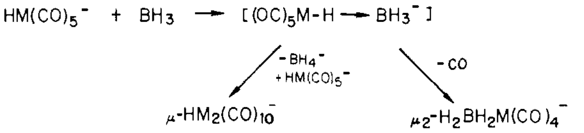
J. Am. Chem. Soc. 1981, 103, 5915-5916



(9)

from strict octahedral symmetry (C_{trans}–Cr–C_{cis} = 95.4°).[11] As evidenced by the CMR data the $HCr(CO)_5^-$ anion shows an intramolecular CO_{cis}–CO_{trans} exchange process that is currently under investigation.[12]

Acknowledgment. The support of this work by the National Science Foundation (Grant CHE 79-23204) is gratefully acknowledged. Helpful discussion with D. J. Darensbourg and A. Rokicki and the generous assistance of the latter is much appreciated.

---

[11] A full report of the X-ray crystal structures of $HCr(CO)_5^-$ and μ_2-$H_2BH_2Cr(CO)_4^-$ and the acid/base chemistry involved in their interconversions is being prepared.

[12] Darensbourg, D. J.; Darensbourg, M. Y.; Rokicki, A.; Slater, S., manuscript in preparation.

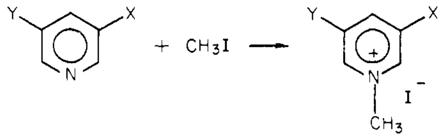
Transition-State Variation in the Menshutkin Reaction

J. Milton Harris,* M. Steven Paley, and
Thomas W. Prasthofer

Department of Chemistry
The University of Alabama in Huntsville
Huntsville, Alabama 35899

Received May 11, 1981

The concept of a variable transition state (TS) has been of great use in explaining the properties of organic reactions, and several theoretical methods for predicting variations in TS structure have seen extensive application.[1-7] However, several groups have recently observed invariant selectivity for reactions showing large changes in reactivity.[8-11] Since this finding is most simply interpreted as indicating a constancy in TS structure, it has led to questioning of the otherwise successful methods for predicting TS variation.[9] Alternative, more convoluted, arguments can be made to retain TS variability in these cases,[1b,4a] and it is quite possible that selectivity is sometimes an insensitive probe of TS structure. The general importance of this question prompted us to apply another probe of TS structure to one of the reactions reported to give invariant selectivity. Thus we have determined kinetic α-deuterium isotope effects (α-d's) for the same series of reactants found by Arnett and Reich[8] to give invariant selectivity in the Menshutkin reaction (reaction 1).



(1)

Table I. α-Deuterium Isotope Effects for Reaction of 3-X-5-Y-Substituted Pyridines with Methyl Iodide in 2-Nitropropane at 25 °C

3-X	5-Y	rel rate	k_{CH_3I}/k_{CD_3I}
CH_3	CH_3	389	0.908 ± 0.002
CH_3	H	214	0.851 ± 0.001
H	H	138	0.850 ± 0.001
Cl	H	10.8	0.835 ± 0.002
Cl	Cl	1	0.810 ± 0.003

[a] Rate constants were determined conductimetrically as described in ref 8 and are the result of at least five runs. Error limits of the isotope effects are calculated from the standard deviations of the mean for the individual rate constants for protium and deuterium by use of the formula $s_{\alpha\text{-d}} = k_H/k_D(s_H/k_H + s_D/k_D)$ where $s_{\alpha\text{-d}}$ represents the standard deviation of the mean for the α-d, and s_H and s_D represent the standard deviations of the mean for protium and deuterium.

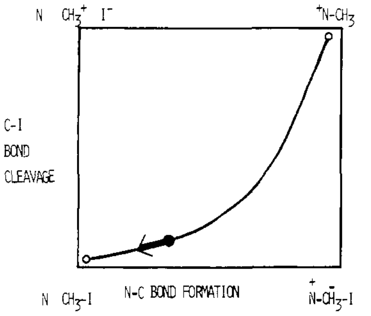


Figure 1. A potential energy diagram for a Menshutkin reaction in which N–C bond formation precedes C–I bond cleavage. Energy maxima and minima are represented by closed and open circles, respectively.

