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Theoretical Studies of the Lithiation of Enamines

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Abstract: In order to probe the origin of regioselectivity of the lithiation of enamines with alkyllithium reagents in hydrocarbon solvents, ab initio calculations were carried out on the reactions of lithium hydride and methyllithium with a series of vinylamines at the 3-21G level. The calculations indicate that the reactions occur via a cyclic transition state in which the base attacks the acidic proton in an almost collinear (anion–proton–base angle = 155–166°) fashion regardless of the ring size. A favorable transition state involves the achievement of both the stereoelectronic requirement for deprotonation and stabilizing coordination of the lithium cation with the base, the nitrogen of the enamine, and the developing anionic center. The rates of deprotonation are dependent upon favorable Li$^+$ coordination, not anion stability. There is good qualitative accord with experimental deprotonation preferences and with ^{13}C spectral changes upon coordination of *n*-BuLi with the enamines.

Regioselective heteroatom-facilitated metalation is rapidly gaining a place in the standard repertoire of the synthetic organic chemist.[1] Mechanistic details of such metalations (β- or orthometalation) have been the subject of considerable interest,[2] beginning with the pioneering work of Gilman,[3] Morton and others,[4] and continuing to the present.[5] While early examples of orthometalation were restricted mostly to aromatic substrates, functionalized olefins have been receiving more attention lately as synthetic reagents.[6] Generally, olefins give products arising from allylic metalation or α-metalation.[1] Recently, Stork has reported the β-lithiation of enamines containing an additional amine or ether moiety by using *t*-BuLi in *hydrocarbon* solvents[7] (Figure 1). Experiments have shown that these metalations are subject to additional steric restrictions not ordinarily observed in deprotonations of similar substrates (e.g., **5**,[6c] **6**,[6f] **8**,[6d] and **9**,[6a] Figure 2) performed in donor (e.g., Et$_2$O, THF, TMEDA) solvents[6] (vide infra).

Enamines of types **1** and **2** were lithiated quantitatively by *t*-BuLi in hexane or cyclohexane.[7a] The dienamines **10a** and **10b** (Figure 2) could only be lithiated to the extent of 75%, regardless of stoichiometry, temperature, or duration of reaction time. The related compound **13** could be lithiated without difficulty. The reaction failed completely in the presence of donor ligands such as THF or TMEDA. Incorporation of additional coordination sites in the enamine moiety (see **12**) also gave negative results.

No β-lithiation is possible if the β-position of the enamine is substituted with a methyl group. Treatment of **3** or **4**, formed by methylation of **1** or **2**, respectively, with *t*-BuLi in hexane resulted in deprotonation of the methyl group to give the expected allylic anions.[8] When the β-methyl group was replaced by an ethyl group (by ethylation of **1** or methylation of **3**), the resulting compounds were not metalated as before: when an α-hydrogen was available (aldehyde-derived enamine) it was removed;[6d] when there was no α-hydrogen available (ketone-derived enamine), the compound was inert. While a *trans*-phenyl group (**2**, R = Ph) did not alter the reactivity pattern (β-lithiation), an additional *cis*-phenyl group (**11a** and **11b**) rendered the compound inert (no α-lithiation). Since **2a** did not equilibrate with lithiated **2b** even at reflux and vice versa,[29] it is safe to say that the lithiation is a kinetic process.

The fact that the lithiations proceed only in hydrocarbon solvent suggests that a *specific* Lewis acid–base interaction is a necessary requirement for deprotonation. This is consistent with quite a number of proposals invoking a *cyclic transition state* to rationalize the observed regiochemistry of such reactions.[9]

In order to understand the transition-state geometries of proton removal, we have undertaken ab initio calculations on the transition structures of hypothetical reactions between LiH and various vinylamines. The modeling of alkyllithium aggregates of solvated species by LiH is, of course, a gross approximation dictated by our desire to carry out these model studies in a reasonable period of time. The major difference between LiH and LiR in calculations is the difference in the Li–base distance (1.6 versus 2.0 Å, respectively, in LiH and LiCH$_3$) and the fact that the interaction of LiH as a Lewis base is nondirectional, while for an alkyl group the basicity is directed along the axis of the hybrid orbital. To overcome the shortcomings of using LiH as a model base, we have performed calculations on selected reactions with LiCH$_3$ as a base. Furthermore, our previous calculations on additions of LiH, LiCH$_3$, and their dimers to alkenes and carbonyl compounds showed that the qualitative features of the angle of attack and metal coordination are similar for these different species.[10] Since solvent interactions are much less energetic in hydrocarbon solvents than in donor solvents, calculations (which do not include the effects of solvation) should more closely mimic these reactions

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(1) (a) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1. (b) Gilman, H.; Morton, J. W., Jr. *Ibid.* **1954**, *8*, 258. (c) Narasimhan, N. S.; Mali, R. S. *Synthesis* **1983**, 957.

(2) (a) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356. (b) Klumpp, G. W. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 1.

(3) (a) Gilman, H.; Young, R. V. *J. Am. Chem. Soc.* **1934**, *56*, 1415. (b) Sunthankar, S. V.; Gilman, H. *J. Org. Chem.* **1951**, *16*, 8.

(4) (a) Conant, J. B.; Wheland, G. W. *J. Am. Chem. Soc.* **1932**, *54*, 1212. (b) McEwen, W. K. *Ibid.* **1936**, *58*, 1124. (c) Morton, A. A. *Chem. Rev.* **1944**, *35*, 1. (d) Roberts, J. D.; Curtin, D. Y. *J. Am. Chem. Soc.* **1946**, *68*, 1658. (e) Morton, A. A. *Ibid.* **1947**, *69*, 969. (f) Morton, A. A.; Cluff, E. F. *Ibid.* **1952**, *74*, 4056.

(5) (a) Comins, D. L.; Killpack, M. O. *J. Org. Chem.* **1987**, *52*, 104. (b) Feit, B. A.; Haag, B.; Schmidt, R. R. *Ibid.* **1987**, *52*, 3825.

(6) (a) Baldwin, J. E.; Hofle, G. A.; Lever, O. W., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 7125. (b) Schmidt, R. R. *Organic Synthesis: an Interdisciplinary Challenge* (Proceedings *of the 5th IUPAC Symposium on Organic Synthesis* Streith, J., Prinzbach, H., Schil, G. Eds.; Blackwell Scientific Publications: Oxford, 1985; p 281. (c) McDougal, P. G.; Rico, J. G. *Tetrahedron Lett.* **1984**, 5977. (d) Bates, R. B.; Beavers, W. A.; Blacksber, I. R. *Abstr. Pap. Am. Chem. Soc.* **1975**, 169th National Meeting of the ACS, Philadelphia, Pennsylvania. (e) Bibang, C.; Ekogha, B.; Ruel, O.; Julia, S. A. *Tetrahedron Lett.* **1983**, 4825. (f) Beak, P.; Kempf, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 4550. (g) Brandsma, L.; Verkruijsse, H. *Preparative Polar Chemistry*; Springer Verlag: Berlin, 1987; Vol. 1. (h) Eyer, M.; Seebach, D. J. *J. Am. Chem. Soc.* **1985**, *107*, 3601 and references 10 and 13 therein.

