable under conditions that lead to formation of discrete products. Details of these studies are given below.

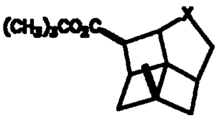
Preparative experiments

The [4.4.4.5]fenestrane skeleton has limited thermal stability,[1] and we wished to avoid high temperatures in preparation of **2a-c**, in order to minimize thermal fragmentation unconnected with the reactive center under examination. With this in mind we chose to use photochemical reactions to reach these intermediates. Iodide **3a** then is an attractive precursor for both **2a** and **2c**, because irradiation of iodides in polar solvent furnishes carbocations,[3] and the reaction of alkyl iodides with trialkylstannanes to form carbon-centered radicals can be initiated photochemically.[4] Iodide **3a** was available on treatment of tosylate **4b**[1] with freshly prepared magnesium iodide in ether.[5] These conditions typically give clean inversion in the iodide formed, including displacements on five-membered rings, and we accordingly assign the stereochemistry of **3a** as depicted. Since tosylhydrazone salts undergo photochemical decomposition to form carbenes,[6] a suitable precursor for carbene **2b** was salt **1b**, which was prepared in the usual fashion from ketone **1a**. An authentic sample of methyl ether **4d** was



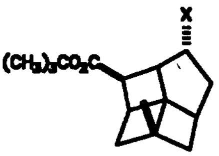
1

a, X = O
b, X = N–NTs⁻ Na⁺



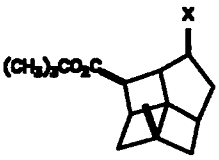
2

a, X = CH⁺
b, X = C:
c, X = CH·



3

a, X = I
b, X = OTs
c, X = H



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d, X = OCH_3
e, X = OH

required, and this was available on treatment of **4e**[1] with sodium hydride followed by methyl iodide. The assigned stereochemistry of ether **4d** and alcohol **4e** rests on the X-ray structure determination previously carried out on derived tosylate **4b**.[1] The structure of **3c**, the product obtained from radical **2c**, was substantiated by hydride reduction of **3c** to the previously described[1] alcohol **5**.

Results

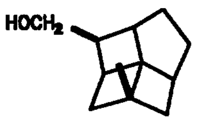
Irradiation of **3a** (λ > 340 nm) in methanol led to a mixture of reduction product **3c** (38%) and methyl ether **4d** (36%). In pentane as solvent the only product found was **3c** (84%). Iodide **3a** was converted to radical **2c** on irradiation in pentane containing tributylstannane and azoisobutyronitrile; the only product obtained (75%) was **3c**. Photolysis of **1b** in methanol solution yielded methyl ether **4d** as essentially the only product. Photolysis of **1b** in tetrahydrofuran or thermolysis at 150 ° C furnished no isolable products. Under each of these latter conditions analytical gas chromatography indicated formation of a large number of volatile substances, all in very small yield. Tosylhydrazone **1b** was recovered unchanged from attempted thermolysis at 65 ° C.

Discussion

The fenestrane skeletone proves to be resistant to rearrangement of reactive intermediates **2a-c**. Attempts to increase the lifetimes of these species by reducing the availability of trapping agents or to increase their reactivity by raising the reaction temperature resulted only in intractable mixtures of products. This kinetic stability is in contrast to the expected thermodynamic stability of reasonable rearrangement products. MNDO calculations[7] suggest, for example, that β-cleavage of **2c** to give **6** should be favorable by more than 13 kcal/mol.[8] The clean formation of **3c** by way of **2c** on reaction of **3a** with tributylstannane is therefore somewhat unexpected.

