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Investigation into the mechanism of lithiation of 2,3-dihydrooxepin

Zhiqing Yan and John F. Sebastian*

Department of Chemistry and Biochemistry, Miami University, Oxford, OH 45056, USA

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Abstract—The NMR characterization of the trienolate product of lithiation of 2,3-dihydrooxepin with 6-lithiodihydropyran in THF is reported. The NMR spectra also support a direct ring opening upon allylic lithiation via an E2-type mechanism rather than vinylic lithiation or stepwise allylic lithiation. We also found the structure of the trienolate product of this reaction to be the *Z*, *Z* configuration.

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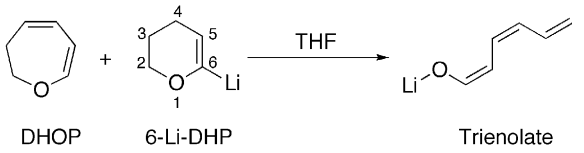
α-Lithiated cyclic vinyl ethers and their reactions with organic compounds have been extensively studied both experimentally and computationally because they are used as acyl anion synthons and precursors of cuprates.[1] The vinylic lithiation of dihydrofuran (DHF) and dihydropyran (DHP) by ^{n}BuLi is well known. The internal angles of the corresponding anions is one of several factors expected to affect the regioselectivity of such lithiation reactions.[2] In previous work, our group has observed vinylic lithiation of 2,3,4,5-tetrahydrooxepin experimentally by ^{13}C NMR spectroscopy.[3] The extended conjugation of the C=C–O moiety in 2,3-dihydrooxepin (DHOP) led us to suspect that it might be a good candidate for allylic deprotonation (provided that the neighboring oxygen does not dominate the regioselectivity). However, it was found that the seven-membered ring of DHOP was cleaved upon reaction with 6-lithiodihydropyran (6-Li-DHP), and a trienolate product was formed (Scheme 1).[3] Although the initial structure of this trienolate might be expected to have the *Z*,*Z* configuration, other configurations are possible: *E*,*E*; *E*,*Z*; or *Z*,*E*. Neither the detailed structure of the trienolate nor the mechanism of this reaction was established in previous work.



Scheme 1.

Here we wish to report our recent results in elucidating the structure of the trienolate and a proposed mechanism for this reaction based on isotopic labeling and NMR experiments.

We believe there are three possible pathways for the reaction (Scheme 2). In Pathway 1, the vinylic–allylic lithiation mechanism, vinylic lithiation happens first, then the resulting vinyl-Li-DHOP abstracts an allylic hydrogen of another DHOP molecule to form the trienolate product. Starting with 7-deuterio-DHOP, we should be able to follow the formation of a normal (unlabeled) DHOP during the reaction; the trienolate product should be a mixture of 2-protiotrienolate and 2-deuteriotrienolate (see Fig. 1, for numbering system). In Pathway 2, the cyclic allylic lithiation mechanism, allylic lithiation occurs first, and then the ring opens up (overall a two-step process). If the lithiation reaction is quenched with D_2O in the middle of the consumption of DHOP, we should be able to obtain the allylic deuterio-DHOP. Pathway 3 is the direct ring-opening mechanism: the lithiation takes place at the allyl position with concomitant ring opening. Actually, Pathway 3 is supported by our density functional theory (DFT) computational research that will be published elsewhere.

Experimental tests of these proposed mechanisms began with preparation of the necessary starting materials. The preparations of 6-deuterio-DHP (Scheme 3), and DHOP (Scheme 4) are based on work previously reported.[3,4]

Keywords: Trienolate; Lithiation; 2,3-Dihydrooxepin.