According to current interpretation, the α-d is a sensitive probe of the relative extent of crowding in the TS and in the reactant, so that a decrease in crowding results in an α-d greater than unity and an increase in crowding results in an α-d of less than unity.[12,13] Further, a gradual change in α-d is interpreted as indicating a gradual change in TS structure, and a constancy in α-d is interpreted as indicating an invariance in TS structure.[8] The α-d thus appears to be a suitable probe for investigating the proposal of an invariant TS for the Menshutkin reaction.

The results of our kinetic measurements are presented in Table I. Obviously, the α-d's do change, thus indicating variation in TS structure for this reaction, despite conclusions to the contrary based on the RSP.[8] Explanations of the failure of selectivity to vary with reactivity have been presented elsewhere and we will not detail them here.[1b,4a] Simply put, selectivity is a relatively insensitive probe and frequently does show an invariance in cases in which the TS does vary.

Current theories of TS variation can be used to explain the trend in α-d's observed for the Menshutkin reaction. The exothermicity,[8] sensitivity to steric effects ($k_{MeI} > k_{EtI}$),[8] and inverse α-d's (Table I)[14] for this reaction are consistent with an early, crowded TS in which bond making between nitrogen and carbon is more advanced than bond breaking between carbon and iodine.[15] The extent of N–C bond formation in the TS is indicated by four different probes to be about 30% of a complete N–C bond.[8,16-18] These

---

[1] (a) Jencks, D. A.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 7948. (b) Young, P. R.; Jencks, W. P. *Ibid.* **1979**, *101*, 3288.

[2] (a) Thornton, E. R. *J. Am. Chem. Soc.* **1967**, *89*, 2915. Winey, D. A.; Thornton, E. A. *Ibid.* **1975**, *97*, 3102.

[3] Gajewski, J. J.; Conrad, N. D. *J. Am. Chem. Soc.* **1979**, *101*, 6693.

[4] (a) Harris, J. M.; Shafer, S. G.; Moffatt, J. R.; Becker, A. R. *J. Am. Chem. Soc.* **1979**, *101*, 3295. (b) Shafer, S. G.; Harris, J. M., *J. Org. Chem.* **1981**, *46*, 2164.

[5] Shiner, V. J., Jr.; Seib, R. C. *J. Am. Chem. Soc.* **1976**, *98*, 862.

[6] (a) Bernasconi, C. F. *Acc. Chem. Res.* **1978**, *11*, 147. (b) Bernasconi, C. F.; Gandler, J. R. *J. Am. Chem. Soc.* **1978**, *100*, 8117.

[7] (a) Albery, W. J.; Kreevoy, M. M. *Prog. Phys. Org. Chem.* **1978**, *13*, 87. (b) Albery, W. J. "Progress in Reaction Kinetics"; Pergamon: Oxford, 1967; Vol. 4, p 355. (c) More O'Ferrall, R. A. *J. Chem. Soc. B* **1970**, 274. (d) Bunnett, J. F. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 225.

[8] Arnett, E. M.; Reich, R. *J. Am. Chem. Soc.* **1980**, *102*, 5892.

[9] Bordwell, F. G.; Hughes, D. L. *J. Org. Chem.* **1980**, *45*, 3314, 3320.

[10] Koshy, K. M.; Roy, D.; Tidwell, T. T. *J. Am. Chem. Soc.* **1979**, *101*, 357.

[11] (a) Pross, A. *Adv. Phys. Chem.* **1977**, *14*, 69. (b) Giese, B. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 125.

[12] Shiner, V. J., Jr. In "Isotope Effects in Chemical Reactions"; Collins, C. J., Bowman, N. S., Eds.; Van Nostrand Reinhold: New York, 1970; Chapter 2.

[13] (a) Melander, L.; Saunders, W. H., Jr. "Reaction Rates of Isotopic Molecules"; Wiley: New York, 1980. (b) Knier, B. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1980**, *102*, 6789.