In general, photochemical decomposition of iodides leads to homolysis of the C-I bond followed by electron transfer to form a carbocation and iodide ion. Both radical and ionic products are then possible from this reaction, with the proportion of radical products typically higher in nonpolar solvents. In addition α-elimination to a carbene intermediate is sometimes observed (up to 30%).[3] In view of these earlier findings, the photolysis of **3a** in methanol is most simply interpreted as leading to formation of **4d** from the desired carbocation **2a**, along with formation of **3c** from radical **2c**. Apparently, only the latter radical pathway operates in pentane. Once again, a reasonable path of rearrangement is not taken: 1,2 hydride shift in **2a** to form the vicinal tertiary carbocation should be exothermic,[9] but no evidence for this shift is found. The highly stereoselective formation of only methyl ether **4d** with no evidence for the epimeric **3d** also requires comment. Models suggest no great difference in stability between **4d** and **3d**, and this conclusion is supported by calculations.[10] The possibility that topside attack results from charge delocalization as shown in **7** can be dismissed on energetic grounds. Although the rearrangement related to such delocalization has been long known in the bicyclic parent ion **8**,[11] MNDO suggests that the analogous bond shift in **2a** would be endothermic by $\sim$70 kcal/mol. It is likely that the observed high stereoselectivity is the result of a memory effect in which the large departing iodide ion shields the lower surface of **2a** from approach of methanol on that side.

In contrast, it remains unclear why insertion of carbene **2b** into the solvent O-H bond should also show such high specificity. There is previous evidence for a modest steric effect in O-H insertion, at



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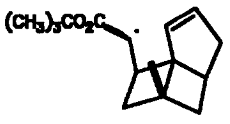

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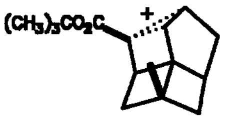

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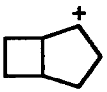

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least with an unsaturated carbene,[12] but models of **2b** suggest that approach from the top to form **4d** is no less hindered than approach from the bottom.

EXPERIMENTAL SECTION

General

All operations were carried out under an inert atmosphere (argon) unless otherwise mentioned. Melting points were determined by using a Thomas-Hoover capillary melting point apparatus and are corrected. IR spectra were determined on a Perkin-Elmer 1870 Fourier Transform spectrometer or a 1420 ratio recording instrument, either neat or in KBr pellets, and absorption values are given in reciprocal centimeters (s, strong; m, medium; w, weak; br, broad). NMR spectra were recorded on a Nicolet/Oxford Model NT-360 (360 MHz) instrument and are reported in parts per million downfield from tetramethylsilane employed as an internal standard (δ) in $CDCl_3$ (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad). Mass spectral analyses were performed on a VG-70250 magnetic sector instrument. All spinning-disk chromatographic separations were carried out on a Chromatotron (Harrison Model-7924 T) using silica gel (silica gel 60, PF 254; EM Science cat. #7749-3) coated glass rotors (1, 2 or 4 mm thick). Gradient elution (step gradients) from batchwise addition of mobile phase (mixtures with increasing amounts of polar solvents) was performed by gravity flow method. For visualization of bands, a multiband ultraviolet lamp (Mineralight UVGL-58) was used. Analytical GLC was carried out isothermally on a Hewlett-Packard model HP 5890 instrument using an Alltech Econo-Cap (30 m × 0.25 mm) SE 30 capillary column with a film thickness of 0.25 μm. Preparative VPC was carried out on a Varian Aerograph model 920 instrument using a 20% SE-30 (10 ft × 0.25 in.) column. Flash chromatography was performed with 230-400 mesh silica gel (Merck 9385-5). All organic extracts were washed with saturated aqueous NaCl and dried over anhydrous $MgSO_4$ prior to solvent removal. Solutions for photolysis were purged with argon for a period of 15 min prior to irradiation. A medium pressure 450-Watt Hanovia mercury arc lamp or a Rayonet photochemical reactor fitted with 254-nm lamps were used for irradiations. All solvents were purified and/or dried before use wherever it was deemed neccessary.

