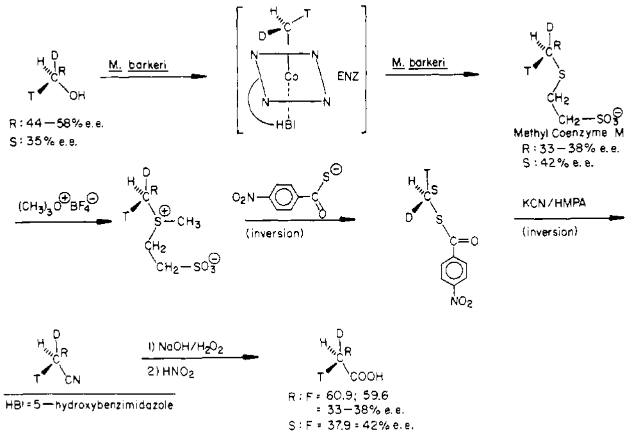
Scheme II. Steric Course of the Enzymatic Synthesis of Methyl Coenzyme M from Methanol and Configurational Analysis of Methyl Coenzyme M



of the methyl group of methyltetrahydrofolate to homocysteine, catalyzed by the B_{12}-dependent methionine synthase from *E. coli*, which we have demonstrated also occurs with net retention of methyl group configuration.[26] Both reactions pose the same question of how a relatively inert bond, the C–O bond of methanol in the present case or the C–N bond of methyltetrahydrofolate in the case of methionine synthase, is cleaved in the transfer of a methyl group.

Acknowledgment. We thank Mrs. Kyungok Lee for chirality analyses of acetate, Dr. Thomas Spratt for the synthesis of some of the intermediates, and the OSU Cancer Center for use of the Radiochemistry Laboratory. Financial support by the National Institutes of Health (research Grant GM 32333 to H.G.F. and postdoctoral fellowship ES05306 to T.M.Z.), the U.S. Department of Energy (Grant DE-ACO2-81ER10945 to J.N.R.), and by Proctor and Gamble (predoctoral fellowship to L.D.Z.) is gratefully acknowledged.

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(25) Floss, H. G.; Tsai, M. D. *Adv. Enzymol.* **1979**, *50*, 243.

(26) Zydowsky, T. M.; Courtney, L. F.; Frasca, V.; Kobayashi, K.; Shimizu, H.; Yuen, L.-D.; Matthews, R. G.; Benkovic, S. J.; Floss, H. G.; *J. Am. Chem. Soc.* **1986**, *108*, 3152.

Low Temperatures Favor Kinetic 1,4- over 1,2-Addition of Organolithiums to α-Enones. The Crucial Role of Ion Pairing[1]

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We present here a straightfoward and theoretically satisfying model which explains and *predicts* the effects of reaction conditions and organolithium structure in promoting the kinetic 1,2- or 1,4-addition to enones.[2,3] The key feature of the model (Scheme I) is a rapid[4] equilibrium between contact ion pairs **1** and solvent-separated ion pairs **2**.[5]

Scheme I

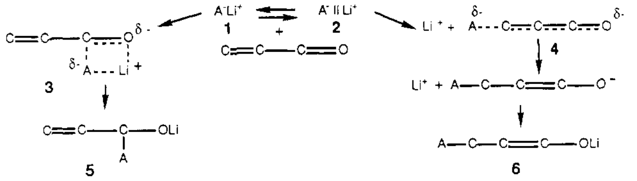

Table I. Conjugative vs 1,2-Addition of **7a–c** (Eq 1) and **10** (Eq 2) in THF

entry	RLi	temp, °C	yields[a] 1,4:1,2
1	**7a**	−100	56:20
2	**7a**	−23	39:32
3	**7a**	10	29:36
4	**7b**	−78	58:4
5	**7c**	−78	58:3
6	**10**	−100	62:35
7	**10**	−78	54:43
8	**10**	−78	59:37[b]
9	**10**	−50	51:47
10	**10**	−50	52:44[c]
11	**10**	0	35:61
12	**10**	−78	44:51[d]
13	**10**[e]	−78	24:47[d,f]
14	**10**	0	81:8[g]
15	**10**	0	31:57[h]

