The influence of distal substitution on the base-induced isomerization of long-chain terminal alkynes

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When compared to a long-straight chain terminal alkyne, a long chain terminal alkyne with a distal isopropyl unit (isobranched) isomerizes about two times faster when treated with strong base under identical conditions, and appears to follow pseudo first order kinetics. In both cases, equilibration to a 95–97:5–3 mixture of terminal:internal alkyne accompanies isomerization. The difference in rate may be due to an unusual folding of both long-chain alkynes, bringing the distal substituent close to the carbon-carbon-triple bond moiety. The distal isopropyl moiety may provide unanticipated steric hindrance that disrupts such folding, making the propargylic proton more available for reaction with base.

Introduction

Inflammatory periodontal disease in adults is initiated with the accumulation of specific bacteria in the sulcus around the teeth, followed by a chronic inflammatory reaction by the host against the colonizing microorganisms. The anaerobic Gram-negative organism, Porphyromonas gingivalis, is thought to be a major periodontal pathogen1 associated with destructive periodontal disease in adults. P. gingivalis and other phylogenetically related organisms produce a variety of novel lipids,2 including phosphorylated dihydroceramide lipids (see 1).3 More recent work in our laboratories identified serine dipeptide lipid classes in P. gingivalis that comprise a new class of ligands (see 2 and 3) for Toll-like receptor 2 (TLR2).4 These agonists are also produced by common oral and intestinal Bacteroidetes,5 and they are recovered in chronically inflamed human tissues including destructive periodontal disease and atherosclerosis tissues.2

The base-induced isomerization of the triple bond of terminal alkynes is well known,6 proceeding through an allene intermediate.7 This isomerization typically requires a strong base and KOH in alcohol, but sodium amide in DMSO has been used.8 Small amounts of the allene were sometimes isolated during the isomerization reaction9 although the allene was prone to polymerization and was not always detected. In another study,10 a mechanism for the isomerization of pent-1-yne was proposed, using KOH in ethanol, in a sealed tube at 175 °C, deprotonation led to allene formation, which led to the thermodynamically more stable internal...
alkyne, pent-2-yne. Analysis of the products for this latter study showed the presence of 1–4% of pent-1-yne, with some penta-1,2-diene.

In previous work, we synthesized the putative C17 and C19 dihydroceramides (1) to prove their structure and showed that the long aliphatic chain terminated in an isopropyl unit, and that this terminal isopropyl unit is critical for expression of the biological activity. Two TLS2 ligand are serine dipeptide lipid classes that were labeled lipid 430 and lipid 654, 2 and 3 respectively. Recently we observed that the lipid 654 can be hydrolyzed by specific lipases to lipid 430. A terminal isopropyl unit in a long aliphatic chain is hereafter referred to as an isobranch. We recently reported the convergent synthesis of 2 and 3.

Results and discussion

To determine the kinetics of base-induced isomerization, we required an unambiguous synthesis of both the straight-chain alkyne (5) and the distal isobranched terminal alkyne (9). The synthesis of the straight-chain alkyne proceeded without problem, via coupling of lithium acetylide with commercially available 1-bromohexadecane (4), in dry DMSO, to give octadec-1-yne (1) in 73% yield (see Scheme 1). We prepared the isobranched intermediate, 13-methyl-1-bromotetradecan-1-ol (7), using, in part, methodology reported by Singh and by Mori. This synthesis began with a lithium tetrachlorocuprate-mediated coupling reaction of the Grignard reagent prepared in situ by reaction of 1-bromo-2-methylpropane with commercially available 11-bromoundecan-1-ol (6), which gave 13-methyltetradecan-1-ol (7) in 79% yield. Conversion to the bromide (8) with NBS and PPh3 (81% yield) was followed by reaction with lithium acetylide to give 15-methylhexadec-1-yne (9) in 77% yield.

The kinetics for both 5 and 9 were obtained in DMSO at 55 °C and also at 75 °C, temperatures at which reasonable data could be collected. Samples were prepared that were 0.042 M alkyne in DMSO. Potassium tert-butoxide was added to each sample and aliquots were removed at the time intervals shown in Figs. 1 and 2, quenched with water, the products extracted with hexane, and 1H NMR was used to monitor the reaction.

We plotted [alkyne] vs. time, ln [alkyne] vs. time and 1/[alkyne] vs. time, but the linear plots were obtained only for ln [alkyne] vs. time. Our results point to a pseudo first order reaction for all rate constants reported herein. This observation is reasonable if one of the reactants, possibly the base, is in excess relative to the deprotonation reaction with the alkyne. Fig. 1 shows a comparison of the reactions of 5 and 9 at 55 °C and 75 °C. Fig. 2 shows the changes in rate at 55 °C and at 75 °C for 5 and for 9.

