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AN APPARENT DIRECT-INDIRECT COMBINED MECHANISM IN TEMPLATE-DIRECTED ELECTROCHEMICAL STEROID CHLORINATION

Ronald Breslow* and Richard Goodin

Department of Chemistry, Columbia University, New York, New York 10027

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We have described the use of templates[1,2,3] to direct the free radical chlorination of steroids to specific positions. It seemed likely that such template methods should also be applicable to electrochemical functionalization, in particular halogenation.

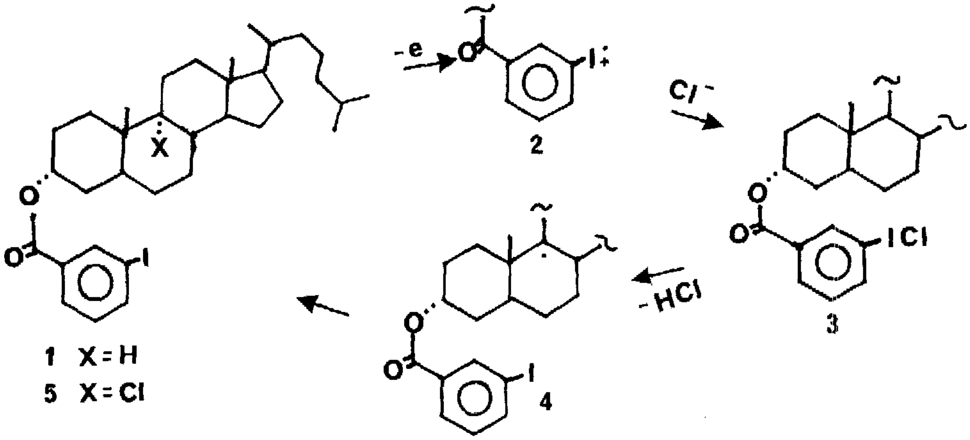
When a substrate is anodically oxidized in the presence of chloride ion, it can be chlorinated by either of two mechanisms.[4] In the indirect process, the chloride is oxidized to Cl_2, which then performs the halogenation of the substrate. In the direct mechanism, the substrate itself is oxidized to a cation radical, which captures Cl^- as a step in the overall halogenation of substrate. We have now found that steroid 1 can be anodically chlorinated electrochemically to 5 in a template-directed selective process. Novel tests allow us to distinguish between the direct and the indirect mechanism; interestingly, it seems that both are involved.

Controlled potential electrolyses of 0.01 M solutions of 1 were performed in a divided three-compartment cell purged with argon, using a silver wire pseudoreference electrode. Results were essentially indistinguishable using acetonitrile or propionitrile solvent with 0.1 M tetrabutylammonium perchlorate, lithium perchlorate, or tetrabutylammonium fluoborate supporting electrolytes, and either platinum gauze or carbon rod anodes. Cyclic voltammetry at platinum reveals that 1 itself can be oxidized at approximately 2.6 V vs. Ag, while Cl^- has a broad anodic peak at approximately 1.0 V.[5] Preparative electrolysis of a solution of 1 was performed with one equivalent of Cl^- present initially, and 2 equivalents more added dropwise during the course of the reaction.

Passage of 3 F/mol at 1.8 V vs. Ag led to no halogenation of 1 in the dark, and a trace of chlorination at C-9 in room light. Thus, the oxidation of Cl^- to Cl_2 at the electrode involves no species which is able to transfer a chlorine atom to 1 to generate intermediate 3, although with light some photochemical initiation of a halogenation by Cl_2 is detected. By contrast, electrolysis under the same conditions (dark) except at a potential of 2.7 V vs. Ag results in a very effective template-directed chlorination of the steroid at C-9 to produce 5, identical with authentic material, leading to an overall isolated yield[7] of 35-71% of Δ9(11)-cholesten-3α-ol after saponification of the reaction mixture.

At first sight this appears to be a direct electrochemical halogenation, since oxidation of substrate 1 to the cation radical 2 is appare~~ntly~~ required. If 2 captures a chloride ion it can produce intermediate radical 3, the species which performs selective hydrogen abstraction. However, the result of such a hydrogen abstraction would be 4, a carbon radical at C-9, and one must then wonder how 4 is converted to the 9-chloro product 5. One likely possibility[8] is reaction of this steroid radical with electrochemically generated Cl_2, but such a reaction generates a new chlorine atom and thus might initiate a free radical chain halogenation (the indirect mechanism). Trapping studies prove that this is indeed the course of the reaction. Thus, when the electrolysis at 2.7 V is conducted in the presence of O_2, NO, or Br_2, the steroid functionalization is largely suppressed and high yields of the steroid can be recovered unchanged with a sufficient concentration of these added reagents. With Br_2, for instance, this must mean that the initial direct functionalization reaction through intermediates 2 and 3 leads to a steroid radical which is then captured by Br_2, not Cl_2. The resulting bromine atom is not then able to initiate a chain halogenation process. Apparently only a small amount of functionalization occurs by the direct mechanism.

Thus, it seems that anodic oxidation of the substrate is needed to initiate the halogenation, but that the bulk of the halogenation in this reaction then occurs by the indirect mechanism involving electrochemically generated Cl_2. The simple electrochemical criterion is thus deceptive as a clue to the mechanism. As with other radical halogenations, this process shows excellent selectivity and may be an attractive variant of these template-directed free radical methods.



The Direct Mechanism

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3. B.B. Snider, R.J. Corcoran, and R. Breslow, *J. Amer. Chem. Soc.*, **97**, 6580 (1975).
4. Cf. L. Eberson in *Organic Electrochemistry*, M. Baizer, Ed., Marcel Dekker, 1973, p. 798.
5. The Cl^- oxidation peak shows variable behavior depending upon the nature of the solution and presumably upon the surface condition of the electrode.[6]
6. J.-C. Marchon and J. Badoz-Lambling, *Bull. Soc. Chim. France*, 4660 (1967).
7. Recoveries were generally 70-90%, with 50-85% product and the remainder unfunctionalized steroid. No isomeric steroid olefins could be detected. At 2.7 V there is significant background current, and 5-10 F were passed. Since both perchlorate and fluoborate electrolytes could be used, electrolyte oxidation is apparently not a necessary part of the process.
8. The alternative is oxidation to steroid cation, which captures Cl^-. The product was unchanged by the addition of N_3^-, F^-, or CF_3COO^-. In other controls, no functionalization occurred in the absence of Cl^-, or with the non-iodinated benzoate corresponding to 1.