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DIRECTED STEROID CHLORINATION CATALYZED BY AN ION-PAIRED TEMPLATE

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Summary: 3-α-Cholestanyltrimethylammonium cation is catalytically chlorinated by iodobenzenesulfonate anions with geometric control and catalytic turnover of the template anion. Steroid sulfates with cationic templates also show directed catalysis.

We have described a process of template-directed radical relay chlorination by which steroids are selectively functionalized, with geometric control, by the use of attached iodoaryl or arylsulfide groups.[1] These are catalytic processes, since under the reaction conditions the steroids are not chlorinated unless the template group is attached, but the catalysis is only formal. The template species, such as m-iodobenzoic acid, is stoichiometrically covalently attached to a sterol as an ester; only on workup can the catalyst species be recovered and recycled. An improvement was our recent report[2] that one template group can catalytically direct the chlorination of three steroids if it is attached to all three as a silyl triether. However, for true turnover catalysis one would need a transient association of templates and substrates.

Since the halogenations are generally performed in non-polar solvents, ion-pairing or hydrogen-bonding are appropriate candidates as binding forces between catalysts and substrates. Indeed we have described[3] benzophenone photochemical functionalizations of flexible molecules in which two hydrogen bonds (between carboxyls and carboxylates) or two ion pairs (between quaternary ammonium groups and carboxylates) bound and oriented the reagent and substrate. However, the HCl produced by many chlorination processes would be expected to disrupt such interactions. For this reason we have examined ion pairing using a single $SO_3^-...N^+$ interaction. We find that this indeed promotes association to permit template-catalyzed radical relay chlorination of cholestane derivatives. Furthermore, in some cases the resulting geometric control is rather selective. Finally, in at least one case we have shown that true turnover catalysis is achieved, as a template anion moves to successive substrate cation species.

3-α-Cholestanyltrimethylammonium[4] salts of m-iodobenzenesulfonate (1), of o-iodobenzenesulfonate (2), of m-iodobenzoate (3), and of hexafluorophosphate (4) were prepared by standard ion-exchange and neutralization procedures.[5] The dry salts were dissolved at 10 mM in CH_2Cl_2, then $PhICl_2$ (3.6 equiv) was added and after degassing the system was irradiated (275 w sunlamp) for ca. 30 minutes under N_2. After solvent evaporation the residue was taken up in 10 ml 10%

KOH/MeOH, which was evaporated and heated at 150-170° for 30 minutes. Hoffmann elimination and dehydrochlorination produced a mixture of cholestenes and cholestadienes (60% recovery; the degradation of 1 produced only 71% of cholestenes). The product was selectively hydrogenated in ring A with $Rh(Ph_3P)_3Cl$ to afford a mixture of cholestane, of 9(11)-cholestene, and of 14-cholestene, which was separated from polar impurities by short column chromatography. Product ratios, listed in Table 1, were determined by quantitative PMR spectra. The products were isolated by flash chromatography on $SiO_2/AgNO_3$ and identified by comparison with authentic samples.

When the products were treated with mild base, to promote loss of HCl without Hoffman degradation, the same mixture of 9(11) and 14 olefins was produced in the same ratio, as judged by PMR. Furthermore, controls show that 9(11) and 14 olefins are untouched by the hydrogenation. Thus we conclude that our assay correctly reflects the products. The 9(11) olefin is the product normally seen from 9-chlorosteroids, while 14-chlorination leads, on workup, to the 14 olefin.[1] Thus we have listed the products of these chlorinations, in Table 1, in terms of their original chlorination positions.

As Table 1 shows, chlorination of 1 affords a 3.5/1 preference for halogenation at C-9 over C-14, and even with the excess chlorinating agent 1 was still 22% unfunctionalized. As expected, the shorter template in 2 moves the preferred functionalization even more toward C-9, with a 9:14 ratio of 5.7/1, but now 80% of 2 was unfunctionalized. In our previous work,[1] o-benzoate derivatives were poor templates, probably for steric reasons. On the other hand, compound 4 without an ion-paired catalytic template undergoes no detectible chlorination under our conditions, even after 45 minutes irradiation. As anticipated, the ion pair with a carboxylate ion in 3 is not very effective, affording a 2/1 9:14 ratio with only 15% total functionalization.

We also prepared salts of 3-α-cholestanyl sulfate[6] with m-iodophenyltrimethylammonium cation (5), with the corresponding p-isomer (6), with simple trimethylanilinium (7), and with tetraethylammonium (8) cations.[5] These were again submitted to radical relay chlorination conditions as above, but the products were identified by acid-catalyzed removal of the sulfate group and conversion of the chlorocholestanol products to 3-α-acetoxycholest-9(11)-ene and 3-α-acetoxycholest-14-ene by procedures described previously.[1]

As Table 1 shows, the m-iodophenyl template of 5 again gave preferential chlorination of C-9, with a 9:14 ratio of 2.4/1. Both the selectivity and conversion were poorer with this more flexible ion pair, whose sulfate group can have various orientations, than for the more rigid ion-pair 1. The para isomer 6 gave more 14 attack, as expected, with a 9:14 ratio of 1/1. Remarkably, the simple anilinium cation in 7 is very selective for C-9, although the conversion is low. If the chlorine atom in a complex with 7 is bound to the phenyl ring, the effective length of the template is much shorter than in our other systems

