trans-Hydroboration–oxidation products in Δ⁵-steroids via a hydroboration-retro-hydroboration mechanism†

J. Ciciolil Hilario-Martínez, Fernando Murillo, Jair García-Méndez, Eugenia Dzib, Jesús Sandoval-Ramirez, Miguel Ángel Muñoz-Hernández, Sylvain Bernès, László Kőrti, Fernanda Duarte, Gabriel Merino and Maria A. Fernández-Herrera

Herein, we report for the first time a “trans-hydroboration–oxidation product” isolated and characterized under traditional hydroboration–oxidation conditions using cholesterol and diosgenin as substrates. These substrates are excellent starting materials because of the rigidity and different structural environments around the double bond. Further investigations based on experimental evidence, in conjunction with theoretical studies, indicate that the formation of this trans-species occurs via a retro-hydroboration of the major product to generate the corresponding Δ⁵-structure and the subsequent hydroboration by the β-face. Besides, the corresponding Markovnikov type products have been isolated in synthetically useful yields. The behavior of the reaction under a range of temperatures is also investigated.

Introduction

The addition of electron-deficient boranes to alkenes is one of the most common reactions to produce organoboranes. The resulting alkylboranes are easy-to-handle and highly versatile intermediates that participate in many synthetically useful transformations. Perhaps the most common reaction of organoboranes is their oxidation by hydrogen peroxide in an alkaline medium to furnish the corresponding alcohols regio- and stereospecifically. The hydroboration (HB) of alkenes is a traditional and well-known organic transformation where the governing stereochemical principle is the addition of hydrogen and BH₂ to the same π-face (syn-addition). This reaction, in principle, proceeds via a four-membered transition state (Scheme 1). Most alkenes readily undergo HB under the latter conditions, usually giving the corresponding anti-Markovnikov product, and the subsequent oxidation step with hydrogen peroxide proceeds with retention of configuration.

These observations lead to the generalization that HB takes place via an anti-Markovnikov syn-addition from the less hindered side of the double bond. Even the HB of terminal alkynes occurs in an anti-Markovnikov stereosepecific fashion, where the syn addition also results from HB on the same side of the alkyne.

After a plethora of literature reports on olefin HB reactions, the following question arises: is it possible to obtain a trans-hydroboration product? The answer is yes, but it has never been reported under traditional HB conditions. To the best of our knowledge, no examples of olefin trans-HB have been described in the literature. Herein, we report a trans-hydroboration–

![Scheme 1 General mechanism for the hydroboration reaction of alkenes.](image-url)
oxidation product from a hydroboration–retro-hydroboration pathway employing cholesterol (1) and diosgenin (2) as substrates. These outcomes violate, in principle, all HB reported mechanisms so far.

**Results and discussion**

The first application of the hydroboration–oxidation (HBO) procedure to the double bond in cholesterol (1, Fig. 1) was reported in 1959 simultaneously by Wechter and Sondheimer. Wechter reported that the HB reaction employing BH₃/THF yielded a mixture of dialkyl boranes in 98% of isolated yield. Upon oxidation (H₂O₂/NaOH), the crude product was found to consist of 5α-choleste-3β,6α-diol (1a, 78%), 5β-choleste-3β,6β-diol (1c, traces), and a third compound reported as “not characterized” (see Fig. 1). In parallel, Sondheimer reported the use of BH₃·OEt₂ and cholesterol to deliver, after oxidation using H₂O₂ in ethanolic KOH, a mixture of compounds consisting of 1a (68%), 1c (20%), and recovering some 1 (9%). In general, most of the HBO studies on Δ⁵-steroids describe the generation of only one alcohol with the stereochemistry of 1a.

We decided to perform the HBO of 1 and 2 (Fig. 1). The reactions were subjected to a thorough temperature study (from 20 °C to −20 °C). In our hands, for both substrates, the crude contained three main components and ultimately four products were isolated and fully characterized.

Due to the steric shielding exerted by Me-19, not surprisingly the major products (1a and 2a) arose via hydroboration of the steroidal face. It is remarkable that the lowering of the reaction temperature led to lower yields of compounds type a (see Table 1). Compounds 1b and 2b are the Markovnikov addition products. These compounds have been recently reported employing transition-metal-catalyzed asymmetric HB reactions. However, under the typical HB conditions (as in our case), they were unexpectedly obtained in synthetically meaningful yields (8–18%). It is also notable that their formation is favored with the decrease of temperature. The isolation of compounds type c was challenging. However, after several purifications by column chromatography, both 1c and 2c successfully crystallized from an enriched fraction of c. The full 1D and 2D NMR characterization data are detailed in the ESI. Compounds of type d were not detectable, and the unreacted starting materials were not recoverable from any of the reactions.