Based on the results in Figs. 1 and 2, it is clear that isomerization of the isobranched alkyne is faster than that of the straight-chain alkyne.
chain alkyne. However our results also show that for both 5 and 9,
the isomerization does not go to completion, but rather reaches an
equilibrium of about 95–97% internal + 3–5% terminal alkyne.

Indeed, we observed a late-reaction change in rate data that we
believe reflects the point where this equilibrium is reached. The
plots in Figs. 1 and 2 only show the rate data pertinent to the iso-
merization, and do not show this equilibrium that occurred only
after extended reaction times. We did not observe signals in the
$^1$H NMR that correspond to the presence of allene or the alk-3-
yne, although we cannot completely rule out their presence.

We calculated a rate constant at $55^\circ C$ using the slope of the
distances seen in Figs. 1 and 2 and obtained a value of
$-4.403 \times 10^{-3} \text{mol}^{-1} \text{min}^{-1}$ for the isobranched alkyne (9) and
$-2.075 \times 10^{-3} \text{mol}^{-1} \text{min}^{-1}$ for the straight chain alkyne (5). A
similar plot done at $75^\circ C$ is shown in Figs. 1 and 2, and gave a rate of $-2.27 \times 10^{-2} \text{mol}^{-1} \text{min}^{-1}$ for 9 and $1.702 \times 10^{-2}$
$\text{mol}^{-1} \text{min}^{-1}$ for 5. Calculations showed that $E_a$ for
9 = $-9.63 \times 10^{-4} \text{J mol}^{-1}$, and $E_a$ for 5 = $-2.88 \times 10^{-4} \text{J mol}^{-1}$.

The results of our calculations for the pseudo first-order rate
constants and the activation energies are shown in Table 1

<table>
<thead>
<tr>
<th>Alkyne</th>
<th>Pseudo First Order Rate Constant (55°C) $\text{mol}^{-1} \text{min}^{-1}$</th>
<th>Pseudo First Order Rate Constant (75°C) $\text{mol}^{-1} \text{min}^{-1}$</th>
<th>Activation Energy $\text{J mol}^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>$-2.075 \times 10^{-3}$</td>
<td>$-1.702 \times 10^{-2}$</td>
<td>$-2.88 \times 10^{-4}$</td>
</tr>
<tr>
<td>9</td>
<td>$-4.403 \times 10^{-3}$</td>
<td>$-2.271 \times 10^{-2}$</td>
<td>$-9.63 \times 10^{-4}$</td>
</tr>
</tbody>
</table>

Conclusions

We have shown that a distal isobranch in a long-chain terminal
alkyne influences the rate of isomerization to an internal alkyne.
Indeed, we have shown that alkyne 9 isomerizes 2.1 times faster
than alkyne 1 at 55°C, and alkyne 5 isomerizes 1.33 times faster
than alkyne 5 at 75°C. We speculate that coiling in long-chain
alkynes, perhaps due to aggregation effects, is operative in the
DMSO solvent and that the distal isobranch disrupts the coiling
sufficiently to allow more rapid deprotonation and allene
formation.
The proposal for folding and increased steric hindrance at the site of reaction, due to a distal methyl group, is certainly speculative. Although soluble, the non-polar nature of the long-chain alkynes in the polar, aprotic DMSO may provide the 'encapsulation' or aggregation phenomenon that leads to folding or coiling of the alkynes. It is reasonable to assume that differences in rate are due to either an aggregation effect or an intramolecular interaction related to conformation that makes the isobranchied alkyne more available for reaction. The literature provides some precedent for either case. As noted above, we determined that 4.38% of water available for reaction. The literature provides some precedent for alkynes.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2017.09.020.

References

14. A solution of 0.042 M of 5 or 9 in DMSO was prepared and treated with 1 equiv of potassium tert-butoxide. Aliquots were collected at the time intervals of 10 min, quenched with water, the products were extracted with hexane and proton NMR data were collected on 300 MHz and 400 MHz Progress of the isomerization was monitored by disappearance of proton signals at 1.87 ppm, 2.13 ppm and appearance of new signals at 1.72 ppm, 2.06 ppm. Based on the integrations of proton signals relative percentages of external and internal alkynes were calculated by the following equation and from the mmol were calculated. The integral% of external alkene = a. The integral% of external alkene = b. The relative% of external alkene = B. The equilibrium concentrations of alkynes at 55 °C. For 9: mmol of 2-alkyne 0.020550847, mmol of 1-alkyne 0.000635593. The equilibrium constant = [2-alkyne]/[1-alkyne] = 0.01958/0.00042 = 46.6
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