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The Question of Remote Steric Effects

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Abstract: Remote steric effects, thought to arise from long hydrocarbon chains coiling about reactive sites, are absent in three non-aqueous systems designed to maximize the effect.

During the course of past work on synthetic lipids[1], we have noticed, but never carefully verified, that long-chain compounds seemed to react more slowly than their short-chain counterparts. Other research groups engaged in lipid research have mentioned to us a similar observation. Rate inhibitions by a long chain cannot be explained by classical steric effects induced by atoms bonded near the reactive site. Remote carbons in a long chain could, however, retard a reaction if the chain coiled around the reactive center, thereby blocking approach of a reagent or second molecule. It is the purpose of the present article to measure quantitatively the rate effect (if any) imposed by the presence of a long chain.

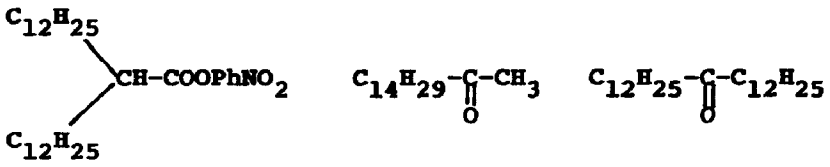
Two previous articles are particularly relevant to this study. In 1962, van Tamelen and Curphey[2] selectively oxidized (with NBS in glyme-water) the terminal double bond of squalene. The internal double bonds were virtually untouched, a selectivity that was lost in pure organic solvents. One possible explanation is that squalene coils in protic solvents so as to shield the internal double bonds; the terminal olefin remains exposed for reaction.

In a second article, Jiang, Fan, and Hui[3] found that the two terminal functionalities of p-nitrophenyl 16-mercaptohexadecanoate react intramolecularly in DMSO-water to close a 17-membered ring. It was postulated that hydrophobic forces within the hexadecanoate chain induce "self-coiling" that brings into proximity the reactive termini.

Since it was not known whether long-chain "steric effects" might also manifest themselves in non-aqueous solvents (in which most synthetic reactions are run), we examined three reactions in organic media: aminolysis of p-nitrophenyl 2-n-dodecyltetradecanoate 1 in CH_3CN and lithium tri-tert-butoxyaluminohydride reduction of 2-hexadecanone 2 and 13-pentacosanone 3 in THF. Comparison with short-chained analogs allowed us to assess the effect of self-coiling.

Pseudo-first-order rate constants for aminolysis of 1 were determined spectrophotometrically (427 nm) following a published procedure[4] and using these conditions: 0.10 M pyrrolidine and 5×10^{-5} M 1 in HPLC-grade CH_3CN at 25.0 ± 0.2° C. The k_{obs} was found to equal

0.29 min^{-1} compared with 0.27 min^{-1} for a short-chain analog (p-nitrophenyl 2-ethylbutyrate) under the same conditions. Long-chain inhibition is clearly absent.



1 2 3

Reduction rates of ketones 2 and 3 by the aluminohydride were estimated from the disappearance of the IR carbonyl band (scanning periodically from 1825 to 1650 cm^{-1}). The IR cell contained initially 44 mM 2 or 3 in THF plus 56 mM aluminohydride (with pure THF in the reference cell). Owing to experimental difficulties (including temperature control), accurate rate constants were not obtained, but it was obvious that: (a) ketone 2 and 2-hexanone were reduced at identical rates (i. e. reaction times of 15 min) and (b) ketone 3 and 3-pentanone were reduced at rates differing by less than a factor of two. Once again, a chain inhibition was not observed despite the bulky reducing agent selected specifically to maximize the effect.

In summary, we could find no rate differences between long-chained and short-chained analogs in organic solvents (CH_3CN and THF). Thus, the hypothesis of "remote steric effects" has to be rejected for the particular cases at hand. Of course, if aqueous solvents are used, then self-coiling might indeed adversely affect reaction rates,[2,3] although aggregation phenomena and insolubility problems could also lower yields or force the use of more stringent conditions.[5]

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5. Compound 1 was prepared by the malonic ester synthesis and characterized by ^1H-NMR, ^{13}C-NMR, IR, elemental analysis, and MS (low resol SIMS). The ketones are commercially available compounds.

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