(7) (a) Stork, G.; Shiner, C. S.; Cheng, C. W.; Polt, R. L. *J. Am. Chem. Soc.* **1986**, *108*, 304. (b) Polt, R. L.; Stork, G.; Williard P. G.; Carpenter, G. B. *Ibid.* **1984**, *106*, 4276. (c) Polt, R. L. Thesis, Columbia University, 1986. (d) Cheng, Che-Wen, Thesis, Columbia University, 1981.

(8) (a) Ahlbrecht, H. *Chimia* **1977**, *31*, 391. (b) Julia, M.; Schouteeten, A.; Baillarge, M. M. *Tetrahedron Lett.* **1974**, 3433. (c) Evans, D. A.; Mitch, C. H.; Thomas, R. C.; Zimmerman, D. M.; Robey, R. L. *J. Am. Chem. Soc.* **1980**, *102*, 5955.

(9) See ref 1–4 for the development of this idea. (a) Hartmann, J.; Schlosser, M. *Helv. Chim. Acta* **1976**, *59*, 453. (b) Schlosser, M. *Struktur und Reactivität polarer Organometalle*; Springer Verlag: Berlin, 1973. (c) Beak, P.; Hunter, J. E.; Jun, Y. M. *J. Am. Chem. Soc.* **1983**, *105*, 6350.

(10) (a) Kaufmann, E.; Schleyer, P. v. R.; Houk, K. N.; Wu, Y. D. *J. Am. Chem. Soc.* **1985**, *107*, 5560. (b) Houk, K. N.; Rondan, N. G.; Schleyer, P. v. R.; Kaufmann, E.; Clark, T. *Ibid.* **1985**, *107*, 2821.

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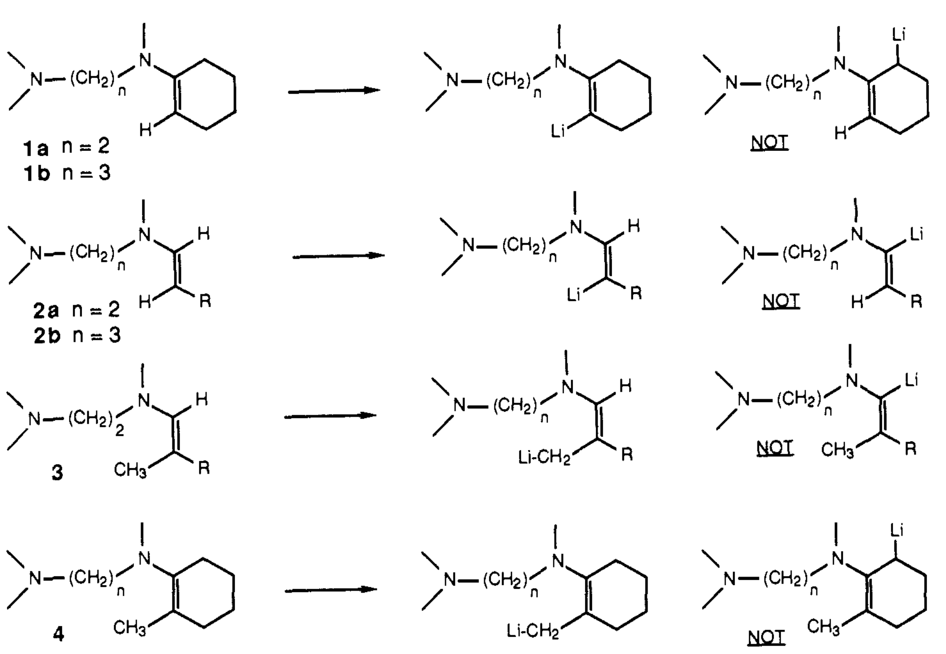

Figure 1. Regioselective lithiation reactions of enamines with *t*-BuLi in hydrocarbon solvent.

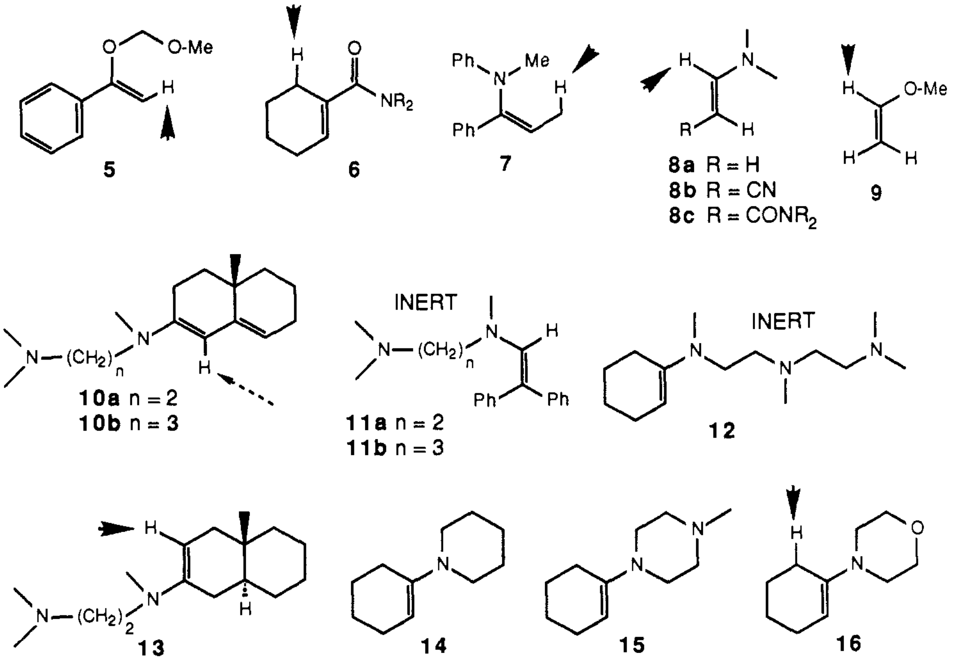

Figure 2. Examples of regioselective lithiation of heteroatom-substituted olefins; the positions of deprotonation are indicated by arrows.

than in the case of donor solvents.

Computational Method. Ab initio molecular orbital calculations were carried out with the restricted Hartree–Fock (RHF) theory and the 3-21G basis set using the GAUSSIAN 82 series of programs.[11] Analytical second derivative calculations were employed to locate the minima and saddle points on the reaction potential surface.

This theoretical model has been widely used in studying various reactions.[12] However, the incorporation of diffuse functions in the basis set is found to be necessary for adequate description of anionic moelcules.[12] In addition, as a consequence of basis set inadequacies, the stabilities of lithium bridging compounds are overestimated in the absence of a set of diffuse s and p functions on carbon.[13] Unfortunately, the addition of diffuse functions significantly raises the computational cost, and a compromise between accuracy and feasibility has to be made in this study. The geometries optimized for the neutral species in our studies are expected to be reasonably reliable at the 3-21G level. Single point calculations at the MP2/6-31G* level[11c] were carried out on the selected species, which indicates that the calculated relative energies at the 3-21G level are unchanged upon higher level calculations.

