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# SELECTIVE CHLORINATION OF $C_{12}$ AND $C_{16}$ AMIDES VIA SOLVENT DICTATED CONFORMATIONS

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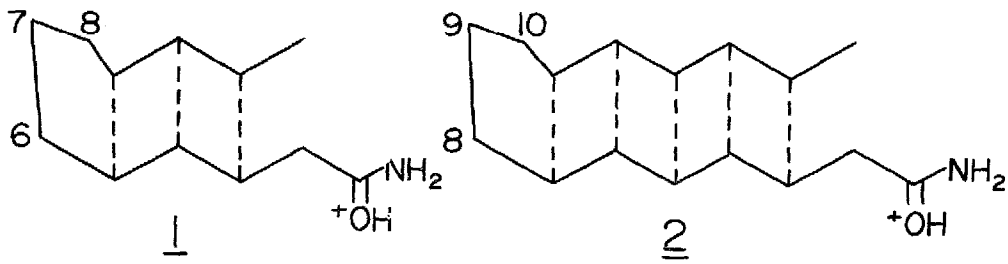
Conformational effects in biological systems have long been known and recognized as major factors affecting product formation. It is usually presumed that substrate conformations are dictated by the folds and convolutions of the enzyme catalyst, though there has been a persistent suspicion that some of the conformational direction may come from the medium itself. We wish to report a striking example of this latter effect.

Previously it had been found that chlorination of $C_5$-$C_8$ alcohols, acids, etc. gives 70-90% selectivity for chlorination at the $\omega$-1 position using N-chloroamines in 70-90% $H_2SO_4$.[1-3] The reaction proceeds through aminium radicals and the polar effects are enormous.

When this type of chlorination was extended to dodecanoamide (lauramide) using 70% acetic acid-30% concentrated sulfuric acid as a solvent, a pattern of remote chlorination was again observed (Table). The selectivity for the $\omega$-1 position was reduced to 39%, but this was to be expected due to the increase in chain length. Remote selectivity was still dominant as shown by 91% of the chloro on the $C_8$-$C_{11}$ positions (Table). The results were changed little by replacing the isopropyl group in $R_2NCl$ by isobutyl or cyclohexyl.

When the solvent was changed to 80% aqueous $H_2SO_4$, a dramatic shift in product distribution occurred. The amount of $\omega$-1 chloro dropped to 8%, and 88% of the chloro appeared on $C_6$-$C_{10}$ (Table). This pattern can be characterized as central chlorination. These results must arise from altered conformations in dodecanoamide caused by the change in solvent and are explained in more detail as follows.

In acetic-sulfuric acids, the dodecanoamide exists in relatively random conformations and H abstraction by $R_2NH^{\ddagger}$ occurs remote from the protonated amide group. In 80% $H_2SO_4$, the solvent is virtually a fused salt, $H_3O^+HSO_4^-$.[4] Under these more polar conditions, hydrophobic effects[5] are intensified and the chain folds back on itself as schematically illustrated in structure 1. The dotted lines indicate hydrophobic interactions. With charge repulsions as the factors controlling selectivity,[2,3] the favored sites for chlorination become $C_7$, $C_8$, and $C_9$ since they are the most spatially remote from the protonated amide group. The $C_6$ and $C_{10}$ positions are the next most remote sites and they are chlorinated about half as much as the $C_7$-$C_9$ sites.




In the 16-carbon analog, there are additional hydrophobic interactions as a result of folding back (structure 2). Due to this increase, hexadecanoamide (palmitamide) will be more prone to exist in a folded back conformation. Accordingly, it gave central chlorination in the less polar acetic-sulfuric acids (Table), conditions in which dodecanoamide showed remote chlorination. Furthermore, the positions most chlorinated, $C_8$-$C_{10}$, are again the most distant from the protonated functional group. The pattern of central chlorination was only slightly altered in going to the N,N-dimethyl and the N,N-dicyclohexylhexadecanoamides.[6]

A possible complexity in this conformational analysis is that significant amounts of dodecanoamide or hexadecanoamide exist in micelles. If so, we presume that the usual structure

of micelles shields the chain from reaction with $R_2NH^+$ and that the reaction is taking place on amide molecules outside the micelle.

The chlorinations were conducted using photoinitiation as described.[3] The chlorinated amides were isolated by dilution with water and extraction with benzene. The distribution of chloro substituents was determined by HCl elimination (72 hour reflux with potassium t-butoxide in t-butanol), treatment of the unsaturated acids with $O_3$ followed by $H_2O_2$,[7] conversion of the diacids to dimethyl esters with methanol and $H_2SO_4$,[8] and gas chromatography of the dimethyl esters as described.[9] The distribution of chloro was calculated on the basis that the HCl elimination went equally in both directions except that the terminal alkene was not formed.

Table

Relative[a] Yields of Chloroamides from Photochlorination of Lauramide and Palmitamide with N-Chlorodiisopropylamine at 25°

| Position | Lauramide | | | Palmitamide |
|---|---|---|---|---|
| | 70% AcOH 30% $H_2SO_4$ | 40% AcOH 60% $H_2SO_4$ | 20% $H_2O$ 80% $H_2SO_4$[b] | 70% AcOH 30% $H_2SO_4$ |
| 2,3,4-Cl | 0 | 0 | 0 | 0 |
| 5-Cl | 0 | 1 | 4 | 0 |
| 6-Cl | 3 | 6 | 11 | 6 |
| 7-Cl | 6 | 11 | 21 | 13 |
| 8-Cl | 10 | 15 | 26 | 16 |
| 9-Cl | 15 | 15 | 17 | 17 |
| 10-Cl | 27 | 24 | 13 | 21 |
| 11-Cl | 39 | 28 | 8 | 13 |
| 12-Cl | 0 | 0 | 0 | 6 |
| 13-Cl | -- | -- | -- | 5 |
| 14-Cl | -- | -- | -- | 3 |
| 15-Cl | -- | -- | -- | 0 |
| 16-Cl | -- | -- | -- | 0 |

(a) Overall yields of 70-90% can be achieved using a 10% excess of N-chloroamine.

(b) 96% $H_2SO_4$.

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