[a] Isolated in entries 4–14; additions to cyclohexenone were exceedingly clean. In entries 1–3, HPLC ratios were determined on isolated binary mixtures. [b] LiI (4 equiv) added. [c] Concentration (0.009 M) 20 times less than in other additions of **10**. [d] THF–pentane 20:3. [e] Potassium analogue.[32] [f] Bis(phenylthio)methane (15 %) recovered. [g] HMPA (4 equiv) present. [h] TMEDA (2 equiv present).

To a first approximation, the contact ion pairs (CIP, **1**) are assumed to undergo only 1,2-addition, which is believed to involve a four-center transition state **3**[6-8] and very low activation energy.[6] Conjugate attack of **1** on enones such as cyclohexenone, which cannot attain a cisoid configuration, requires rupture of the carbon–lithium bond without the energetic compensation arising from simultaneous formation of an oxygen–lithium bond.

Correspondingly, solvent-separated ion pairs (SSIP, **2**) are assumed to undergo only 1,4-addition. Attack of the anion of the SSIP **2** on the 4-position of the enone (directly or via electron transfer[3f]) is more likely than attack at the carbonyl carbon atom. In an early transition state, the position of attack should be determined by the relative magnitudes of the LUMO coefficients at the 4 and 2 carbon atoms[7] and possibly by electrostatic repulsion between the carbonyl oxygen atom and the anionic nucleophile;[9] in acrolein, the 4-carbon atom has the larger LUMO coefficient.[7,10] In a late transition state, the position of attack would be governed

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(1) Taken in part from the Ph.D. Thesis of Michael Myers, Department of Chemistry, University of Pittsburgh, 1987.

(2) Review through 1979: Krief, A. *Tetrahedron* **1980**, *36*, 2531.

(3) Recent work: (a) Otera, J.; Niibo, Y.; Aikawa, H. *Tetrahedron Lett.* **1987**, *28*, 2147. (b) Zervos, M.; Wartski, L.; Seyden-Penne, J. *Tetrahedron* **1986**, *42*, 4963. (c) Ager, D. J.; East, M. B. *J. Org. Chem.* **1986**, *51*, 3983. (d) Binns, M. R.; Chai, O. L.; Haynes, R. K.; Katsifis, A. A.; Schober, P. A.; Vonwiller, S. C. *Tetrahedron Lett.* **1985**, *26*, 1569. (e) Berrada, S.; Metzner, P.; Rakotonirina, R. *Bull. Soc. Chim. Fr.* **1984**, 881. (f) Chung, S. K.; Dunn, L. B. *J. Org. Chem.* **1984**, *49*, 935. (g) Dumont, W.; Luchetti, J.; Krief, A. *J. Chem. Soc., Chem. Commun.* **1983**, 66. (h) Binns, M. R.; Haynes, R. K. *J. Org. Chem.* **1981**, *46*, 3790.

(4) Grutzner, J. B.; Lawlor, J. M.; Jackman, L. M. *J. Am. Chem. Soc.* **1972**, *94*, 2306.

(5) Reviews: (a) Smid, J. In *Ions and Ion Pairs in Organic Reactions*; Szwarc, J., Ed.; Wiley: New York, 1972; Chapter 3. (b) Smid, J. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 112. (c) Müllen, K. *Chem. Rev.* **1984**, *84*, 603. (d) Buncel, E.; Menon, B. In *Comprehensive Carbanion Chemistry: Part A*; Buncel E., Durst, T., Eds.; Elsevier: New York, 1980; Chapter 3. Recent pertinent results: (e) Fraenkel, G.; Hallden-Abberton, M. P. *J. Am. Chem. Soc.* **1981**, *103*, 5657. (f) Seebach, D.; Gabriel, J.; Hassig, R. *Helv. Chim. Acta* **1984**, *67*, 1083.

