ORGANIC LETTERS

2007
Vol. 9, No. 10
1911−1914

Computational Study of the Stereochemistry of Intramolecular Carbolithiation of an Alkene by a Secondary Alkyllithium: Stereochemistry Change Caused by a Single THF Molecule of Solvation

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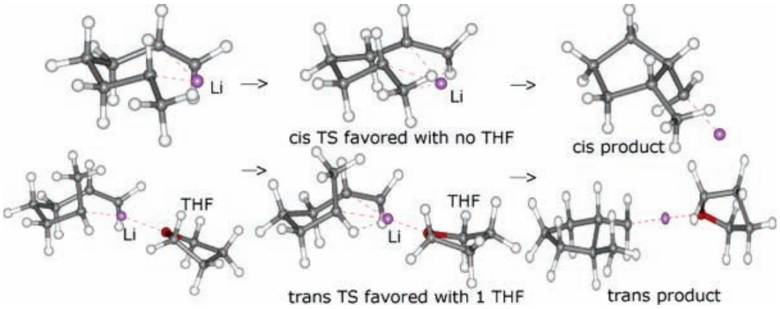
Received February 23, 2007

ABSTRACT



Theoretical calculations reveal that the 40:1 ratio of *trans*- to *cis*-2-methylcyclopentylmethyllithium formed in the cyclization of 6-lithio-1-heptene by intramolecular carbolithiation is due to steric crowding in the transition state for the *cis*-cyclization pathway when a single THF molecule complexes the lithium cation. In the absence of this specific solvation, the *cis*-cyclization pathway is predicted to be slightly favored.

The intramolecular addition of alkyllithiums to unactivated alkenes is rapidly growing in popularity as a preparative method for cyclopentylmethyllithiums and their heterocyclic analogs.[1,2] The attraction of this methodology lies in the high regio- and stereoselectivity when a carbon−carbon bond is formed and in the possibility of trapping the resulting cyclized organolithium with various electrophiles to introduce diverse functionality into the cyclized products. A simple chairlike molecular model for the cyclization of 6-lithio-1-hexene, **1** (Figure 1), consistent with the computed structures for the intermediate and transition state for this cyclization, was developed by Bailey et al.[3] This model successfully accounted for the experimentally determined stereochemistry of the products when methyl groups were at the 3-, 4-, or 5-positions of **1**.

However, it does not predict the correct stereochemical result for the cyclization of 6-lithio-1-heptene (one configuration of which is shown in Figure 1 as **2**), which has been prepared in THF by reductive lithiation of the corresponding

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(1) (a) Reviews: Bailey, W. F.; Ovaska, T. V. In *Advances in Detailed Reaction Mechanisms*; Coxon, J. M., Ed.; JAI Press: Greenwich, CT, 1994; Vol. 3, pp 251−273. Mealy, M. J.; Bailey, W. F. *J. Organomet. Chem.* **2002**, *646*, 59−67. Clayden, J. *Organolithiums: Selectivity for Synthesis*; Pergamon Press: New York, 2002; pp 293−335. (b) Recent papers: Bailey, W. F.; Jiang, X. L. *Tetrahedron* **2005**, *61*, 3183−3194. Coldham, I.; Price, K. N.; Rathmell, R. E. *Org. Biomol. Chem.* **2003**, *1*, 2111−2119.

(2) Deng, K.; Bensari, A.; Cohen, T. *J. Am. Chem. Soc.* **2002**, *124*, 12106−12107. Deng, K.; Bensari-Bouguerra, A.; Whetstone, J.; Cohen, T. *J. Org. Chem.* **2006**, *71*, 2360−2372.

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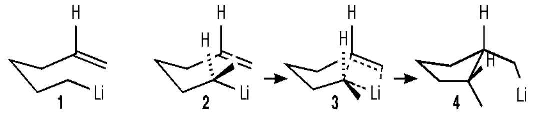

Figure 1. Simple model of secondary alkyllithium cyclization to *cis* product

phenyl thioether[2] and in pentane-ether by Li−I exchange.[4] In both cases, the cyclization at −78 °C was highly stereoselective with *trans* to *cis* ratios of 40:1 or greater.[5] Examination of the simple model for **2**, in which the C−Li bond is arranged parallel to the C═C bond[6] prior to formation of the 4-center transition state **3**,[3] reveals that the methyl group can take up a position pointing outward, away from the remainder of the molecule, as in **2**, or inward toward the remainder of the molecule (the epimer of **2**). If the former, apparently less crowded, configuration were maintained in the transition state, the *cis* product **4** would result.[7]

In order to elucidate the factors responsible for this deviation of the experimental result from that expected on the basis of the model of Bailey et al., we have undertaken a computational study of the cyclization of **2**. Since the lithiophilic solvent THF used in ref 2 might play an important role in this stereochemical preference, we have also examined the effect of solvation of the lithium cation.

Calculations employing the B3LYP hybrid density functional method[8,9] and Møller−Plesset second-order perturbation theory (MP2)[10] were used to investigate the mechanisms of the cyclization of the secondary carbanion 6-lithio-1-heptene (**2**). The geometries of the reactants, products, and transition states of the gas-phase molecule were fully optimized using both the B3LYP and MP2 methods and the 6-31+G(d) basis set.[11,12] The synchronous transit-guided, quasi-Newton (QST3)[13,14] method was used to locate the transition states. Single-point calculations using the MP2 method with the aug-cc-pVTZ[15,16] basis set were carried out using the MP2/6-31+G(d) optimized geometries.