* Corresponding author. Tel.: +1-513-529-3337; fax: +1-513-529-5715; e-mail: sebastjf@muohio.edu

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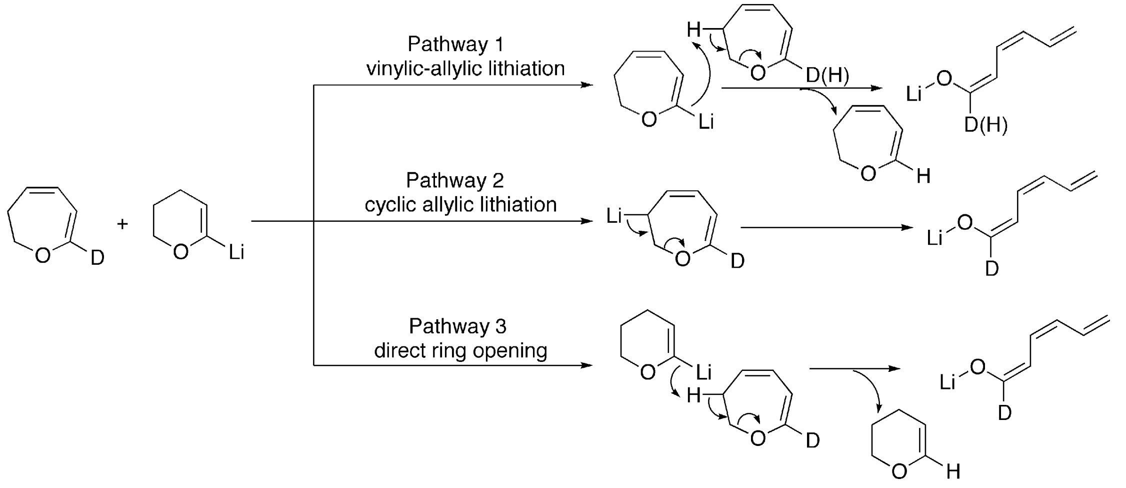


Scheme 2.

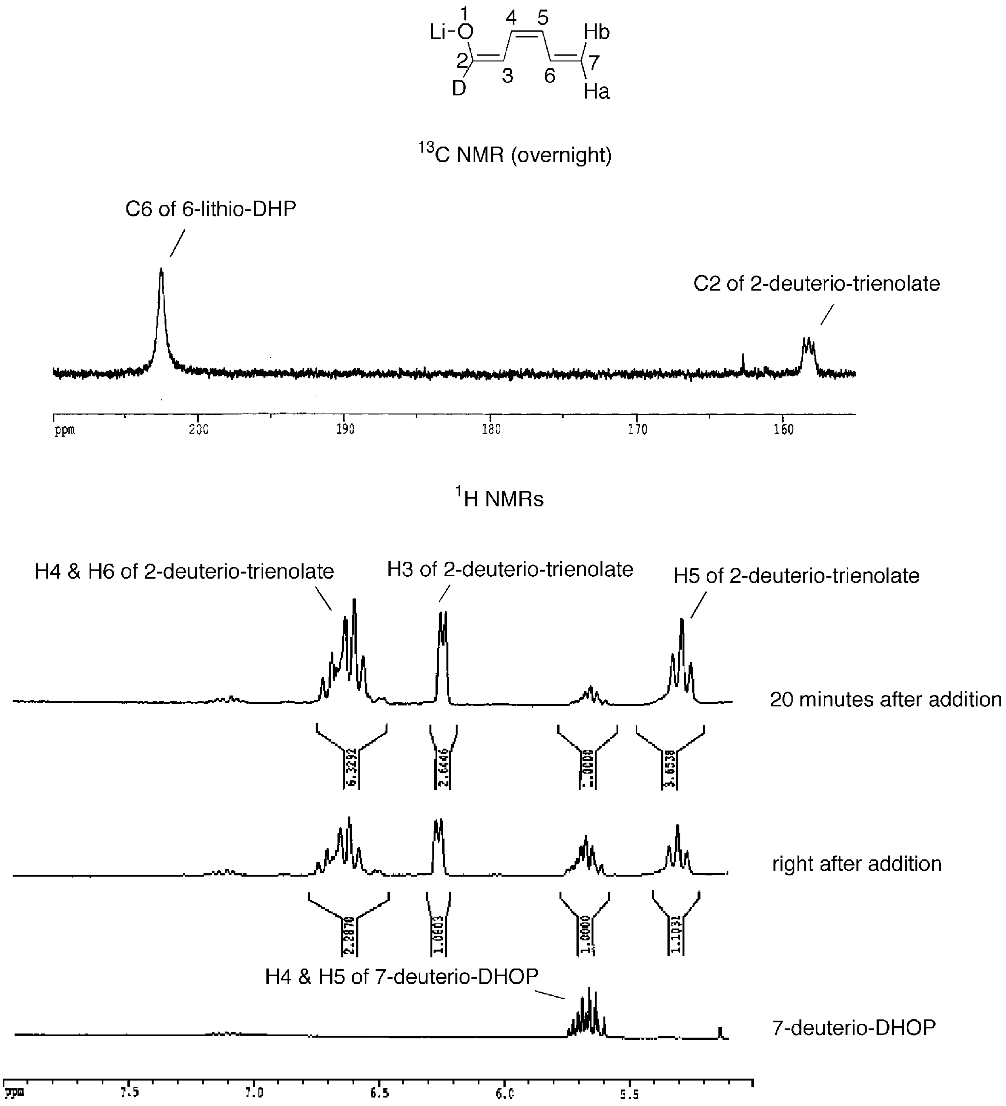
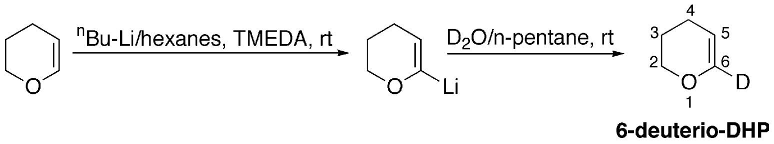
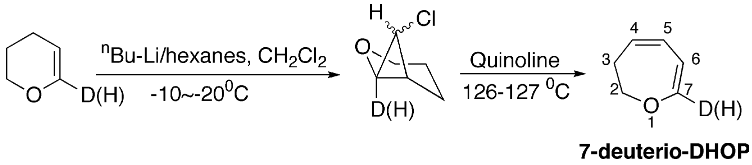