(6) (a) Kaufmann, E.; Schleyer, P. R.; Houk, K. N.; Wu, Y.-D. *J. Am. Chem. Soc.* **1985**, *107*, 5560. (b) Bachrach, S. M.; Streitwieser, A., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 3946.

(7) Lefour, J.-M.; Loupy, A. *Tetrahedron* **1978**, *34*, 2597, and citations therein.

(8) There is some evidence that when there is no vacant coordination site on the metal, 1,2-addition of its ligand is inhibited leading to 1,4-addition: Gammill, R. B.; Sobieray, D. M.; Gold, P. M. *J. Org. Chem.* **1981**, *46*, 3555. Sworin, M.; Neumann, W. L. *Tetrahedron Lett.* **1987**, *28*, 3217.

(9) (a) Loupy, A.; Lefour, J.-M.; Deschamps, B.; Seyden-Penne, J. *Nouv. J. Chim.* **1980**, *4*, 121. (b) Zervos, M.; Wartski, L *Tetrahedron Lett.* **1986**, *27*, 2985.

(10) Houk, K. N.; Strozier, R. W. *J. Am. Chem. Soc.* **1973**, *95*, 4094.

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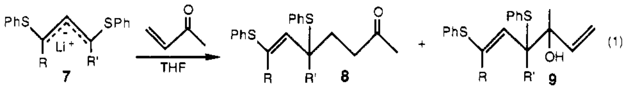
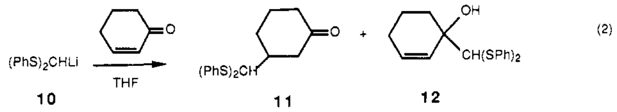
by the relative stabilities of an enolate anion and an unconjugated oxyanion; the former is clearly more stable.[11,12]

The known facts[2,3] that are rationalized by the scheme are the promotion of conjugate addition by (1) increased delocalization of the charge on the nucleophile, (2) increased size of the nucleophile, and (3) increased solvent polarity, including the addition of hexamethylphosphoric triamide (HMPA); all favor SSIP.[5,14] Scheme I leads to the following predictions: (1) Lower temperatures, which strongly favor SSIP,[5,16] should promote conjugate addition;[17] the opposite prediction has been made.[2] (2) Despite the effect of HMPA in promoting conjugate addition, tetramethylethylenediamine (TMEDA), another strong complexing agent for lithium cations,[18] should *not* have this effect since this additive is ineffective at separating CIP,[5a,b,15a,b] presumably because of the difficulty in accommodating two TMEDA molecules, with their eight methyl groups, around a lithium ion.[19] (3) The replacement of a lithium by a potassium counterion will favor 1,2-addition since this change of cations shifts the ion pair equilibrium $\mathbf{1} \rightleftharpoons \mathbf{2}$ to the left;[5] however, this prediction is less certain than the other two since the effect of replacement of Li^+ by K^+ in **1** could alter the rate of **1** (K^+) → **5** (K^+) in an unknown way.

As expected,[20] we have found that a number of sulfur-stabilized organolithium compounds add primarily in a conjugate fashion to enones in THF.[21] Those of our examples which give a competitive degree of 1,2-addition are shown in eq 1 and 2 and Table I. It is clear that the products are formed under kinetic control.



a R=R'=H[22] **b** R=R'=$(CH_2)_3$[22] **c** R=PhS; R'=H[23]



In the case of entry 7, it was demonstrated that the product composition did not vary with time, while in that of entry 1, it did not vary when the product mixture was warmed to 0 °C. More convincing evidence is that the lithio derivatives of the 1,2-adducts, **9a** and **12** (in the latter case, in the presence and absence of HMPA), are stable at the highest temperatures at which the additions were studied.