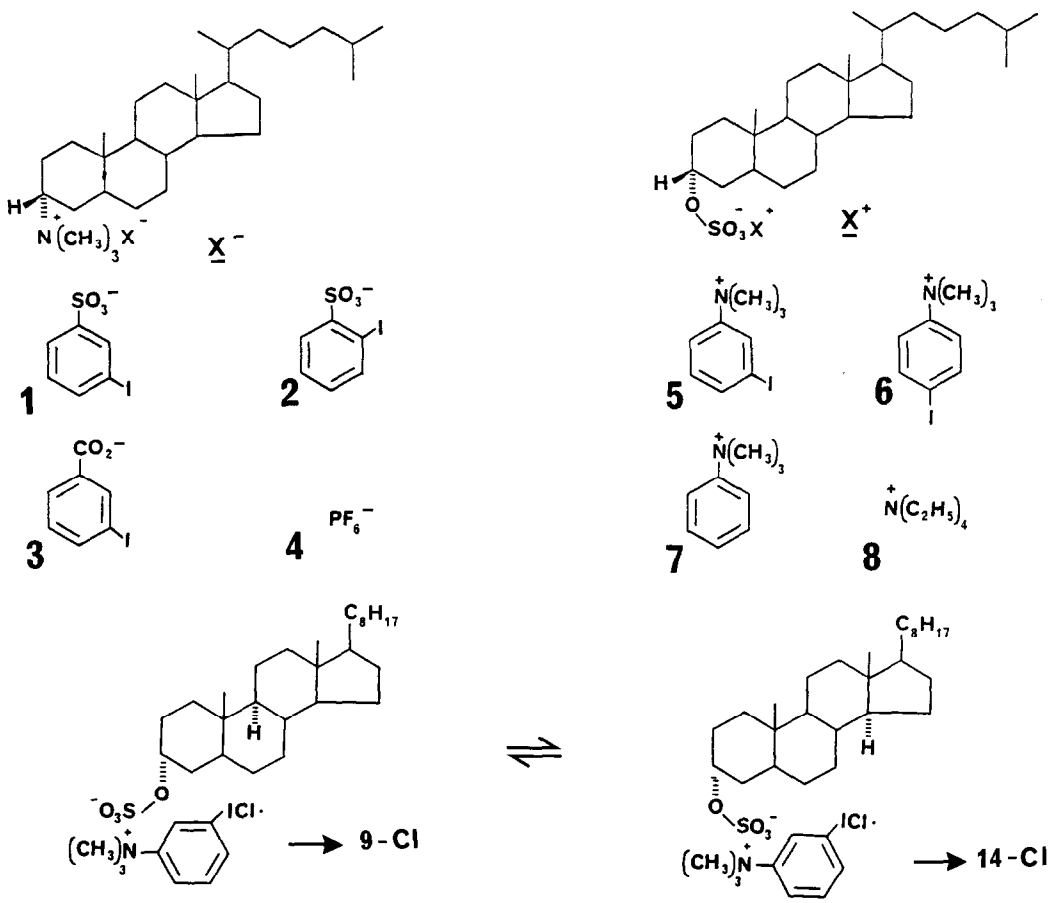


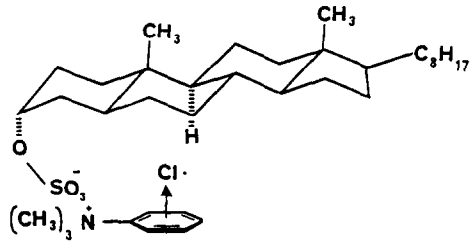
Table 1

Chlorination Using Ion Paired Templates[a,b]

Cholesteryltrimethylammonium	C-9	C-14	Unreacted
m-iodobenzenesulfonate (1)	57	16	22
o-iodobenzenesulfonate (2)	17	3	80
m-iodobenzoate (3)	10	5	85
PF_6^- (4)	-	-	100
Cholesteryl sulfate			
m-iodotrimethylanilinium (5)	22	9	44
p-iodotrimethylanilinium (6)[c]	6	6	76
trimethylanilinium (7)	20	0	60
Et_4N^+ (8)	-	-	100

a) At 25° with 10 mM substrate in CH_2Cl_2 and 3.6 equiv. of $PhICl_2$.
b) Product ratios determined by ^1H NMR. c) Only 1.2 equiv. $PhICl_2$ used.

in which a peripheral iodine binds and delivers the chlorine atom. Again, in the absence of a template the ion-pair 8 is not chlorinated under our conditions.



To examine turnover catalysis, we took a one-to-two mixture of compound 1 and 4, containing one template for three steroid substrates. At a total steroid concentration of 10 mM, with 90 mM $PhICl_2$ and 120 minute irradiation, there was a 42% conversion of the total steroid to the normal 3.7/1 ratio of 9:14 chloroproduct. Thus the templates are recycling with fresh substrate cations.

These ion-pair directed chlorinations are not yet as selective or efficient as are the analogous reactions with covalently-attached templates.[1] However, the finding that ion-pair association produces catalysis with reasonable selectivity, and permits turnover of the catalyst in solution, suggests that this modification of our template-directed processes could have useful applications.

References

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5. Characterized by nmr and, for 1, combustion analysis. m.p.'s: (1), 248-252° d.; (2), 262-266° d.; (3), 208-210° d.; (4), 248-254° d.; (5), 204.5-205.5°; (6), 211-213°; (7), 205-207°; (8), 183-185° d.

6. Using the general procedure of A.E. Sobel and P.E. Spoerri, J. Am. Chem. Soc., 63, 1259 (1941).

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