Figure 1. 300 MHz ^{1}H and 75 MHz ^{13}C NMRs for lithiation (with 6-Li-DHP) of 7-deuterio-DHOP at −20 °C (selected regions shown).

The compound 7-deuterio-DHOP was prepared similarly to that of normal DHOP, except that we started from 6-deuterio-DHP (Scheme 4). Using GC–MS, we observed the parent molecular ion of DHOP and 7-deu-



Scheme 3.



Scheme 4.

Table 1. ^{1}H, ^{13}C NMR data of 6-deuterio-DHP and 7-deuterio-DHOP

	6-Deuterio-DHP	7-Deuterio-DHOP	
	200 MHz ^{1}H NMR (at rt, in $CDCl_3$)	300 MHz ^{1}H NMR (at −20 °C, in THF-d_8)	75 MHz ^{13}C NMR (at −20 °C, in THF-d_8)
2	3.94 (t)	4.10 (t)	70.31
3	1.83	2.52 (q)	35.20
4	1.98	5.64–5.76	125.01
5	4.63 (t)	5.64–5.76	130.53
6	—	4.80 (d)	102.32
7	—	—	149.12 (t)

terio-DHOP. Table 1 shows the ^{1}H NMRs and ^{13}C NMR chemical shifts of these starting materials (see Schemes 3 and 4 for numbering system).

In Figure 1 we show selected regions of the NMR spectra obtained in the reaction of 7-deuterio-DHOP with 6-lithio-DHP.[5] The ^{13}C NMR spectrum of the product shows a 2-deuterated trienolate product, but there is no evidence of a product with a hydrogen atom attached to C2. Neither did we observe the presence of normal (undeuterated) DHOP during the reaction. The ^{1}H NMR spectra show the consumption of 7-deuterio-DHOP and the accumulation of the trienolate product. All of these results suggest that Pathway 1, the vinyl lithiation mechanism, did not happen.

