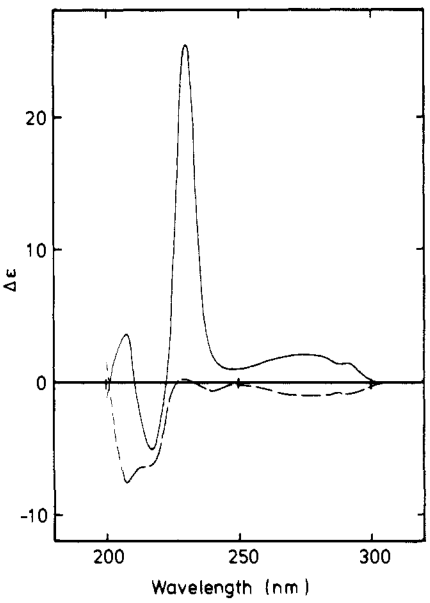

Figure 2. CD spectra of side chains (—) and backbone (- - -) separated from natural CD of PLT in 2ME by the FDCD technique. The $\Delta\epsilon$ values are expressed in term of the concentration of residues in cm^{-1} M^{-1}.

where $\Delta\epsilon_{PLT}$, $\Delta\epsilon_{side}$, and $\Delta\epsilon_{back}$ are the molar CD of PLT, side chain, and backbone, respectively. ϵ_{PLT} is the molar extinction coefficient of PLT. It was assumed that little interactions of $\mu1$–$\mu2$ between amide and indole chromophores exist and that amide chromophores are not fluorophores and energy transfers between amide and indole chromophores are negligible. Furthermore, the assumption was made that the absorpsion of PLT above 200 nm is almost solely due to the indole chromophores.[7]

Figure 2 shows the resultant spectra of $\Delta\epsilon_{side}$ and $\Delta\epsilon_{back}$. The shape of the backbone CD spectrum closely resembles that of a typical α-helical CD spectrum.[8] This verifies that PLT adopts a right-handed α-helical conformation in 2ME and shows that the above assumptions are reasonable.

The formation of the negative dichroic band for the backbone in the ^{1}L region is of interest. In the ^{1}L region, no CD bands exist for the separated backbone CD spectrum (if the optical activity in this region originates from only one fluorescent species) because of no contribution of the amide chromophores here. However, if more than one optically active fluorescent species i, such as ^1L_a and ^1L_b transitions, is present, and the quantum yields Φ_i of these species are different from each other, then the g_f value obtained from FDCD experiment is expected to behave according to eq 3.[3] The g_f is not in agreement with $\Delta\epsilon_{PLT}/\epsilon_{PLT}$.

$$g_f = \frac{\sum_i \Phi_i \Delta\epsilon_i}{\sum_i \Phi_i \epsilon_i} \qquad (3)$$

When taking into account the possibility of energy transfer between these species, the g_f value is expressed more complicatedly.[3] Therefore, the origin of the negative CD band for the backbone in the ^{1}L region is due to the difference between $\Delta\epsilon_{PLT}/\epsilon_{PLT}$ and the g_f value.

A negative CD band at around 240 nm for the backbone may be produced for the same reason as mentioned above.[9,10] In this region, the overlapping of the ends of ^1L_a and ^1B_b absorption bands is expected. Of course we cannot deny the possibility of the contribution of amide chromophores in this band. Our FDCD experiments did not indicate the existence of a ^{1}C symmetry-forbidden transition of indole chromophore.[11]

The side-chain CD obtained indicates that a positive intense CD band at 230 nm, whose pair is an ~217-nm negative band, originates from the formation of exciton coupling between indole chromophores. Moreover, the greatly different intensities of these two exciton bands and the existence of an ~207-nm positive band show that the $\mu1$–$\mu2$ mechanism may not only occur between ^1B_b transitions but between ^1B_a and ^1B_b transitions.

A more detailed investigation for optical activity of PLT is now in progress by our group.

Our FDCD technique for PLT can be applied to the conformational analysis of similar peptides such as poly-L-tyrosine.

Acknowledgment. We thank Dr. Tsugikazu Tomono and Tohru Suzuki (Department of Research and Development, Japanese Red Cross Plasma Fractionation Center) for permission to use the J-500C spectropolarimeter. We also thank Yasunobu Komiyama for the contribution to the early development of our FDCD instrument.

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[7] Rosenheck, K.; Doty, P. *Proc. Natl. Acad. Sci. U.S.A.* **1961**, *47*, 1775–1785.

[8] Woody, R. W. *J. Polym. Sci. Macromol. Rev.* **1977**, *12*, 181–321.

[9] Steen, H. B. *J. Chem. Phys.* **1974**, *61*, 3997–4002.

[10] Tatischeff, I.; Klein, R. *Photochem. Photobiol.* **1975**, *22*, 221–229.