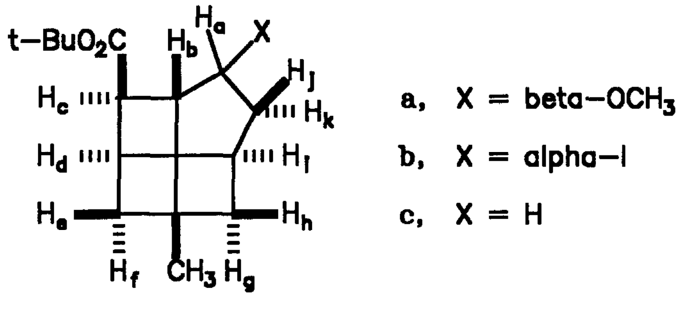
Preparative and Photochemical Experiments

Tosylhydrazone of *tert*-Butyl 5-Oxo-1-methyl[4.4.4.5]fenestrane-7β-carboxylate (1a).

A solution of the keto ester **1a**[1] (88.3 mg, 0.337 mmol) and tosylhydrazine (62.7 mg, 0.337 mmol) in a minimum quantity of absolute ethanol (1.00 mL) was heated under reflux for a period of 10 min followed by cooling to 0 °C. Slow addition of cold water (dropwise) precipitated the tosylhydrazone. This was filtered and vacuum dried to obtain a light yellow powder, which upon crystallisation (CCl_4:hexane 1:9) furnished pure tosylhydrazone (103 mg, 71%). mp 132-133 °C. **NMR** δ 7.840 (*m*, 2 H); 7.334 (*m*, 2 H); 3.812 (*dd*, 8.28 Hz, 2.16 Hz); 2.928 (*m*, 2 H); 2.702 (*m*, 1 H); 2.598 (*m*, 1 H); 2.432 (*s*, 3 H); 2.173-2.469 (*m*, 2 H); 1.788-1.988 (*m*, 1 H); 1.480 (*s*, 9 H); 1.035-1.504 (*m*, 2 H); 1.116 (*s*, 3 H). **IR** 3421 (s), 1721 (s), 1658 (w), 1597 (m), 1338 (s), 1239 (m), 1170 (s), 1140 (s). **MS** *m/z* 431.1976 [$(M + 1)^+$, calcd. for $C_{23}H_{31}N_2O_4S$, 431.2004].

Photolysis of Tosylhydrazone Sodium Salt (1b). (a) in Methanol.

NaH [1.046 mg, (80% dispersion in oil), 0.035 mmol] was added to anhydrous methanol (25 mL) followed by the above tosylhydrazone (10 mg, 0.023 mmol) and bubbled with argon for 30 min. This degassed solution was irradiated in a Pyrex vessel using a 450-W lamp for 1 h. After irradiation, the solution was evaporated to dryness and the residue was taken up in ether (50 mL). This was washed



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with dil HCl followed by aqueous bicarbonate solution (15%), which upon drying and evaporation afforded a yellow mass. Chromatographic separation of this material yielded ether **4d** (4 mg) as a colorless oil in 62% yield.

(b) In Tetrahydrofuran.

The above tosylhydrazone (10 mg, 0.023 mmol) was added to CH_3ONa (2 mg, 0.037 mmol) in methanol and stirred for 30 min after which the solution was evaporated to dryness and washed thoroughly with dry pentane. To the fine powder thus obtained was added dry THF (25 mL). The solution was stirred for 20 min, during which time part of the salt dissolved. This suspension was degassed and irradiated with a 450-W lamp through Pyrex for 1 h. GLC analysis of the product obtained after usual workup showed a large number of products which were not identified.

Authentic *tert*-Butyl 1-Methyl 5β-methoxy[4.4.4.5]fenestrane-7β-carboxylate (4d).