In Figure 2 we show the selected regions of the ^{13}C NMR spectrum of the mixture derived from the lithiation of DHOP quenched by D_2O in 10–20 min (at only partial completion of reaction). The triplet at about 144 ppm belongs to the deuterated α-carbon of DHP and results from deuteration of the conjugate base of DHP. The singlet at the same region is due to undeuterated DHP resulting from protonation of the DHP conjugate base. The peak at about 149 ppm is of DHOP, indicating the reaction had not gone to completion. The peak at 34 ppm is due to C3 of DHOP. We examined the spectrum carefully around this region, but did not see any evidence of a triplet expected for C3-D. This could mean that no 3-lithio-DHOP was formed, thus excluding Pathway 2.[6]

To further clarify the chemical shifts of the trienolate product, we also recorded a 2D HSQC spectrum on a 500 MHz spectrometer to assign the resonances of each carbon and each proton in the molecule (Fig. 3). Table 2 shows the chemical shifts and coupling constants of the trienolate product obtained from the 500 MHz ^{1}H and 125 MHz ^{13}C NMR spectra. The 500 MHz ^{1}H NMR clearly indicates that the double bond between C2 and C3 has the *Z* configuration with $^3J_{23} = 4.9$ Hz, and that the one between C4 and C5 is also *Z* with $^3J_{45} = 11.2$ Hz. The coupling constant $^3J_{23}$ is small due to the effects of the neighboring electronegative O atom.

In conclusion, we have found that the lithiation of DHOP follows Pathway 3, direct ring opening upon allylic lithiation (the E2-type mechanism), based on NMR spectra and deuteration studies. This verifies our previous expectation of DHOP being an allylic deprotonation candidate by extending the conjugation of the C=C–O moiety. We also determine the structure of the trienolate product of this reaction to have the *Z*, *Z* configuration experimentally.

Typical procedure for lithiation of DHOP (including 7-deuterio-DHOP, and normal DHOP with 6-Li-DHP): 6-Li-DHP was first prepared according to the literature procedure.[3] THF-d_8 (0.5 mL) was added and the suspension then centrifuged; the resulting top layer solution was transferred into an NMR tube. To this solution, 0.02 mL of DHOP (or 7-deuterio-DHOP) was added (a bath was used to maintain the desired temperature). After swirling, the sample was ready for NMR. For experiments reported in Figure 2, the lithiation reaction was carried out in a larger scale in THF and was quenched by adding D_2O after 10–20 min. The resulting mixture was separated, the top organic layer was dried and the solvent was removed by evaporation. Then the residue was used in NMR experiments.

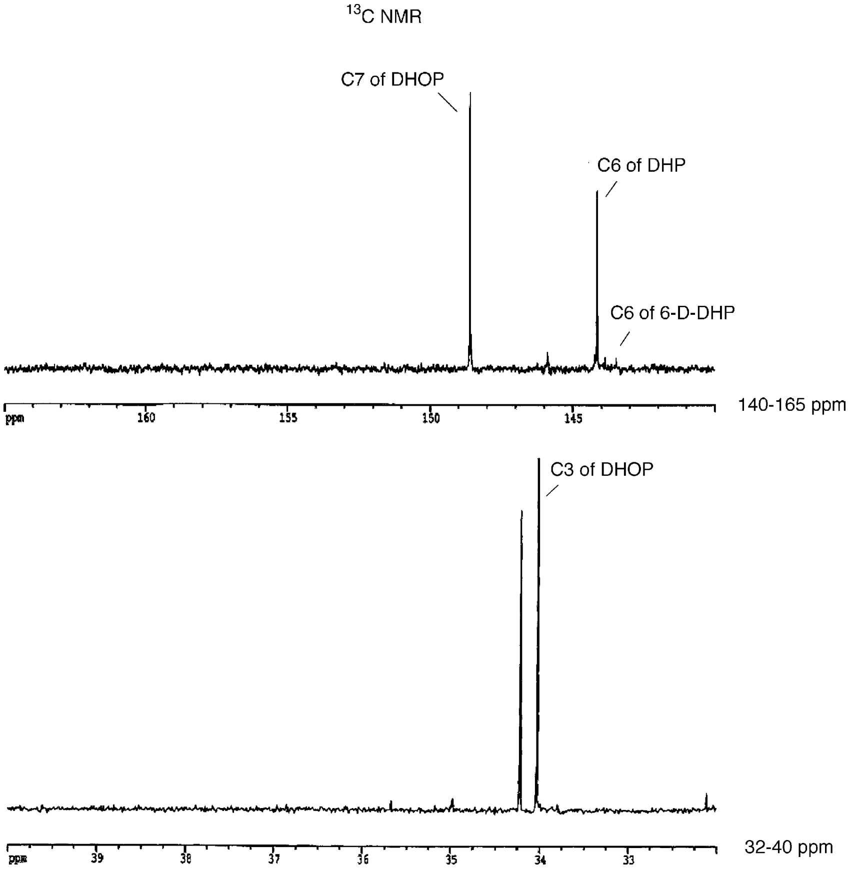


Figure 2. 75 MHz ^{13}C NMRs for lithiation (with 6-Li-DHP) of DHOP at −20 °C and then quenched by D_2O (selected regions shown).