Complexation of Enamines with Alkyllithium. Reactions involving alkyllithiums are complicated by aggregation phenomena and solvent interactions. Nevertheless, as a first step in modeling such processes, the reactions of vinylamine with monomeric LiH were studied using the RHF theory. The relative energies of the complexes of $CH_2{=}CH{-}NH_2$ with LiH and the optimized ge-

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[11] (a) Binkley, J. S.; Whiteside, R. A.; Krishnan, R.; Seeger, R.; DeFrees, D. J.; Schlegel, H. B.; Topiol, S.; Kahn, L. R.; Pople, J. A. GAUSSIAN 80, Quantum Chemistry Program Exchange, No. 406; Indiana University: Bloomington, IN. GAUSSIAN 82, Carnegie-Mellon University: Pittsburgh, PA. (b) Binkley, J. S.; Pople, J. A.; Hehre, W. J. *J. Am. Chem. Soc.* **1980**, *102*, 939. (c) Moller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *64*, 618.

[12] Hehre, W. J.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.

[13] (a) Kaneti, J.; Schleyer, P. v. R.; Clark, T.; Kos, A. J.; Spitznagel, G. W.; Andrade, J. G.; Moffat, J. B. *J. Am. Chem. Soc.* **1986**, *108*, 1481. (b) Wurthwein, E. U.; Sen, K. D.; Pople, J. A.; Schleyer, P. v. R. *Inorg. Chem.* **1983**, *22*, 496.

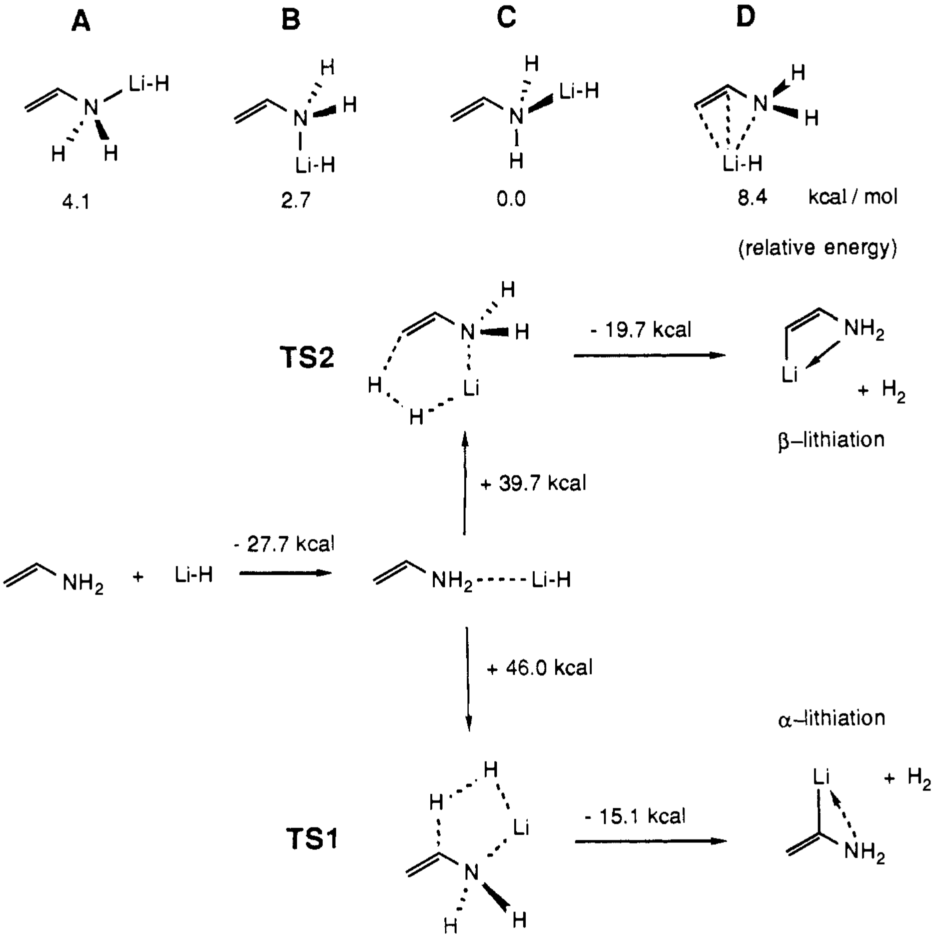

Figure 3. Relative energies (kcal/mol) and the geometries of the complexes of vinylamine with LiH (distances in Å, angles in deg).

ometries are shown in Figure 3. In addition, complexes of both simple and chelating enamines with *n*-BuLi in cyclohexane-d_6 were examined using ^{13}C NMR in an effort to discern the nature of the lithiation mechanism. The less reactive *n*-BuLi complexes were used because, unlike the *t*-BuLi complexes, they did not undergo fast metalation in this solvent.

The complexation of LiH with vinylamine is calculated to be stabilizing by 28 kcal/mol at the 3-21G level, which is of the same order as the calculated complexation energy of formaldehyde with LiH (29 kcal/mol). The rotational barrier around the C–N bond is lowered by 5 kcal/mol upon the coordination of the nitrogen atom by lithium, as expected, due to the removal of the nitrogen lone pair from conjugation. The conformations that are necessary for the intramolecular α-lithiation (A) and β-lithiation (B) are only 3 and 4 kcal/mol higher, respectively, than the most stable conformation C, while the barrier for the rotation around the C–N bond in vinylamine is ~8 kcal/mol at the same level. The coordination of the enamine nitrogen with Li^+ clearly reduces the extent of conjugation between the occupied lone-pair orbital and the π-system. This is further manifested in the shortening of the CC double bond and lengthening of the C–N bond upon complexation.

Coordination of LiH with the π-system[14] of vinylamine (D) is less favorable by 8 kcal/mol as compared with A. This is reasonable, since the coordination of Li^+ with NH_3 is calculated to be exothermic by 39 kcal/mol, while the coordination of Li^+ with ethylene is calculated to be exothermic by only 18 kcal/mol. These calculated values correspond well to experimental values obtained by ion-cyclotron resonance measurements.[15] Earlier calculations performed at the STO-3G level on 7-lithionorbornadiene indicate that π-Li^+ interactions can be quite substantial when the geometry is ideal.[14e]

Several groups have used ^{13}C NMR to examine olefin complexes with *transition metals*.[16] Transition metal–olefin interactions involve metal d-orbital to olefin back-bonding. In some instances this is the dominant mechanism of coordination. Consequently, all the complexes studied to date show an upfield shift (lower δ) due to *increased* electron density on the carbons. Chemical shifts in the olefinic carbon resonances are believed to correlate well with electron density on those carbons in enamines and other heteroatom substituted alkenes.[17] Proton shifts,[14c] on the other hand, are very susceptible to anisotropic effects and, hence, difficult to ascribe to any particular molecular features or specific interactions. The best analogy to Li^+ which has been studied is Ag^+, which generally shows relatively small (~5 ppm) upfield shifts.