The previously mentioned known facts 1, 2, and 3 are in evidence in Table I (compare entries 1 and 2 with 5 and 4, 7 with 12, and 11 with 14). The predictions concerning the effects of temperature,[24] TMEDA compared to HMPA as additive,[25] and replacement of Li^+ with K^+[26] are also validated. It is unlikely that the temperature effect is caused by a change in relative rates of **1** → **5** and **2** → **6** since the very low activation energy[14] of the former assures a negligible rate decrease upon cooling. Nor is it likely that this effect is caused by a change in the state of aggregation (lower temperatures favor less aggregation[27]) since the product ratio is independent of concentration (entries 9 and 10). Finally, the insensitivity of the product ratio to added LiI (entries 7 and 8) shows that coordination of *external* lithium ion with the carbonyl oxygen does not occur.

The role of CIP and SSIP has not been cited previously in explanation of the 1,2/1,4 competition in organolithium addition to enones except for the result of HMPA addition,[14] nor was it mentioned in the only review on this subject.[2] The widely promoted concept[28] that soft nucleophiles tend to attack the 4-position, which has a larger LUMO coefficient than the 2-position, may still play a role in influencing the product distribution by affecting the rate of **2** → **4**.

The state of ion pairing undoubtedly also affects the product distribution of other reactions,[29] and the effect of temperature and of TMEDA vs HMPA should be valuable probes.[31] In a subsequent report, it will be demonstrated that this type of analysis readily rationalizes the regiochemistry of attack of carbonyl compounds on the lithio derivatives of allyl phenyl sulfides.

Acknowledgment. We thank the National Institutes of Health for financial support and Dr. Alvin Marcus for recording the mass spectra.

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(11) (a) If, as is likely, $\mathbf{1} \rightleftharpoons \mathbf{2}$ is faster than **1** → **5** and **2** → **6**, the Curtin–Hammett principle would allow an analysis on the basis of the energies of the two transition states, **3** and **4**. However, our considerable knowledge of ion pair equilibria, of attack of organolithium ion pairs on carbonyl groups, and of attacks of anions on enones makes the present analysis more easily applicable.

(12) In this first paper, only organolithiums in which the negative charge is expected to reside primarily on carbon are considered; α-lithiosulfoxides and -nitriles and lithium enolates present complications[13] due to uncertainties as to the position of the lithium ion. We also shall not deal with the well-known use of organocopper nucleophiles: Erdik, E. *Tetrahedron* **1984**, *40*, 641.

(13) (a) Stork, G.; Maldonado, L. *J. Am. Chem. Soc.* **1974**, *96*, 5272. (b) Binns, M. R.; Chai, O. L.; Haynes, R. K.; Katsifis, A. A.; Schober, P. A.; Vonwiller, S. C. *Tetrahedron Lett.* **1985**, *26*, 1569. (c) Chassaing, G.; Marquet, A. *Tetrahedron* **1978**, *34*, 1399. (d) Hünig, S.; Wehner, G. *Chem. Ber.* **1980**, *113*, 302. (e) Bürstinghaus, R.; Seebach, D. *Chem. Ber.* **1977**, *110*, 841.

(14) (a) Bryson, who first reported that HMPA allows 1,4-addition of even mildy (by one phenylthio group) stabilized anions, attributed its effect to its ability to cause CIP to convert to SSIP, by now a well-known property of HMPA.[5,15] Dolak, T. M.; Bryson, T. A. *Tetrahedron Lett.* **1977**, 1961. See, also: Wartski, L.; El Bouz, J.; Seyden-Penne, J.; Dumont, W.; Krief, A. *Tetrahedron Lett.* **1979**, 1543. (b) Chalcone appears to be a special case in which HMPA unprecedentedly promotes 1,2-addition of certain organolithiums.[3g]

(15) (a) Abatjoglou, A. G.; Eliel, E. L.; Kuyper, L. F. *J. Am. Chem. Soc.* **1977**, *99*, 8262. (b) Ahmad, N.; Day, M. C. *J. Am. Chem. Soc.* **1977**, *99*, 941. (c) Panek, E. J.; Rodgers, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 6921. (d) Tanaka, J.; Nojima, M.; Kusabayashi, S. *J. Am. Chem. Soc.* **1987**, *109*, 3391.

