Formation of 3,3,4-Trimethyl-1,7-dibromonorbornane-2-one: a Spectroscopic and Computational Study

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ABSTRACT
The structure and origin of the major by-product in the synthesis of 8-bromocamphor from (+)-3,3,8-tribromocamphor has been confirmed using NMR, coset and single crystal X-ray analysis and DFT-level computational techniques.

KEYWORDS
Camphor derivatives, skeletal rearrangement, DFT calculations, NMR, coset analysis.

1. Introduction
In our research on the development of multidentate ligands for the construction of ruthenium complexes as novel metathesis catalysts,1 we have targeted the D-(+)-camphor (1)-derived, tridentate ligand 2 in the expectation that coordination with ruthenium would afford the chelated analogue 4 of the first-generation Grubbs catalyst 3.2 Application of the method reported by Money and co-workers3–6 afforded the critical precursor, 8-bromocamphor 5, in 33 % overall yield from (+)-3-endo-bromocamphor 6. In the final step [a Zn dust/ AcOH-mediated reaction of (+)-3,3,8-tribromocamphor 8] in the synthesis of this precursor, we isolated the desired product 5 in 44 % yield together with the major by-product, 3,3,4-trimethyl-1,7-dibromonorbornane-2-one 10, in 10 % yield (Scheme 1). In this communication, we discuss the characterisation of 3,3,4-trimethyl-1,7-dibromonorbornane-2-one 10 and the use of DFT calculations to resolve conflicting mechanistic explanations for its formation.

One- and two-dimensional NMR spectroscopy of a by-product isolated during the synthesis of (+)-8-bromocamphor 5 appeared to be consistent with (1R,4S)-3,3,4-trimethyl-7,7-dibromonorbornan-2-one 9. It was assumed that the by-product is formed during the reaction of the dibromo compound 7, but the results of a coset analysis of possible rearrangement pathways from 3,3-dibromocamphor 7 to compound 9 challenged this structural assignment.

In the coset analysis the maximum number of rearrangement steps in a given sequence was limited to 13 and the permissible operations to: Wagner-Meerwein rearrangements (WM), 2,3-exo-(23x), 2,3-endo-(23e) and 6,2- (62) shifts. Within these limits, the analysis generated the four potential pathways summarised in Fig. 1 for formation of compound 9 (in its protonated form 9H+) from the protonated dibromocamphor starting material 7H+. The rearrangement was expected to be acid-catalysed, thus warranting the use of protonated species.

The shortest sequence, the 7-step pathway (1) outlined in Scheme 2, commences with a Wagner-Meerwein rearrangement, followed by a 2,3-endo-methyl shift, a second Wagner-Meerwein and a 2,3-endo-bromide shift to afford intermediate iv. However, neither of the two subsequent steps, viz. the 2,3-exo-hydride shift to intermediate v nor the 2,3-endo-bromide shift to the gem-dibromide species vi, would be expected to be
energetically favoured. The 2,3-exo-hydride shift, while not impossible, is not likely to result in the relief of steric strain or the generation of a more highly substituted carbocation, while the 2,3-endo-bromide shift leads to the more sterically hindered species vii.

An examination of the alternative routes (2–4) to the cationic species 9H+ (Fig. 1) revealed the same energetically unfavourable hydride and bromide shifts in each pathway. These observations raised doubt concerning the assignment of structure 9. Money and co-workers10 had also isolated a by-product to which they assigned structure 10 using 1H NMR data; this was subsequently supported by X-ray crystallographic analysis.11 Re-examination of our one- and two-dimensional NMR data confirmed their consistency with structure 9. Thus, the 1H NMR spectrum clearly indicates the presence of: three methyl singlets at 1.08, 1.23 and 1.39 ppm; multiplets characteristic of the 5- and 6-methylene groups; and a singlet at 4.22 ppm corresponding to the relatively deshielded 7-methine proton. The 13C NMR spectrum revealed the requisite number of methine, methylene, methyl, quaternary and carbonyl carbon signals, while the HMOC and HMBC data confirmed the proton-carbon connectivities – all of which, superficially at least, are consistent with structure 9. Single crystal X-ray analysis of the by-product isolated in our study12 confirmed it to be the same as the compound isolated previously by Money and co-workers,9 viz. 3,3,4-trimethyl-1,7-dibromonorbornan-2-one 10.

There remains, however, some disagreement about the mechanistic pathways followed in the transformation of 3,3-dibromocamphor 7 to the by-product 10. Money and co-workers had proposed13 that 3,3,4-trimethyl-1,7-dibromonorbornan-2-one 10 was formed from the protonated intermediate 7H+ via the Wagner-Meerwein rearrangement, and the 2,3-endo-methyl and 2,3-exo-bromide shifts illustrated in Pathway I (Scheme 3). Antkowiak and Antkowiak,14 on the other hand, argued that the Wagner-Meerwein shift from intermediate 12 to intermediate 13 was not feasible unless the carbon attached to the cationic centre bears two bromine atoms, as in structure 16, reasoning that the steric effect of the dibromomethyl group renders the Wagner-Meerwein rearrangement 16 → 17 energetically preferable to the competing 2,3-methyl shift (as in the monobromo-methyl case 15 → 20). Consequently, they favoured Pathway II, in which compound 10 is formed as an intermediate during the final Zn dust/AcOH-mediated reaction of compound 19 which leads to 8-bromocamphor 25 and 3,3,4-trimethyl-1,7-dibromonorbornan-2-one 10. Pathway III leads to the formation of 8-bromocamphor 5 from the intermediate 15, as explored in our earlier paper.2