Unexpectedly, we also found the “trans”-HBO products, 1e and 2e, under classical HB conditions! The yields of these unexpected stereoisomers are 21–38%, surprisingly high when considering their nature. At room temperature, yields of products type e are about one-third of the HBO products type a. The 5α,6β-stereochemistry of 1e and 2e is confirmed by NMR; for further details, see the ESI.

For structures b, c, and e, the observed stereochemistry in solution is supported by the single-crystal X-ray crystallography structure determinations of compounds 2b, 1c, 2c, and 1e, respectively (see ESI and CIF files deposited with the CCDC). Of particular interest is the “trans” product 1e, in which the 6β-OH and 19-Me groups are assumed to induce steric repulsion (Fig. 2). Indeed, the O6–C19 separation, 3.029(4) Å, is shortened by 0.19 Å as compared to the van der Waals distance. However, since the OH group is free to rotate, there are no

![Fig. 1] Structures of four possible products derived from the HBO reaction of substrates 1 and 2 (structures type a–d).

<table>
<thead>
<tr>
<th>Diols derived from cholesterol (1)</th>
<th>20°C</th>
<th>10°C</th>
<th>0°C</th>
<th>−10°C</th>
<th>−20°C</th>
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<tbody>
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<td>62</td>
<td>59</td>
<td>54</td>
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<tr>
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<td>10</td>
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</table>

<table>
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<tr>
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<th>10°C</th>
<th>0°C</th>
<th>−10°C</th>
<th>−20°C</th>
</tr>
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<tr>
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<td>23</td>
<td>26</td>
<td>29</td>
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</table>

Table 1 Isolated yields from HBO of 1 and 2 at different temperatures

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occurrences of destabilizing H···H contacts, and both 3β and 6β hydroxyl groups are engaged in classical intermolecular hydrogen bonds, to form supramolecular chains in the crystal. The same situation is observed for 1c and 2c.

To elucidate the formation of the unexpected HBO products type e, we performed a series of quantum chemical computations at the DLPNO-CCSD(T)\textsuperscript{19–21}/def2-TZVP\textsuperscript{22} level by taking the PBE0 (ref. 23) structures from a model composed of two rings (a decalin framework, see Fig. 3), and considering the solvent effects (THF) via the SMD\textsuperscript{24} approximation. Entropic contributions and thermal corrections were computed at the SMD-PBE0-D3 (ref. 25)/def2-TZVP level at 273.15 K. Hydroboration has been theoretically studied by several groups.\textsuperscript{26–28} Validation of this methodology and further details are provided in the ESL.\textsuperscript{†} All these computations were done in Gaussian 16\textsuperscript{(ref. 29)} and Orca 4.1.1.\textsuperscript{30} Considering that the alcohol is formed with retention of configuration in a subsequent oxidation step, we focus our analysis on the HB mechanism; thus, we label the alkylborane system as 1a that produces 1a after the oxidation.

The Gibbs energy pathways for the suprafacial HB additions of 1 are illustrated in Fig. 3. The smallest barrier (\(\Delta G^\ddagger = 2.7\) kcal mol\(^{-1}\)) is obtained for one of the \(\alpha\)-additions. It is easily explained due to the presence of Me-19. As is expected, the difference between anti-Markovnikov and Markovnikov barriers (\(\Delta \Delta G^\ddagger = 3.4\) kcal mol\(^{-1}\)) favors the former addition. Since the addition involves the bridgehead C-5, these transition states (TSs) are connected to twisted-chair conformations (INT-1a and INT-1b\textsuperscript{1}), which are more stable than the reactants by 5.4 and 4.5 kcal mol\(^{-1}\), respectively. The barriers to obtain the final products are relatively low (2.2 and 3.2 kcal mol\(^{-1}\)) and correspond to a conformational arrangement to form the final products with a \(\text{trans-A/B}\) rings fusion. The formation of both 1a\textsuperscript{1} (\(\Delta G_{\text{rxn}} = 13.5\) kcal mol\(^{-1}\)) and 1b\textsuperscript{2} (\(\Delta G_{\text{rxn}} = 10.4\) kcal mol\(^{-1}\)) is exergonic in nature. At this point, there are no surprises.