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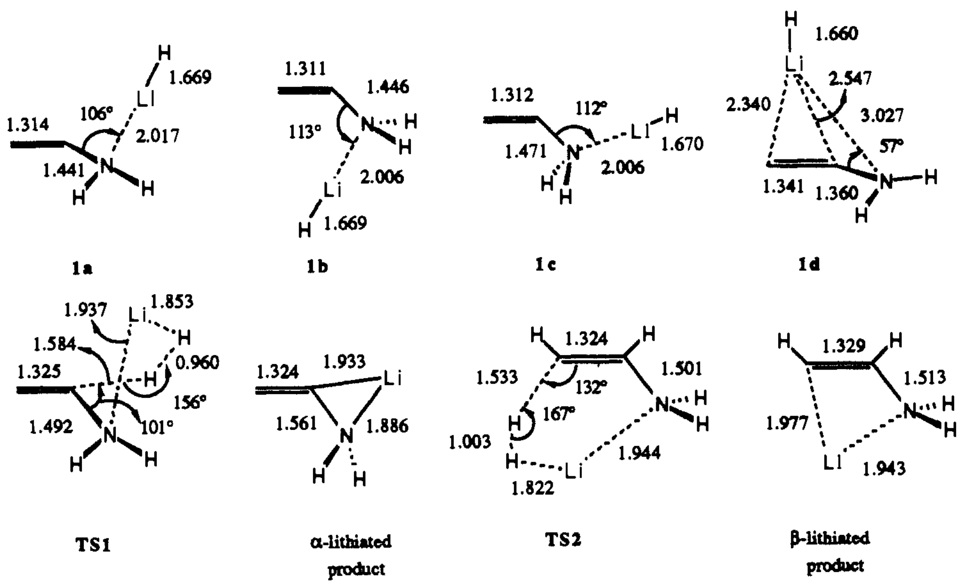
(14) There is a good deal of evidence, both theoretical and experimental, for such interactions. For example: (a) Jemmis, E. D.; Chandrasekhar, J.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1979**, *101*, 2848, and references therein. (b) Posner, G. H.; Lentz, C. M. *Ibid.* **1979**, *101*, 934. (c) Oliver, J. P.; Smart, J. B.; Emerson, M. T. *Ibid.* **1966**, *88*, 4101. (d) Staley, R. H.; Beauchamp, J. L. *Ibid.* **1975**, *97*, 5920. (e) Nagase, S.; Houk, K. N. *Tetrahedron Lett.* **1982**, 19. (f) Winkle, M. R.; Ronald, R. C. *J. Org. Chem.* **1982**, *47*, 2101. (g) Ronald, R. C.; Winkle, M. R. *Tetrahedron* **1983**, *39*, 2031. (h) Shirley, D. A.; Hendrix, J. P. *J. Organomet. Chem.* **1968**, *11*, 217. (i) Del Bene, J. E.; Frisch, M. J.; Raghavachari, K.; Pople, J. A.; Schleyer, P. v. R. *J. Phys. Chem.* **1983**, *87*, 73.

(15) Staley and Beauchamp obtained values of 38 kcal/mol for NH_3-Li^+ and 24 kcal/mol for CH_2CHCH_3-Li^+, ±2 kcal/mol. The value for propene is expected to be higher than the value for ethylene due to the methyl substitution. See ref 14d.

(16) (a) Parker, R. G.; Roberts, J. D. *J. Am. Chem. Soc.* **1970**, *92*, 743. (b) Olah, G. A.; Clifford, P. R. *Ibid.* **1973**, *95*, 6067. (c) Chisholm, M. H.; Godleski, S. *Prog. Inorg. Chem.* **1976**, *20*, 299. (d) Lewandos, G. S.; Gregston, D. K.; Nelson, F. R. *J. Organomet. Chem.* **1976**, *118*, 363. (e) Laycock, D. E.; Baird, M. C. *Inorg. Chim. Acta* **1980**, *40*, 263.

(17) (a) Bedford, G. R.; Taylor, P. J. *Org. Magn. Reson.* **1977**, *9*, 49. (b) Ahmed, M. G.; Hickmott, P. W. *J. Chem. Soc., Perkin Trans. 2* **1977**, 838. (c) Udlund, U. *Chim. Scr.* **1975**, *7*, 85. (d) Tourwe, D.; VanBinst, G.; DeGraaf, S. A. G.; Pandit, U. K. *Org. Magn. Reson.* **1975**, *7*, 433. (e) For an explanation of inductive (I) vs mesomeric (M) effects, see: Clark, D. T.; Murrell, J. N.; Tedder, J. M. *J. Chem. Soc.* **1963**, 1250.



1a **1b** **1c** **1d**

TS1 **α-lithiated product** **TS2** **β-lithiated product**

Figure 4. The 3-21G energetics (kcal/mol) and the optimized geometries of reactant complexes, transition structures, and products for the reactions of vinylamine with LiH (distances in Å, angles in deg).

Since it has little electron density and no occupied d-orbital to use in back-bonding, Li^+ would not be expected to engage in back-bonding, and would be expected to show small *downfield* shifts (higher δ). It should be noted, however, that attempts to rationalize ^{13}C shifts in terms of one factor alone (e.g., relative strengths of σ- and π-bonding or relative charge densities) may not be justified.[16e]

Experimentally, one finds a correlation between the induced chemical shifts (Δδ) of the enamine carbons upon complex formation with *n*-BuLi and the metalation behavior of the enamine.[7c] Whereas the simple piperidine enamine of cyclohexanone, **14** (Figure 2), shows almost no change upon complexation (no lithiation), the corresponding piperazine analogue **15**, shows a strong interaction (allylic lithiation upon certain conditions),[18] and the ethylenediamine enamine, **1a**, is stronger yet (facile β-lithiation). The studies show that the β-carbon of the enamine is most affected by complexation, moving downfield 0.4–2.0 ppm relative to the uncomplexed enamine. The α-carbon, on the other hand, shows almost no change, moving downfield a scant 0.2 ppm. The calculated atomic charge density of the β-carbon changes from −0.52 e in vinylamine to −0.46 e in the N-complex C, and to −0.64 e in the π-complex D, according to a Mulliken population analysis. The calculated density for the α-carbon changes from 0.13 e in vinylamine to 0.01 e in the N-complex C, and to 0.14 in the π-complex D. Thus, according to the calculation, the β-carbon becomes more positive, and the α-carbon becomes less positive upon formation of the N-complex. Assuming that the chemical shifts roughly parallel the charge densities, the experimental ^{13}C results are most consistent with this interpretation (σ-complex). These results suggest that the N-complex C predominates in solution, in accord with the calculations.

Lithiation of Vinylamine by LiH. The transition structures for deprotonation were located by starting with complex A and B and gradually shortening the distance from hydride to the proton being removed, while optimizing all other geometrical features. At the maximum found by this procedure, a stationary point was located with analytical gradient techniques. The transition structure corresponding to the saddle point was characterized by calculations of vibrational frequencies. Each of the transition structures has lithium coordinated to both the nitrogen and the hydride base. The transition structure for α-lithiation with planar symmetry (C_s) constraints has two imaginary vibrational frequencies, one of which is 1473.8i cm^{-1} and the other 153.0i cm^{-1}. The latter corresponds to the motion of the Li–H moiety out of the plane. A more realistic transition structure (3.3 kcal/mol lower in energy) was obtained by removing the C_s symmetry constraints.

The transition structure for β-lithiation has C_s symmetry and has only one imaginary vibrational frequency, which corresponds to the normal mode of movement along to reaction pathway for deprotonation. It is probable that this C_s symmetry would be disturbed to some extent in the actual complex due to aggregation of the *t*-BuLi. No other possible transition structures were examined. The reaction energetics and the optimized geometries for the reactions of vinylamine with LiH are shown in Figure 4.