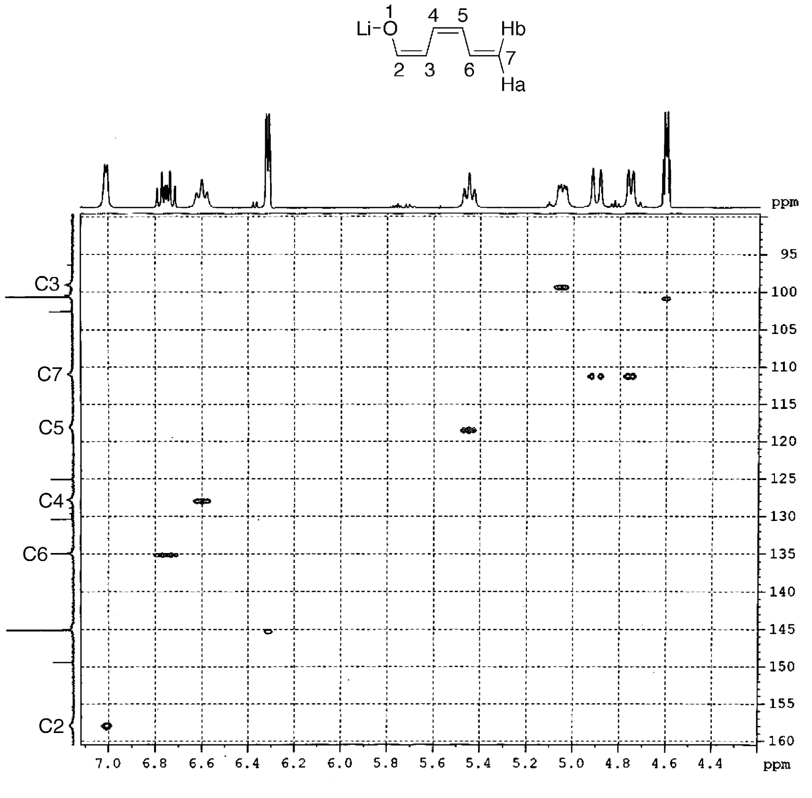


Figure 3. 500 MHz HSQC (2D NMR) for lithiation (with 6-Li-DHP) of DHOP at room temperature (selected regions shown).

Table 2. ^{1}H, ^{13}C NMR data of the trienolate product in THF-d_8

500 MHz ^{1}H/ppm (J/Hz)		125 MHz ^{13}C NMR	
2	7.01 ($^3J_{23} = 4.9$)	2	159.2
3	5.05 ($^3J_{34} = 11.7$)	3	97.6
4	6.60 ($^3J_{45} = 11.2$)	4	129.2
5	5.45 ($^3J_{56} = 10.9$)	5	119.3
6	6.76 ($^3J_{67b} = 16.9$, $^3J_{67a} = 10.6$)	6	136.2
7b (*trans*)	4.90	7	112.0
7a (*cis*)	4.76	—	—

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References and notes

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2. Fristad, W. F.; Han, Y. K.; Paquette, L. A. *J. Organomet. Chem.* **1979**, *174*, 27.
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5. An intractable tar was obtained while using ^{n}BuLi to perform the metalation. We then chose 6-lithio-DHP and found that the lithiation reaction takes place cleanly at a reasonable rate.
6. Deuteration at C5 was not observed. The experiment performed to disprove Pathway 2 tests for the buildup of the intermediate anion. However, if the ring were opened faster than the rate of allylic metalation, the intermediate would not be detected as the detection of small amounts of deuterated C3 (or C5) by this method is, of course, very insensitive.