The formation of 1c\textsuperscript{3} and 1d\textsuperscript{4} involves an additional conformational change to provide the \(\text{cis-A/B}\) rings fusion. The barriers for HB additions at the \(\beta\)-face are similar to that computed for 1b\textsuperscript{2} (\(\sim 6\) kcal mol\(^{-1}\)). The first conformational
barriers through TS2-1c' and TS2-1d' are small (1.1 and 2.8 kcal mol\(^{-1}\)). However, the barriers for the final step are much higher (7.2 and 8.5 kcal mol\(^{-1}\)) and become the rate-limiting steps. This explains why 1d is not formed, despite having an HB barrier similar to 1b, and why 1c is only isolated in traces.

The pathways discussed above are relevant to understand the HB by both \(\alpha\)- and \(\beta\)-face, nevertheless, they do not explain the formation of the \textit{trans}-HB product. We hypothesize that the formation of this product involves a \textit{retro}-hydroboration to regenerate the double bond but at C-6 (Fig. 4). This leads to the formation of the \(\Delta^6\)-steroid 3 (5\(\alpha\)-cholest-6-en-3\(\beta\)-ol), followed by typical HB on the \(\beta\)-face. Our computations indicate that 1 is more stable than 3 by 2.6 kcal mol\(^{-1}\). The formation of 3 from 1a' is concerted via TS1-1e' (\(\Delta G^\neq = 18.0\) kcal mol\(^{-1}\)). The result is the \(\pi\)-complex INT-1e', which is then converted to the \textit{trans}-product (1e') via TS2-1e'(\(\Delta G^\neq = 6.8\) kcal mol\(^{-1}\)) or to 1f via TS1-1f' (7.1 kcal mol\(^{-1}\)). After all the experimental and computational evidence, these results indicate that even though less preferred, a \textit{retro}-hydroboration mechanism is viable under traditional experimental conditions, explaining the formation of 1e.

Conclusions

In summary, we report the complete characterization of the hydroboration–oxidation products of cholesterol and diosgenin. Because of the steric effect exerted by Me-19, the most abundant products are the anti-Markovnikov ones by the \(\alpha\)-steroidal face. Surprisingly, a \textit{trans}-product is also obtained! This is the first time that such a type of structure is synthesized and characterized under typical hydroboration–oxidation conditions. The best way to explain the formation of this “\textit{trans}\textsuperscript{-}species” is via a \textit{retro}\textsuperscript{-}hydroboration of the major product (\(\alpha\)-type products) to generate the corresponding \(\Delta^6\)-structure and the subsequent hydroboration by the \(\beta\)-face. We were lucky to select these steroids as substrates because of the rigidity and different structural environments around the double bond, which allowed us to isolate and characterize the \textit{trans}-product.

Experimental section

General procedure for the hydroboration of \(\Delta^5\)-steroids

To a solution of 1 or 2 (2 mmol) in dry THF (30 mL), NaBH\(_4\) (0.38 g, 10 mmol) was added. The system was kept sealed, under stirring, and under argon atmosphere. The reaction mixture was set at the temperature specified in Table 1 before the addition of BF\(_3\)-OEt\(_2\) (1.65 mL, 13.4 mmol). After stirring for 2 h, the remaining pressure was released, and the work up was performed adding brine (10 mL) dropwise. The THF was evaporated under reduced pressure and the crude product was dissolved in CH\(_2\)Cl\(_2\), washed with brine (1 × 50 mL) and water (3 × 50 mL), dried over anhydrous Na\(_2\)SO\(_4\) and concentrated \textit{in vacuo}. The crude mixture was immediately dissolved in a solution of 2% KOH/MeOH (50 mL) and then 5 mL of 35\% H\(_2\)O\(_2\) were added dropwise. After 1 h of stirring at rt, 200 mL of water...
were added, and the resulting precipitate was filtered off and dried under vacuum. The resultant white solids were purified by flash chromatography on a CombiFlash apparatus using a gradient elution employing hexane/ethyl acetate (see specific details in the ESI†).

Note: all procedures were carried out employing a commercial 1.0 M solution of BH$_3$·THF and the results were the same.

**Author contributions**

JCHM, JGM, JSR, and MAFH carried out the experiments. FM, ED, FD, and GM performed the computational studies. MAMH and SB performed the X-ray determinations. All authors interpreted the results and LK, FD, GM, and MAFH prepared the manuscript. All authors have given approval to the final version of the manuscript.

**Conflicts of interest**

The authors declare no competing financial interest.

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**References**

10. Compound 2a matched an authentic sample of α-chlorogenin.
18. Compound 2e matched an authentic sample of β-chlorogenin.