The activation energy barrier for α-lithiation (TS1, Figure 4) was calculated to be 46 kcal/mol, starting from the complex, or 18 kcal/mol from the isolated reactants. This is 6 kcal/mol higher than the barrier calculated for β-lithiation (TS2). RHF calculations with the 3-21G basis set generally provide reliable geometries for the transition structures, but may not provide a reliable prediction on the energies of the transition structures. In order to establish confidence on the calculations at this level, single point calculations at the MP2/6-31G* level were carried out for the transition structures TS1 and TS2. The transition structure TS1 is calculated to be 5.2 kcal/mol higher in energy than TS2 at the MP2/6-31G* level (6.6 kcal/mol at the RHF/6-31G* level), which indicates that relative energies calculated at the RHF/3-21G level are fairly reliable.

As shown in Figure 4, the breaking C–H bonds in the transition structures are in the range of 1.53–1.58 Å, about 50% stretched. The forming H–H bonds are around 1.0 Å, appreciably stretched from the equilibrium H–H bond length of 0.76 Å. The attack angles (H–H–C) on the protons are 155° and 166° for α- and β-deprotonation, respectively. These results support the hypothesis[3,19,26] that a colinear arrangement (anion–proton–base) is preferred for such reactions. In order to approach this C–H–H angle in the transition structure for α-lithiation (five-membered ring), the N–C⋯H bond angle is deformed nearly 20° as compared with the reactant complex. With the C–H–H angle of 155–165° in a cyclic transition state, the transition structure for β-lithiation (six-membered ring) is likely less constrained than the transition structure for α-lithiation. Thus, a lower reaction barrier is observed for β-lithiation.

Our calculations predict that the β-lithio product is thermodynamically more stable than the α-lithio product, by 11 kcal/mol. This is consistent with Schmidt's experimental observations for β-aminoacrylates as well as his calculations using the semiempirical MINDO/3 method and ab initio calculations with the STO-3G

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(18) Inagaki, S.; Iwase, K.; Goto, N. *J. Chem. Soc., Perkin Trans. 2* **1984**, 2019.

(19) Stewart, R. *The Proton: Application to Organic Chemistry*; Academic Press: New York, 1985.

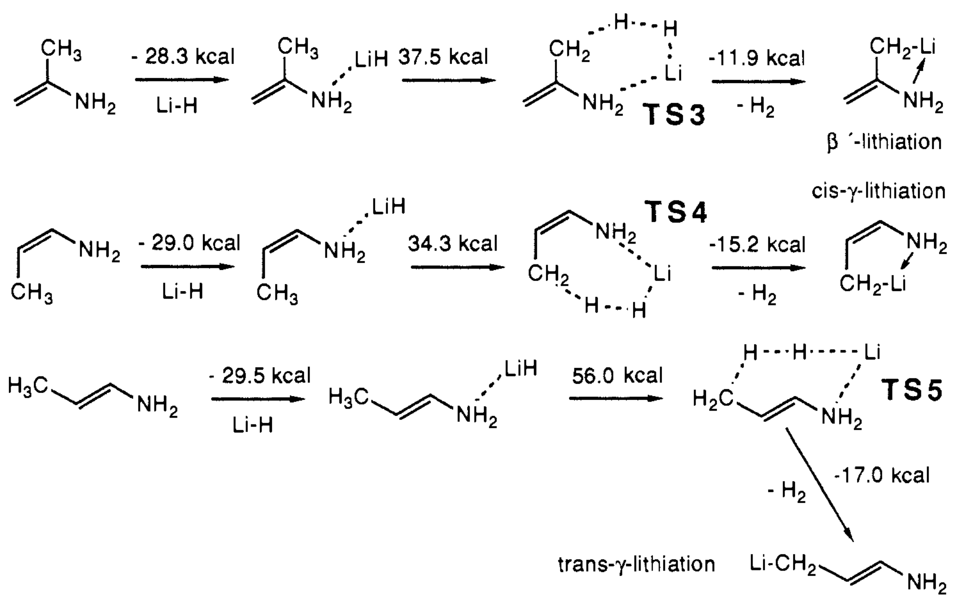

Figure 5. The 3-21G energetics (kcal/mol) for the reactions of methyl-substituted enamines with LiH.

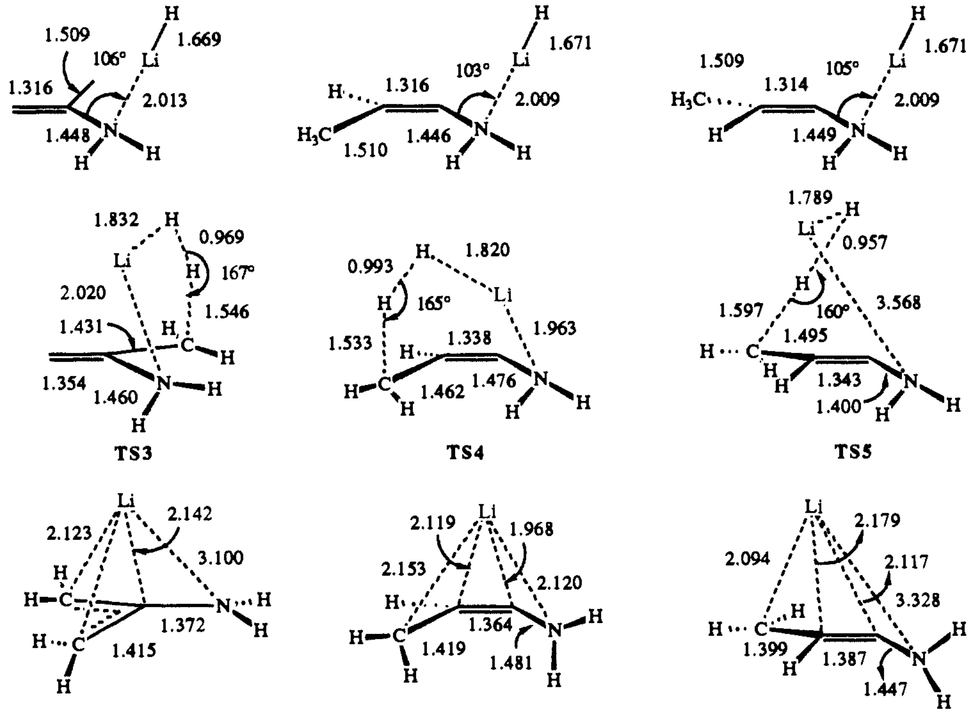

Figure 6. The 3-21G optimized geometries of reactant complexes, transition structures, and products for the reactions of methyl-substituted enamines with LiH (distances in Å, angles in deg).

and 4-31G basis sets.[20] In contrast, the planar carbanion product (no metal) of β-deprotonation is calculated to be 15 kcal/mol less stable than the free carbanion arising from α-deprotonation. This difference in stabilities shows that the factors which determine the stabilities are not the same in the two cases. Presumably a favorable coordination geometry is the predominant effect in the case of lithiated species, whereas the inductive effect determines the stabilities of the free carbanions.