A solution of alcohol[1] **4e** (10 mg, 0.038 mmol) in anhydrous THF (4 mL) was added to a finely divided suspension of NaH (2 mg, 0.082 mmol) in anhydrous THF (4 mL) kept at 0 °C and stirred for 30 min. Methyl iodide (1 mL) was slowly added to this mixture, after which the reaction mixture was brought to room temperature and stirred for 20 h. Usual workup furnished the ether as a mixture of the two isomers (95:5) which were separated by chromatography. The major component isolated was the ether **4d** (7 mg, 67% yield). **IR** 1722 (s), 1455 (m), 1395 (w), 1370 (m), 1250 (m), 1140 (m, br). **NMR** δ (see **9a**) 3.734 (*ddd*, H_a, J_{aj} = 18 Hz, J_{ab} = 10.08 Hz, J_{ak} = 4.32 Hz); 3.477 (*d*, H_c, J_{cb} = 8.28 Hz, J_{cd} = 3.24 Hz); 3.328 (s, 3 H, OCH_3); 2.860 (*dd*, H_e, J_{ef} = 13.68 Hz, J_{ed} = 6.48 Hz); 2.761 (*dd*, H_g, J_{gh} = 12.96 Hz, J_{gi} = 5.76 Hz); 2.359 (*m*, H_b); 2.412 (*dd*, H_f, J_{fe} = 7.56, J_{fd} = 2.88); 2.279 (*ddd*, H_d, J_{de} = 18.36 Hz, J_{dc} = 11.88 Hz, J_{df} = 2.16 Hz); 2.062 (*m*, H_i); 1.976 (*dd*, H_h, J_{hg} = 12.96 Hz, J_{hi} = 9.36 Hz); 1.486 (s, 9 H, $C(CH_3)_3$; 1.443-1.623 (*m*, 2 H). **MS** *m/z* 277.1780 [$(M-1)^-$, calcd. for $C_{17}H_{25}O_3$, 277.1804]

Thermolysis of Tosylhydrazone Salt (1b). (a) In Tetrahydrofuran.

The tosylhydrazone (5 mg, 0.0116 mmol) was stirred with CH_3ONa (3 mg, 0.055 mmol) in dry THF (3 mL) for a period of 2 h. The resultant solution was evaporated to dryness and the solid obtained was suspended in dry THF (5 mL) and heated under reflux for 8 h. After workup the product isolated was identified as the tosylhydrazone of **1a** in quantitative yield.

(b) In Diglyme.

The previous experiment was repeated using anhydrous diglyme (5 mL) as the solvent. The suspension was heated to 150 °C for 2 h, cooled, diluted with ether, washed with dil HCl, dried and evaporated in vacuo. A GLC analysis of the residue obtained showed a large number of peaks which were not identified.

Preparation of *tert*-Butyl 5α-Iodo-1-methyl[4.4.4.5]fenestrane-7β-carboxylate (3a).

To a cold (ice bath) solution of freshly prepared anhydrous MgI_2[7] (46 mg, 0.165 mmol) in dry ether (20 mL) was added a solution of the tosylate **4b**[1] (14 mg, 0.0335 mmol) in dry ether (5 mL) and stirred for 15 min. The solution was then gently heated under reflux for a period of 1.5 h after which it was cooled in an ice bath and water (25 mL) was added. The mixture was extracted with ether (20 mL× 3) and the combined ether layer was washed with aqueous sodium thiosulfate solution (15%) followed by brine. The residue obtained after drying was chromatographed to obtain the iodo compound **3a** as a thick gum (75 mg, 84% yield). **IR** 1719 (s), 1449 (m), 1367 (m), 1348 (m), 1249 (m), 1162 (s), 1132 (s). **NMR** δ (see **9b**) 3.627 (*ddd*, H_a, J_{ak} = 20.88 Hz, J_{ai} = 11.34 Hz, J_{ab} = 4.14 Hz); 3.366 (*dd*, H_c, J_{cb} = 8.64 Hz, J_{cd} = 3.96 Hz); 2.862 (*dd*, H_e, J_{ef} = 13.68 Hz, J_{ed} = 6.48 Hz); 2.859 (*dd*, H_b, J_{bc} = 9.36 Hz, J_{ba} = 4.68 Hz); 2.755 (*dd*, H_g, J_{gh} = 12.96 Hz, J_{gi} = 5.76 Hz); 2.460-2.534 (*m*, H_d + 1 H); 1.867 (*m*, 1 H); 2.428 (*dd*, H_f, J_{fe} = 13.68 Hz, J_{fd} = 10.44 Hz); 2.093 (*m*, H_i); 2.005 (*dd*, H_h, J_{hg} = 12.96 Hz, J_{hi} = 9.36 Hz); 1.485 (s, 9 H, *tert*-butyl); 1.160 (s, 3 H, methyl). **MS** *m/z* 375.0846 [$(M + 1)^+$, calcd. for $C_{16}H_{24}O_2I$, 375.0821].