[14] Leffek, K. T.; McLean, J. W. *Can. J. Chem.* **1965**, *43*, 40.

[15] We differ with the view of Arnett and Reich[8] that the TS for this reaction is loose with the rupture of the C–I bond being almost complete. See also: le Noble, W. J.; Miller, A. R. *J. Org. Chem.* **1979**, *44*, 889 and references cited therein.

[16] Matsui, T.; Tokura, N. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1751.

[17] Abraham, M. H.; Grellier, P. L. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1735.

0002-7863/81/1503-5915$01.25/0

considerations require that the reaction coordinate and TS be positioned as in Figure 1. A change to a better nucleophile (e.g., going from 3,5-dichloropyridine to 3,5-dimethylpyridine in Table I) would stabilize the right-hand corners of Figure 1, and since most of the change is "parallel to" the reaction coordinate at the TS, the prime effect will be to produce an earlier, less crowded TS (as indicated by the arrow in Figure 1).[1-7] Such a change in TS would give the observed increase in α-d with the change to a better nucleophile.

In summary, the present results provide experimental support to the theoretical arguments[1b,4a] that constant selectivity is not sufficient evidence for concluding that the otherwise successful theories for predicting TS variation are invalid.

Acknowledgement is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. We further acknowledge the very helpful communication of unpublished information by Professor E. M. Arnett.

---

(18) Kondo, Y.; Shinzawa, M.; Tokura, N. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 713.

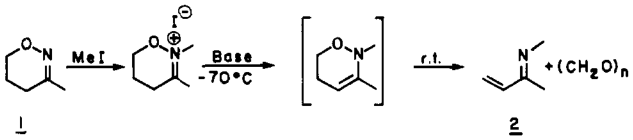
Highly Regiocontrolled and Rapid Lithiation of 3-Methyl-4*H*-5,6-dihydro-1,2-oxazine: Elaboration for α-Methylene Ketone Synthesis

Ramy Lidor and Shimon Shatzmiller*

Department of Chemistry, Tel-Aviv University
Tel Aviv 69978, Israel

Received May 6, 1981

Heterocyclic systems have been used as vehicles to construct functionalized carboskeletons. 1,2-Isoxazolines were used by Jaeger as substrates for 1,3-amino alcohol synthesis and enone synthesis.[1] We have reported that 3-methyl-4*H*-5,6-dihydro oxazine (**1**) is a precursor to the unsaturated imine **2**.[2]



Carbonyl derivatives like **1** have two different types of α protons at the 3-methyl and 4-methylene; regiocontrolled deprotonation and subsequent C–C formation would therefore be of synthetic utility. We now report a successful regioselective lithiation of the cyclic oxime ether **1** and its use for a new α-methylene ketone synthesis.

Papers describing regioselectivity in anion formation syn to the N–O bond in oxime ethers[3] refer to butadiene dianion, presumed to be thermodynamically more stable in the cisoid form.[4] Our efforts focused, therefore, on a kinetically controlled lithiation followed by C–C formation.[5] We used an apparatus (Figure 1) which made possible a simple, convenient way of carrying out lithiations by using a variety of bases, alkylating agents, and solvents at low temperature. The general procedure was as follows: Lithium dialkylamides were prepared in vessel A at the reaction temperature and were added at once to the cold oxime ether **1** in vessel E. The lithiated product was reacted by adding an alkyl halide or ethanol rapidly with a syringe at the desired temperature.[6]

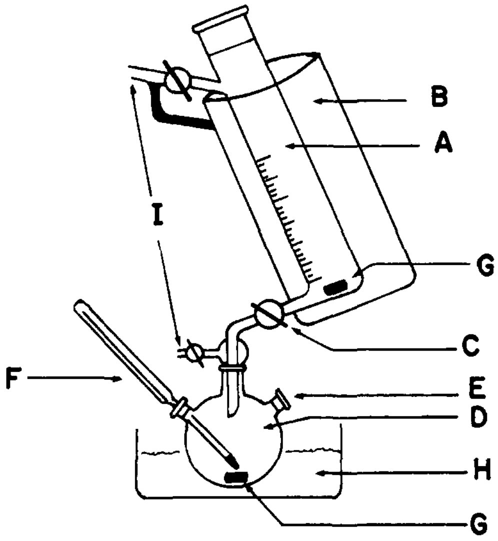
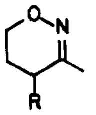
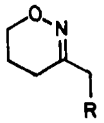