Lithiation of CH_2═$C(CH_3)NH_2$ and CH_3CH═$CHNH_2$ with LiH. The calculated energetic profiles of these reactions are shown in Figure 5. Figure 6 shows the optimized geometries for the reactant complexes, transition structures, and products.

The complexation energies between the enamines and LiH were calculated to be 29 kcal/mol. The calculated reaction barrier of β′-lithiation (TS3) is 38 kcal/mol (or 9 kcal/mol from the isolated reactants), which is some 2 kcal/mol lower than that for β-lithiation. Both the breaking C–H bond and the forming H–H bond in TS3 are in the same range as the previous cases (i.e., product-like). The C–H–H angle is 165°, very similar to that found for β-lithiation. The α-carbon is substantially pyramidal, to accommodate the departure of the proton and arrival of the Li. The favorable transition structure requires the breaking C–H bond to be nearly perpendicular to the plane of the enamine. It may be difficult for compounds such as **1** to achieve this conformation, owing to the constraints imposed by the cyclohexane ring. Consequently, β-lithiation may be preferred over β′-lithiation in these cases.

Although the β′-lithiation is predicted to be a kinetically more favorable process than the β-lithiation, the β-lithio product is more stable than the β′-lithio product by 3.5 kcal/mol. The calculations indicate that allyllithium is 18 kcal/mol more stable than vinyllithium, which is parallel to the stabilities of the free carbanions.[12,21] In the case of lithiated enamines, however, the

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(20) Schmidt, R. R.; Talbiersky, J.; Russegger, P. *Tetrahedron Lett.* **1979**, 4273.

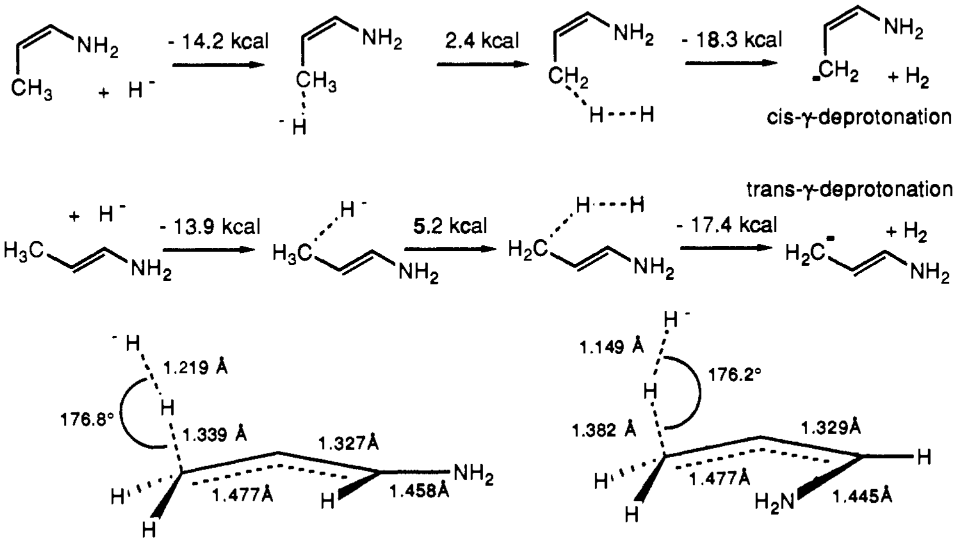
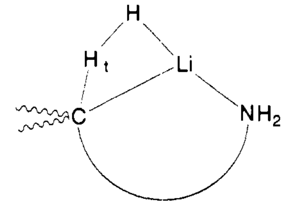


Figure 7. Energetics for the reactions of methyl-substituted enamines with hydride anion (kcal/mol).

stabilities of the allylic product do not parallel the stabilities of the corresponding carbanions. As expected, the allylic carbanion from β′-deprotonation is calculated to be 16 kcal/mol more stable than the vinylic carbanion from β-deprotonation. The fact that the β′-lithio product is less stable than the β-lithio product can be attributed to the poor coordination of the lithium cation with the nitrogen atom which is ~3.1 Å away in the β′-species. In fact, by using a chelating enamine substrate, Inagaki has provided an example of such a β′-lithioenamine (**16**, Figure 2), but successful preparation requires a strongly coordinating solvent (TMEDA in THF) in order to stabilize the allylic anion.[18] Interestingly, the Inagaki study addresses the question of β′- versus γ-deprotonation without considering the possibility of β-lithiation.

The calculated reaction barrier for the cis-γ-lithiation is 34 kcal/mol, which is lower than the barrier for β′-lithiation and trans-γ-lithiation. The kinetically preferred cis-γ-metalation product is also thermodynamically most stable. Experimentally, vinylic- to allylic-carbanion rearrangements are not always fast, even when the allylic species is much more stable.[22] Knorr has determined the activation parameters for this rearrangement and has found that $\Delta S^{\ddagger}$ is large and negative[23] no doubt an expression of the reorganization in the solvent sphere required for such a reaction. A large, negative $\Delta S^{\ddagger}$ is typical for reactions of organolithiums[24] which are highly aggregated and dominated by the energy of solvation.[25]

In order to learn more about the crucial effect of the complexation on the regioselectivities, it was of interest to compare these results with those obtained from the calculations on the deprotonation of *cis*- and *trans*-CH_3—CH=CH—NH_2 with free H^- (Figure 7). Hydride forms a stable ion–molecule complex with both *cis*- and *trans*-1-aminopropene. The reaction barriers from these complexes to the corresponding cis- and trans-γ-allylic carbanions (no metal) were calculated to be only 2.4 and 5.2 kcal/mol, respectively. The cis-γ-deprotonation is easier and the product is more stable because of stabilization of the carbanion by hydrogen bonding to the *cis*-amino group hydrogens. When the Li^+ complexation was included (Figure 5), the calculated cis preference increase to about 20 kcal/mol for both activation energy and product stability. The interaction between the lithium reagent and the enamine nitrogen is the predominant factor controlling the regioselectivity and stereoselectivity of the reaction.



	TS1	TS2	TS3	TS4	TS5
C H_t H	155.5°	166.5°	166.5°	165.2°	160.1°
H_t H Li	70.2°	65.9°	79.1°	68.8°	65.7°
H_t C Li	55.7°	50.3°	46.9°	50.1°	50.0°
C H_t	1.58Å	1.53Å	1.55Å	1.53Å	1.60Å
H H_t	0.96Å	1.00Å	0.97Å	0.99Å	0.96Å
C Li	2.10Å	2.20Å	2.60Å	2.30Å	2.10Å
N Li	1.90Å	1.90Å	2.00Å	2.00Å	3.60Å

Figure 8. Summary of geometric features for the transition structures of the reactions of LiH with enamines (distances in Å, angles in deg).