[11] Auer, H. E. *J. Am. Chem. Soc.* **1973**, *95*, 3003–3011.

Thioxanthones as High Turnover Catalytic Templates in Directed Chlorination Reactions

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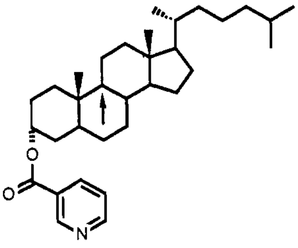
We have recently reported[1] that the steroid nicotinate ester **1** is catalytically chlorinated at C-9 by forming a mixed complex with Ni^{2+} or Cu^{2+} and template **2**. Then PhICl$_2$, with irradiation, starts a chain process in which a chlorine atom is first transferred to the template and then attacks the steroid hydrogen, in a radical relay[2] mechanism. Remarkably, under appropriate conditions the catalyst **2** undergoes 10^9 turnovers.



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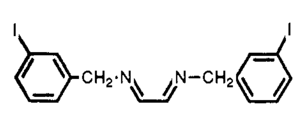

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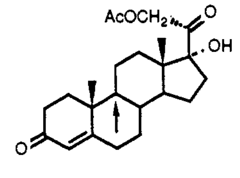

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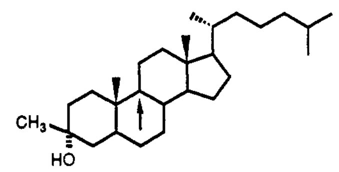

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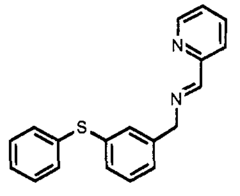

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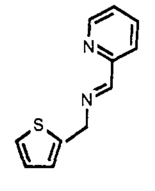

6

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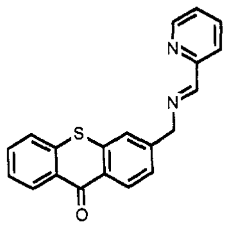
[1] Breslow, R.; Mehta, M. P. *J. Am. Chem. Soc.* **1986**, *108*, 2485–2486.

[2] Breslow, R.; Corcoran, R. J.; Snider, B. B. *J. Am. Chem. Soc.* **1974**, *96*, 6791. For a review, see: Breslow, R. *Acc. Chem. Res.* **1980**, *13*, 170.

Not all catalytic reactions with **2** show such high turnovers. Chlorination of **3** at C-9, or of **4** at C-9, were successful with Ni^{2+} and **2** because of metal coordination to the OH but required stoichiometric amounts.[1] We have now devised a new template catalyst that indeed performs the important C-9 chlorination of **3** with reasonable turnovers. At the same time, we have developed evidence, described in the accompanying paper, that the remarkably high turnovers sometimes observed with **2** and with the new template result from a special new bifunctional chlorination mechanism.

Since the eventual decomposition of **2** involves replacement of iodine by chlorine,[1] we examined the use of sulfur atom templates that might be more stable. The diphenyl sulfide[3] analogue **5** was too easily oxidized, and even a related thiophene[4] system **6** showed only 10^4 turnovers with **1**. However, the thioxanthone template **7** was an excellent catalyst. Substrate **1** was 80% converted to C-9 chlorosteroid, with 20% recovered **1**, when 15 mM **1** was irradiated with 3 equiv. of PhICl$_2$ and 5 equiv. of undissolved KOAc in CH$_2$Cl$_2$ with 15×10^{-9} mM Ni^{2+} and 15×10^{-12} mM **7** for 10 min (275-W sunlamp) at 0 °C (or at 20 °C) and then allowed to react further[5] without irradiation for 1.5 h. Thus 10^{11} to 10^{12} turnovers of **7** are occurring. Template **7** also catalyzed the C-9 chlorination of **3** and **4**, with ca. 10^2 turnovers.



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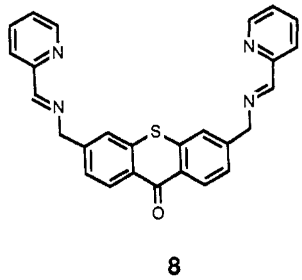

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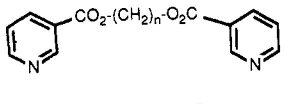
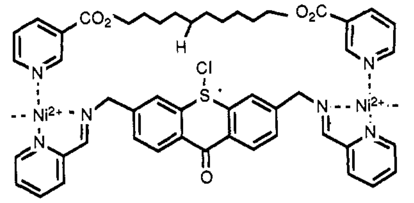