In order to explore the competing mechanistic proposals, we conducted a modelling study using the Accelrys DMol3 DFT code in Materials Studio. Stable ground state structures could not be generated for either of the intermediates 13 or 14 in Pathway I. However, stable structures were located for the intermediates 16 and 18 in Pathway II. These species appear to be linked by a single transition state with a relatively low activation energy (7.59 kcal mol–1), implying that the Wagner-Meerwein rearrangement (16 → 17) and the 2,3-exo-bromide shift (17 → 18) are, in fact concerted. This transformation is detailed in Scheme 4, in which the transition state TSI approximates in structure to the tetrabromo intermediate 17. An energetically favourable Wagner-Meerwein rearrangement of intermediate 18 then affords the tetrabrominated species 19 via a second transition state TSSI (Scheme 5). The computational data for Pathway II are summarised in Table 1 and illustrated in Fig. 2.

In our synthesis of 8-bromocamphor 5, there was no spectroscopic evidence for the presence of the by-product 10 in the reaction mixture until after the final, Zn dust/AcOH-mediated reaction step. Both the computational and experimental evidence thus indicate Pathway II, as proposed by Antkowiak and Antkowiak,15 to be a more likely route to compound 10 than others.

| Reaction | ΔE (kcal mol–1) | E‡ (kcal mol–1) | ΔG0 (kcal mol–1) | ΔG‡ (kcal mol–1) |
|----------|----------------|----------------|-----------------|-----------------|
| 16 → 18  | −4.02          | 8.39           | −5.06           | 7.59            |
| 18 → 19  | −25.75         | 2.78           | −24.75          | 2.45            |
Pathway I, as suggested by Money and co-workers. A combination of techniques, including coset, advanced one- and two-dimensional NMR and theoretical analysis, has thus permitted confirmation of the structure of a minor, terpenoid rearrangement product and provided support for a mechanism involved in its formation.

Scheme 3 Mechanistic pathways previously proposed for the transformation of 3,3-dibromocamphor 7 to the by-product 10.

Scheme 4 Transformation 16 → 18, showing significant inter-nuclear distances.

2. Experimental

2.1. General

NMR spectra were recorded on a Bruker AVANCE 400 MHz spectrometer at 303 K in CDCl₃ and calibrated using solvent signals. Infrared spectra were recorded on a Perkin Elmer FT-IR
Spectrum 2000 spectrometer. Low-resolution (EI) mass spectra were obtained on a Finnigan-Mat GCQ mass spectrometer. Optical rotations were measured on a Perkin Elmer 141 polarimeter using a 1 dm cell, with concentrations cited in g 100 mL⁻¹. Optically pure compounds were derived from commercially available, homochiral, (+)-camphor.

(+)-8-Bromocamphor and (-)-3,3,4-Tribromocamphor

(+)-8-Bromocamphor 8 (8.0 g, 20 mmol) was dissolved in glacial acetic acid (40 mL) in a round-bottomed flask. Zinc dust (4.4 g) was added, and the reaction mixture stirred vigorously while being cooled with ice-water. Stirring was continued for 1 h, during which time the exothermic reaction subsided. The solution was then decanted from the zinc salt into Et₂O (40 mL), and the resulting mixture was washed with water (10 × 50 mL) and dried over anhydrous MgSO₄. Removal of the solvent in vacuo afforded a brown oil (9.7 g) which was chromatographed [flash chromatography on silica gel; elution with hexane-EtOAc (9:1)] to afford two fractions.

Optical rotations were measured on a Perkin Elmer 141 polarimeter using a 1 dm cell, with concentrations cited in g 100 mL⁻¹. Optically pure compounds were derived from commercially available, homochiral, (+)-camphor.

OPTICAL ROTATIONS (lit., 3 83–85 °C); [α]D +76.7 ° (c 1.05, CHCl₃) {lit., 3 [α]D 25 = +72.5 ° (c 1.05, CHCl₃)}.

Figure 2 Free energy diagram for Pathway II (16 → 19; Scheme 3). The gas-phase free-energies are presented in brackets.

### 2.2. Computational Methods

Density functional calculations were conducted using the Accelrys DMol³ DFT code in Materials Studio (version 2.2) on LINUX-based Pentium IV PCs. All calculations involved use of the generalized gradient approximation (GGA) functional by Perdew and Wang (PW91) and the ‘double numerical plus polarization’ (DNP) basis set: a polarized split valence basis set of numeric atomic functions which are exact solutions to the Kohn-Sham equations for the atoms. Geometry optimizations were subjected to convergence criteria of threshold values 2 × 10⁻⁶ Ha, 0.004 Ha/A, 0.005 Å and 10⁻⁶ Ha for energy, force, displacement and self-consistent field (SCF) density, respectively. All calculations employed a method based on Pulay’s¹⁷ direct inversion of iterative subspace (DIZS) technique to accelerate SCF convergence using, where necessary, a small electron thermal smearing value of 0.005 Ha.

Preliminary transition state geometries were obtained using the integrated linear synchronous transit/quadratic synchronous transit (LST/QST) method, and then subjected to full TS optimization using an eigenvector following algorithm. Where necessary, these geometries were confirmed using intrinsic reaction path (IRP) calculations, based on the nudged elastic band (NEB) algorithm, to map the pathways connecting the relevant reactant, transition state and product geometries. All structures identified as stationary points were subjected to frequency analysis, to verify their classification as equilibrium geometries (zero imaginary frequencies) or transition states (one imaginary frequency). The reported energies reflect Gibbs free energy corrections to the total electronic energies at 298.15 K and include zero-point energy (ZPE) corrections.

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