It is interesting that the C–H–H attack angles are in the range of 155–166°, which are quite insensitive to the ring size of the cyclic transition structures. In the transition structure for trans-γ-lithiation, the N–Li distance was calculated to be 3.6 Å, which indicates that N–Li coordination is sacrificed to maintain the proper C–H–H attack angle. When there were no cyclic constraints, the C–H–H angles were calculated to be around 180° as shown in the transition structures for the reactions of enamines with hydride anion. Menger[27] has shown experimentally that base–proton–carbanion angles can be as low as 100° for systems with alkoxide bases, but it is not clear that carbanion bases behave similarly owing to the much higher intrinsic barriers for proton transfers between carbon atoms. Our calculations on the metalation using LiH as a base revealed that all of the transition

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(21) (a) Schleyer, P. v. R.; Clark, T.; Kos, A. J.; Spitznagel, G. W.; Rohde, C.; Arad, D.; Houk, K. N.; Rondan, N. *J. Am. Chem. Soc.* **1984**, *106*, 6467. (b) Schleyer, P. v. R.; Kaufmann, E.; Spitznagel, G. W.; Janoschek, R.; Winkelhofer, G. *Organometallics* **1986**, *5*, 79. (c) Lindh, R.; Roos, B. O.; Jonsall, G.; Ahlbery, P. *J. Am. Chem. Soc.* **1986**, *108*, 6554.

(22) (a) Finnegan, R. A. *Tetrahedron Lett.* **1962**, 429. (b) Hunter, D. H.; Cram, D. J. *J. Am. Chem. Soc.* **1964**, *86*, 5478. (c) Broaddus, C. D.; Muck, D. L. *Ibid.* **1967**, *89*, 6533. (d) Fristad, W. E.; Han, Y. K.; Paquette, L. *J. Organomet. Chem.* **1979**, *174*, 27.

(23) Knorr, R.; Lattke, E. *Tetrahedron Lett.* **1977**, 4655.

(24) (a) Quirk, R. P.; Kester, D. E.; Delaney, R. D. *J. Organomet. Chem.* **1973**, *59*, 45. (b) Quirk, R. P.; Kester, D. E. *Ibid.* **1974**, *72*, C23. (c) Heinzer, J.; Oth, J. F. M.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1848.

(25) (a) Weiner, M. A.; West, R. *J. Am. Chem. Soc.* **1963**, *85*, 485. (b) Brown, T. L. *Acc. Chem. Res.* **1968**, *1*, 23. (c) McKeever, L. D.; Waack, R. *J. Chem. Soc., Chem. Commun.* **1969**, 750. (d) Seebach, D.; Hassig, R.; Gabriel, J. *Helv. Chim. Acta* **1983**, *66*, 305. (e) Fraenkel, G.; Henrichs, M.; Hewitt, M.; Su, B. M. *J. Am. Chem. Soc.* **1984**, *106*, 255. (f) McGarrity, J. F.; Ogle, C. A. *Ibid.* **1985**, *107*, 1805. (g) McGarrity, J. F.; Ogle, C. A.; Brich, Z.; Loosli, H. R. *Ibid.* **1985**, *107*, 1810.

(26) Scheiner, S. *Acc. Chem. Res.* **1985**, *18*, 174.

(27) (a) Menger, F. M.; Chow, J. F.; Kaiserman, H.; Vasquez, P. C. *J. Am. Chem. Soc.* **1983**, *105*, 4996. (b) Also see: Gandour, R. D. *Tetrahedron Lett.* **1974**, 295.

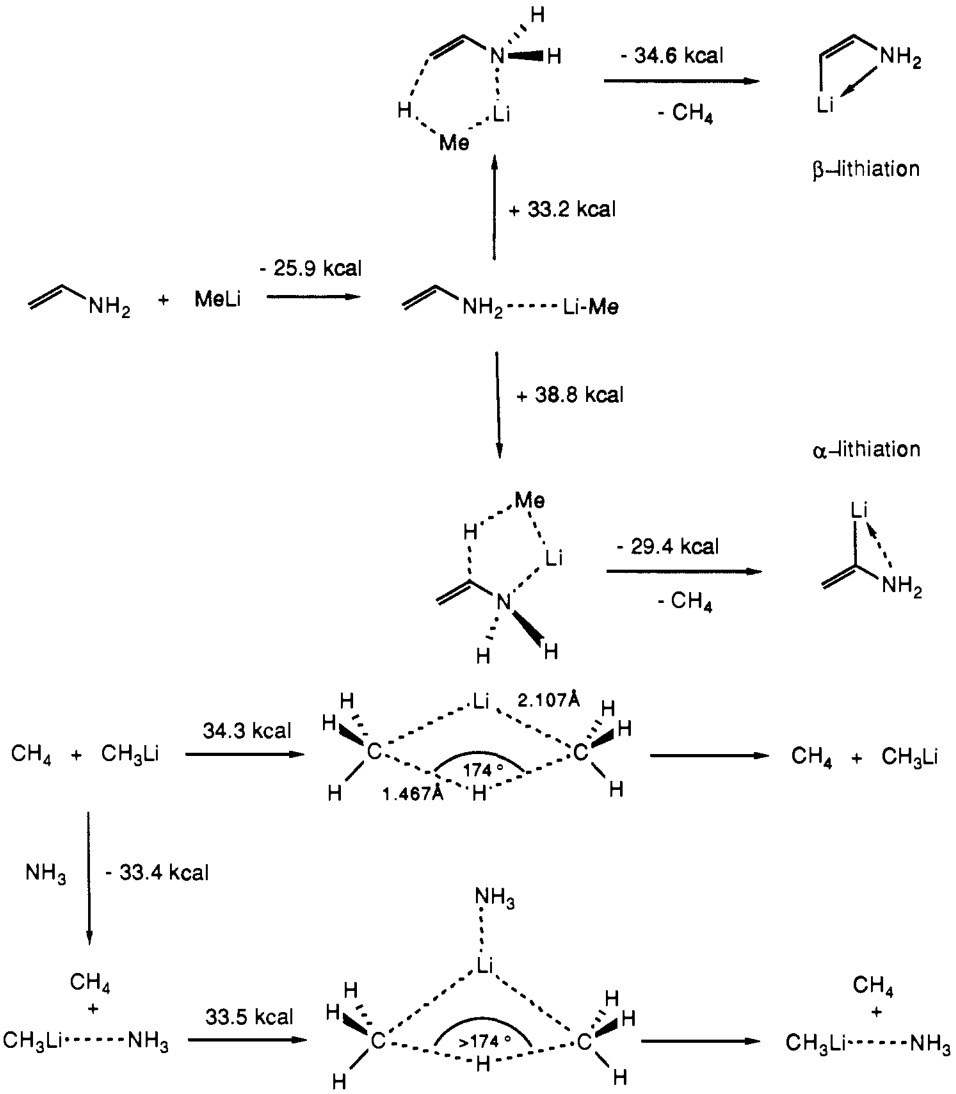

Figure 9. The 3-21G energetics (kcal/mol) for the reactions of vinylamine with methyllithium.