Photolysis of Iodide (3a). (a) In Pentane.

A solution of iodide **3a** (25 mg, 0.668 mmol) in dry pentane (10 mL) was degassed in a quartz tube and irradiated (254 nm) for 5 h. A GLC analysis of the crude product revealed the formation of a single product. This on chromatographic purification furnished **3c** (yield 14 mg, 84%). **IR** 2921 (s), 1723 (s), 1460 (m), 1255 (w), 1155 (m). **NMR** δ (see **9c**) 3.478 (*dd*, H_c, J_{cb} = 14.04, J_{cb} = 7.2 Hz); 2.496 (*m*, H_b + H_d + H_g); 2.333 (m, H_f + H_e); 2.004 (*m*, H_i); 1.880 (*m*, H_h); 1.088-1.677 (*m*, 4 H); 1.449 (*s*, 9 H, *tert*-butyl); 1.181 (*s*, 3 H, methyl). **MS** *m/z* 192 [$(M - C_4H_9 + 1)^+$, calcd for $C_{12}H_{16}O_2$, 192].[13]

(b) In Methanol.

A solution of iodide **3a** (25 mg, 0.668 mmol) in dry methanol (8 mL) was degassed in a quartz tube and was irradiated (254 nm) for 1 h. GLC analysis revealed the formation of methyl ether **4d** and reduced product **3c** in 47:53 ratio, respectively. Chromatographic separation of the mixture afforded the ether **4d** (6 mg, 36%) and the reduced product **3c** (7 mg, 38%). The products were identified by comparison with the samples obtained above.

Reduction of Ester 3c with Lithium Aluminum Hydride.

A solution of 8 mg of **3c** in ether containing a 4-fold molar excess of $LiAlH_4$ was heated at reflux for 5 h and worked up in the usual manner to furnish 5 mg of **5**, which was purified by spinning-disk chromatography and identified by comparison of its NMR spectrum with that previously reported for **5**.[1]

Reaction of Iodide 3a with Tributylstannane.

To a solution of the iodide **3a** (10 mg, 0.0267 mmol) and azoisobutyronitrile (0.8 mg) in dry pentane (5 ml) was added a solution of tributylstannane (8 μL, approximately 0.1 molar excess) in pentane (10 mL) over 4 h using a syringe pump. The reaction mixture was illuminated with a 60-Watt tungsten lamp during the entire reaction period. The reaction was followed by GLC analysis at intervals of 1 h and was found to be over in 5 h since after this time the relative ratio of the products to the starting material remained constant. Careful preparative VPC afforded the reduced product **3c** (5 mg, 75%) which was identified by comparing with the earlier obtained sample.

Acknowledgments

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7. These and subsequently mentioned calculations made use of MNDO (Thiel, W. *QCPE* **1978,** *11,* 353) as revised by K. E. Gilbert and J. J. Gajewski and distributed by Serena Software, Bloomington, Indiana.
8. MNDO ΔH_f's are 67.0 kcal/mol for the unsubstituted [4.4.4.5]fenestrane C(4) radical (parent radical of **2c**) and 53.7 kcal/mol for the unsubstituted parent radical of **6**. Unlike the parent primary radical, **6** is an acyl-substituted secondary radical, and the stabilization resulting from this substitution should increase the exothermicity of the β-cleavage of **2c** to **6** by several kcal/mol.
9. MNDO ΔH_f's are 258.6 kcal/mol for the unsubstituted [4.4.4.5]fenestrane C(4) carbocation (parent ion of **2a**) and 252.2 kcal/mol for its vicinal tertiary C(3) isomer.
10. MNDO ΔH_f's are −2.0 kcal/mol for 1β-methyl-5β-methoxy[4.4.4.5]fenestrane and −1.2 kcal/mol for 1β-methyl-5α-methoxy[4.4.4.5]fenestrane.
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