(16) Gronert, S.; Streitwieser, A., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 7016.

(17) In the case of reversible additions, higher temperatures favor the 1,4-addition product.[2]

(18) Eberhardt, G. G.; Butte, W. A. *J. Org. Chem.* **1964**, *29*, 2928.

(19) Setzer, W. N.; Schleyer, P. R. *Adv. Organomet. Chem.* **1985**, *24*, 353.

(20) Smith, R. A. J.; Lal, A. R. *Aust. J. Chem.* **1979**, *32*, 353.

(21) Cohen, T.; Myers, M., manuscript submitted to *J. Org. Chem.* Myers, M.; Cohen, T., manuscript in preparation.

(22) Cohen, T.; Bennett, D. A.; Mura, A. J., Jr. *J. Org. Chem.* **1976**, *41*, 2506.

(23) Dziadulewicz, E.; Gallagher, T. *Tetrahedron Lett.* **1985**, *26*, 4547.

(24) (a) An unexplained temperature effect similar to that found here has been reported: Ogura, K.; Yamashita, M.; Tsuchihashi, G. *Tetrahedron Lett.* **1978**, 1303. (b) Our result in entry 7 (repeated 3 times) is very different from the NMR value in a recent report in which no temperature effect was found for this reaction.[3c]

(25) Two other reports of the unexplained ineffectiveness of TMEDA in promoting 1,4-additions of organolithiums: ref 3c and Binns, M. R.; Haynes, R. K.; Houston, T. L.; Jackson, W. R. *Tetrahedron Lett.* **1980**, *21*, 573. After submission of our manuscript, R. K. Haynes called our attention to a statement in the Ph.D. Thesis of M. R. Binns (The University of Sidney, 1985) in which a similar explanation of the effect of TMEDA was presented.

(26) (a) Very recently, potassiomethyl isocyanide was reported to give more 1,2-addition to cyclohexenone than the lithio analogue: Westling, M.; Livinghouse, T. *Synthesis* **1987**, 391. (b) The opposite behavior was recently reported for the addition of metallo derivatives of phenylthio(trimethylsilyl)methane to cyclohexenone, but it was not demonstrated that the 1,2-addition is irreversible.[3c]

(27) Seebach, D.; Hässig, R.; Gabriel, J. *Helv. Chim. Acta* **1983**, *66*, 308.

(28) Eisenstein, O.; Lefour, J. M.; Minot, C.; Anh, N. T.; Soussan, G. *C. R. Acad. Sci. Paris Ser. C* **1972**, 1310. Deschamps, B.; Anh, N. T.; Seyden-Penne, J. *Tetrahedron Lett.* **1973**, 527.

(29) (a) Striking examples: ref 14c and Biellman, J. F.; Schmitt, J. L. *Tetrahedron Lett.* **1973**, 4615. (b) This concept, although in a different form, has been invoked in metal hydride chemistry to explain the rates of reduction of carbonyl compounds[7] and the regiochemistry of reduction of enones.[30] In the latter case, the postulation was the opposite of ours, namely that CIP promote 1,4-reduction. In general, it appears that lithium aluminum hydride and related reductions are not closely analogous to alkyllithium additions; in the former case, the metal cation which dissociates in the formation of SSIP is not the same metal atom bearing the ligand that is transferred, and, of course, the charge of the entity bearing this ligand is different in the two types of reactions.

(30) Loupy, A.; Seyden-Penne, J. *Tetrahedron* **1980**, *21*, 1937.

(31) Another would be pressure, an increase of which favors solvent separation.[5]

(32) Schlosser, M.; Strunk, S. *Tetrahedron Lett.* **1984**, *25*, 741.