Figure 1. Apparatus for alkylation at low temperatures: (A) Graduated cylinder for base preparation; (B) cooling sleeve for cylinder; (C) 4-mm Teflon stopcock; (D) reaction flask; (E) serum stopper; (F) thermometer (Hewlett Packard 2802A thermometer); (G) magnetic stirring bars; (H) cooling bath; (I) stopcocks for nitrogen.

We established that deprotonation was completed in less than 2 min at −95 °C using various lithium dialkylamides as bases.[7] Methyl iodide led to extremely fast reactions.[8] Deprotonation with lithium dimethylamide at −95 °C over 30 s followed by reaction with methyl iodide at the same temperature for an additional 30 s afforded **3** in more than 90% yield and over 99% purity.[9] Lithiation of **1** with lithium *tert*-butylisopropylamide



3 R = CH₃
5 R = D



4 R = CH₃
6 R = D

at −65 °C for 2 min and then methylation (MeI) gave **4** in 83% yield in more than 95% purity.[9] Similarly, reaction of each of the isomeric pair of lithiated compounds with CH_3CH_2OD gave (minimum purity >90%) the monodeuterated compounds **5** and **6**.

A solution of lithiated **1** generated with either base in hexane–THF remained unchanged for at least 40 min at temperatures below −45 °C. The distribution of reaction products was not a function of the time elapsed between generation and reaction with MeI. The isomeric lithiated products are thus not interconvertible under these conditions. In contrast, when HMPTA[10] was added to a solution of lithiated **1**, or if deprotonations were carried out in HMPTA, only **3** was isolated.

---

(1) Jaeger, V.; Buss, V.; Schwab, W. *Tetrahedron Lett.* **1978**, *34*, 3133. Jaeger, V.; Grund, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 50.

(2) Hardegger, B.; Shatzmiller, S. *Helv. Chim. Acta.* **1976**, *59*, 2499.

(3) Spencer, T. A.; Leong, C. W. *Tetrahedron Lett.* **1975**, *45*, 3889. Frazer, R. R.; Dhawan, K. L. *Chem. Commun.* **1976**, 674. Ensley, H. E.; Lohr, R. *Tetrahedron Lett.* **1978**, *16*, 4415.

(4) Bingham, R. C. *J. Am. Chem. Soc.* **1976**, *98*, 535 and references cited therein.

(5) Steric factors in the regioselectivity of kinetically controlled α deprotonation from ketone hydrazones in the synthesis of α-alkylated saturated ketones were studied by: Jung, E. M.; Shaw, T. J. *Tetrahedron Lett.* **1977**, 3305.

(6) Reactions were usually carried out in 2-mmol scale in homogeneous 0.2 M solutions. Scaling up to 50 mmol was possible with the same technique.

(7) Although reaction of **1** with *n*-BuLi at low temperature (from −45 to −115 °C) gives mainly deprotonation at the 4-methylene group (>90% yield of methylation product in 95% purity), some (<8%) product of addition to the C=N bond was detected. We surmise that N–O lone pair interaction depresses the electrophilic nature of the 3-C atom, favoring deprotonation.

(8) 50% of the lithiated material reacted at −115 °C within 4 s.

(9) The yield was that of distilled (Kugelrohr) material; purity was established by GC (OV-50, 50-m capillary column). Satisfactory CHN analyses and spectral data (NMR, IR, MS) have been obtained for all new compounds reported.

(10) Szwarc, M. "Ions and Ion Pairs in Organic Reactions; Wiley Interscience: New York, 1972; Volume 1, Chapter 1.