9a: n = 10

9b: n = 6

9c: n = 4



Thioxanthone **7** was easily prepared by reaction of thiosalicylic acid with *N*-(*m*-iodobenzyl)acetamide (irradiation)[6] followed by intramolecular acylation and further obvious steps. In a similar way, using *N*-(*m*-iodobenzyl)acetamide and Na$_2$S and then COCl$_2$, we were able to prepare **8**. This species carries two M^{2+} binding groups, so its double Ni^{2+} or Cu^{2+} complex can coordinate both ends of a flexible substrate and chlorinate the middle.[7]

Indeed, reaction of the decane-1,10-diol derivative **9a** at 15 mM with 3 equiv of PhICl$_2$ and 5 equiv of KOAc along with 15×10^{-4} mM **8** and 30×10^{-3} mM Ni^{2+} (ClO$_4^-$)$_2$ under irradiation for 1 h at 0 °C afforded the monochlorinated **9a** with 32% recovered **9a** (at 15×10^{-3} mM **8**, no **9a** is detected). By methods we have described earlier[8] we were able to establish that the chlorination occurs essentially exclusively at the middle carbon C-5, as expected if **9a** coordinates to a fully extended conformation of the **8**-[Ni^{2+}]$_2$ complex. This conformation is apparently the preferred one, because of electrostatic repulsion[9] by the Ni^{2+} ions, since the shorter hexanediol and butanediol derivatives **9b** and **9c** are not chlorinated by the **8**-[Ni^{2+}]$_2$ complex. Models show that they should also be able to bind at both ends and be chlorinated, if the template does not have the fully extended conformation.

This work shows that catalytic templates based on the thioxanthone system can have even better turnover numbers with steroids, compared with aryl iodide templates. Even a simple underivatized steroid such as **3** can be catalytically functionalized. The thioxanthone system also easily carries more than one binding group, as in **8**, to permit selective catalytic reactions on flexible substrates. In the accompanying paper[10] we will describe the evidence that some thioxanthone or aryl iodide catalyses involve a novel bifunctional mechanism.

Acknowledgment. This work has been supported by the NSF.

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(3) Breslow et al. (Breslow, R.; Wife, R. L.; Prezant, D. *Tetrahedron Lett.* **1976**, 925) report use of an attached diphenyl sulfide group in the radical relay reaction.

(4) Cf., for use of a thiophene template: Breslow, R.; Heyer, D. *J. Am. Chem. Soc.* **1982**, *104*, 2045.

(5) The reaction requires this additional time to go to completion. Such a dark reaction, initiated by irradiation, is not sensible for a normal free radical chain process but is expected for the mechanism proposed in the following paper.

(6) Cf.: Bunnett, J. F.; Creary, X. *J. Org. Chem.* **1974**, *39*, 3173-3174.

(7) For selective benzophenone attack on a flexible chain oriented by double coordination, see: Breslow, R.; Rajagopalan, R.; Schwarz, J. *J. Am. Chem. Soc.* **1981**, *103*, 2905.

(8) Breslow, R.; Rothbard, J.; Herman, F.; Rodriguez, M. L. *J. Am. Chem. Soc.* **1978**, *100*, 1213.

(9) By standard calculations (Cf.: Tanford, C. *J. Am. Chem. Soc.* **1957**, *79*, 5348; a modification of, Kirkwood, J. G.; Westheimer, F. H. *J. Chem. Phys.* **1938**, *6*, 506, 513) we find the interaction energy is large enough (ca. 2.7 kcal/mol) to account for this conformational preference.

(10) Breslow, R.; Mehta, M. P. *J. Am. Chem. Soc.*, following paper in this issue.

A Novel Bifunctional Chlorination Mechanism in Template Catalyzed Directed Functionalization with High Effective Molarities and Rates Approaching Diffusion Control

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We have described the catalytic chlorination of 3-α-cholestanyl nicotinate (**1**) by mixed-metal complexes with an aryl iodide[1] template (**2**) and a thioxanthone[2] template (**3**). These reactions showed very high catalytic turnovers, ca. 10^9 and 10^{11}–10^{12} respectively, but this might simply mean that loss of catalyst through side reactions occurs only very slowly. However, the reactions also involve astonishing apparent effective molarities (EM's) of the catalysts.

At a concentration of 15×10^{-9} mM the catalyst **2**, in a mixed complex, performs an essentially complete (>99%) selective chlorination on 15 mM **1** with 3 equiv. of PhICl$_2$. However, in control reactions under the same conditions uncomplexed aryl iodides such as **2** in the absence of M^{2+}, or PhI itself in the presence of Ni^{2+}, do not perform *any* intermolecular reaction (<4%) even at 15 mM aryl iodide. In such controls we begin to see random intermolecular attack only with 50 equiv of PhICl$_2$ chlorinating

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(1) Breslow, R.; Mehta, M. P. *J. Am. Chem. Soc.* **1986**, *108*, 2485-2486.

(2) Breslow, R.; Mehta, M. P. *J. Am. Chem. Soc.*, preceding paper in this issue.

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