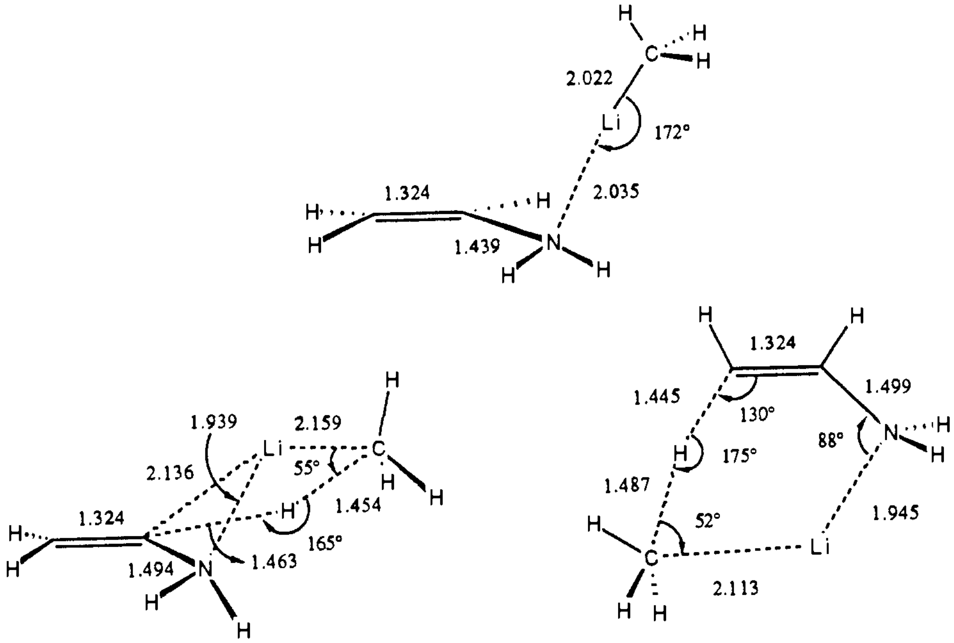

Figure 10. The 3-21G optimized geometries of the reactant complex and transition structures for the reactions of vinylamine with LiH (distances in Å, angles in deg).

structures have the general features shown in Figure 8. In particular, the angle around the transfering H$^+$ is between 155 and 165°, and the angle around the basic H$^-$ is between 65 and 80°. There are substantial interactions between the Li$^+$ and the developing carbanionic center as indicated by the short C–Li distances (2.1–2.3 Å, except in TS3). Because this interaction involves the same developing orbital that the H$^+$ overlaps, the H–C–Li angle is smaller and its variation (47–56°) is smaller than the variation of the H–H–Li angle. The Li–N distance is relatively constant, also, unless a large separation of the carbanionic center and the nitrogen exists as in TS5, which prevents Li–N coordination.

Lithiation of Vinylamine by CH$_3$Li. The complexation energy for $H_2C{=}CH{-}NH_2 + CH_3Li$ was calculated to be 26 kcal/mol at the 3-21G level. The reaction barriers for α- and β-lithiation are 39 and 33 kcal/mol, respectively, as compared with the intrinsic barrier of 34 kcal/mol for the reaction of CH$_3$Li with CH$_4$.[28] As a model for intermolecular coordination, reaction of $CH_3Li \cdots NH_3 + CH_4$ was calculated at the 3-21G level. The energetics of these reactions are shown in Figure 9.

Because of the directionality of the CH$_3$–Li interaction, the H–CH$_3$–Li angles in the transition structures are smaller than those involving hydride as a base. The decrease of the H–CH$_3$–Li angle provides an opportunity for an increase in the CH$_3$–H–C angle, and a better collinear arrangement around the H$^+$ was actually predicted from the calculations. One would expect this angle to be even closer to 180° with *t*-BuLi as a base. The angles around the leaving H$^+$ are 165° and 175° for α- and β-lithiation transition structures, as compared with 174° for the transition structure for CH$_3$Li and CH$_4$. The optimized geometries of the reactant complexes and transition structures are shown in Figure 10.

Based on generalizations from the previous calculations with LiH, it seems reasonable that the essential geometrical features for β'-lithiation and cis- and trans-γ-lithiation with CH$_3$Li as a base would be unchanged vis-à-vis β-lithiation with CH$_3$Li as a base. The "ideal" C–H–C attack angle should be 165–175°, and the Li–CH$_3$–H angle around 45–55°. The H–C–Li angle, the angle around the developing carbanion, should also be 45–55°. Both the forming H–CH$_3$ and the breaking H–C$^-$ bond lengths should be 1.45–1.50 Å, while the distance between the developing carbanion center and lithium should be 2.1–2.3 Å, which is close to the lithium–base distance in the transition structure. Finally, a favorable Li–N coordination involved in the transition structure requires the distance to be 1.9–2.0 Å.

In summary, our calculations are in good agreement with the experimental observations that cis-γ-lithiation and β-lithiation are both preferred over α-lithiation and β'-lithiation. Trans-γ-lithiation is least favored. The transition state for lithiation appears to be very product-like (late transition state) with the new C–Li bond substantially formed at the transition state. ^{13}C NMR experiments with chelating and nonchelating enamine complexes with *n*-BuLi show that the two complexes are qualitatively different. The presence of the second amino group allows for better coordination (chelation effect) to the otherwise weak enamine moiety, thus facilitating lithiation. Additional donor molecules or binding sites on the chelating group may saturate the electrophilic *t*-BuLi, inhibiting binding to the relatively weak enamine nitrogen, thus inhibiting metalation. The chelating group may play an additional role in stabilizing the resulting lithiated species by preventing the solvent reorganization necessary for rearrangement to more resonance stabilized carbanions.

Acknowledgment. We are grateful to the National Institutes of Health and the National Science Foundation for the financial support of this research.

Registry No. $CH_2{=}CHNH_2$, 593-67-9; $CH_2{=}C(CH_3)NH_2$, 4427-28-5; $CH_3CH{=}CHNH_2$, 43691-07-2.

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(28) Rondan, N. G.; Houk, K. N., unpublished results.

(29) **Note Added in Proof:** After prolonged refluxing, lithio-**2a** did not exchange a proton with **2b**, nor did lithio-**2b** exchange a proton with **2a**, as determined by deuterium quenching experiments.

Computational Studies of the Interactions of Chiral Molecules: Complexes of Methyl *N*-(2-Naphthyl)alaninate with *N*-(3,5-Dinitrobenzoyl)leucine *n*-Propylamide as a Model for Chiral Stationary-Phase Interactions

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Abstract: The complexes of (*S*)-methyl *N*-(2-naphthyl)alaninate (NAP) with both enantiomers of *N*-(3,5-dinitrobenzoyl)leucine *n*-propylamide (DNB) were studied as models for the interactions responsible for the separation of enantiomers with the chiral stationary phase systems developed by Pirkle and co-workers. The interaction model investigated is that presented by Pirkle et al. On the basis of molecular mechanics and semiempirical and ab initio quantum mechanical calculations it is suggested that (i) all of the primary components of the interactions of the two complexes are identical in nature and similar in magnitude and (ii) the π–π interactions between the dinitrobenzoyl and naphthyl groups are not the primary components of the complex stabilization and enantiomer separation. Enantiomer differentiation, in this model, could only be achieved via small through-space field effects and not through a classical three-point attachment mechanism. Alternatively, chiral separation is achieved through other mechanisms.

There has been an increasing interest in the separation of enantiomeric compounds by various methods. Theoretical models for the interactions of chiral molecules are often subtle and quite challenging. Indeed, a number of new models have recently been described.[1-4] Of perhaps more practical interest is the increasing awareness of the importance of separating enantiomers. This is particularly true in medicinal chemistry where many drugs often

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(1) Topiol, S. A General Criterion for Molecular Recognition: Implications for Chiral Interactions. *Chirality*, in press.

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