The influence of the THF solvent molecules on the reaction and activation energies was examined through calculations employing the polarizable continuum model (PCM)[17,18] as well as by explicit inclusion of one or two THF molecules coordinated to the Li^+ ion. In the case of a single THF molecule complexed to the Li^+ ion, both the B3LYP and MP2 methods were employed, with the 6-31+G(d) basis set again being used for the geometry optimizations and the aug-cc-pVDZ[15,19] basis set being used for subsequent MP2 single-point calculations (at the MP2/6-31+G(d) optimized geometries), rather than aug-cc-pVTZ. In the calculations including two explicit THF molecules, only the B3LYP method was employed.

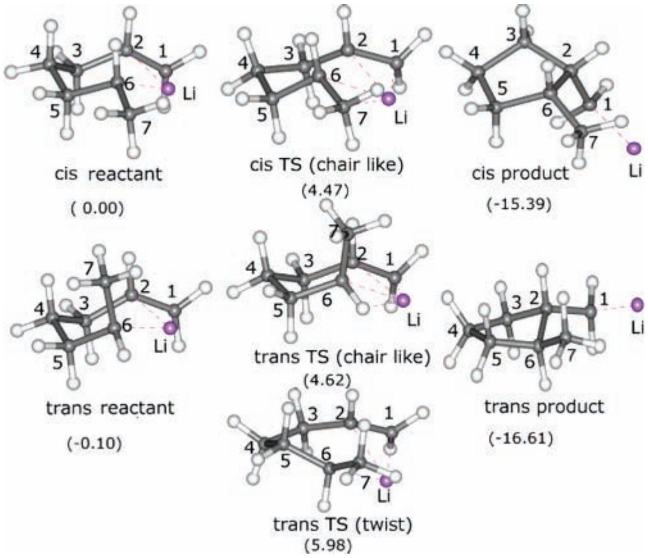

Figure 2. Calculated stationary points of **2** in the gas phase. The numbers in parentheses give the relative free energies (kcal/mol) calculated using the MP2/aug-cc-pVTZ level of theory.

Harmonic frequency calculations were performed using the B3LYP/6-31+G(d) method to establish the nature of each stationary point, to calculate vibrational zero-point energy corrections, and to estimate free energies at the temperature −78 °C. All calculations were performed using the Gaussian 03 program.[20] The picture that emerges from the MP2 calculations concerning the role of the solvent molecules is in qualitative agreement with that from the B3LYP calculations, and in the ensuing discussions we focus on the MP2

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(3) Bailey, W. F.; Khanolkar, A. D.; Gavaskar, K.; Ovaska, T. V.; Rossi, K.; Thiel, Y.; Wiberg, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 5720−5727.

(4) Bailey, W. F.; Nurmi, T. T.; Patricia, J. J.; Wang, W. *J. Am. Chem. Soc.* **1987**, *109*, 2442−2448.

(5) The corresponding carbometallations with Mg and Na, occurring at higher temperatures, also produce mainly *trans* products. (a) Mg: Kossa, J. W. C.; Rees, T. C.; Richey, J. H. G. *Tetrahedron Lett.* **1971**, *12*, 3455−3458. (b) Na: Garst, G. F.; Hines, Jr., J. B. *J. Am. Chem. Soc.* **1984**, *106*, 6443−6445. Garst, G. F.; Hines, Jr., J. B.; Bruhnke, J. D. *Tetrahedron Lett.* **1986**, *27*, 1963−1966.

(6) Houk, K. N.; Rondan, N. G.; Schleyer, P. v. R.; Kaufmann, E.; Clark, T. *J. Am. Chem. Soc.* **1985**, *107*, 2821−2823.

(7) Yus et al. have performed the cyclization of the analogue of **2** in which a *n*-propyl group replaces the methyl group and obtained a single diastereomer the configuration of which was not determined. However, based on an analysis using the molecular model of Bailey et al.,[3] they suggested that the product was most likely *cis*: Yus, M.; Ortiz, R.; Huerta, F. F. *Tetrahedron* **2003**, *59*, 8525−8542.

(8) Becke, A. D. *J. Chem. Phys.* **1993**, *59*, 5648−5652.

(9) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B*, **1988**, *37*, 785−789.

(10) (a) Bartlett, R. J.; Purvis, G. D. *Int. J. Quant. Chem.* **1978**, *14*, 561−565. (b) Pople, J. A.; Binkley, J. S.; Seeger, R. *Int. J. Quant. Chem.* **1976**, *10*, 1−7.

(11) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257−2261.

(12) Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; Schleyer, P. v. R. *J. Comput. Chem.* **1983**, *4*, 294−301.

(13) Peng, C.; Ayala, P. Y.; Schlegel, H. B.; Frisch, M. J. *J. Comput. Chem.* **1996**, *17*, 49−56.

(14) Peng, C.; Schlegel, H. B. *Isr. J. Chem.* **1994**, *33*, 449−454.

(15) Dunning, T. H., Jr. *J. Chem. Phys.* **1989**, *90*, 1007−1023.

(16) Kendall, R. A.; Dunning, T. H.; Harrison, R. J. *J. Chem. Phys.* **1992**, *96*, 6796−6806.

(17) Tomasi, J.; Cammi, R.; Mennucci, B. *Int. J. Quantum Chem.* **1999**, *75*, 783−803.

(18) Cossi, M.; Barone, V.; Cammi, R.; Tomasi, J. *Chem. Phys. Lett.* **1996**, *255*, 327−335.

(19) Woon, D. F.; Dunning, T. H. *J. Chem. Phys.* **1993**, *98*, 1358−1362.

(20) Frisch, M. J. et al. *Gaussian 03*, Revision C.01; Gaussian, Inc.: Wallingford CT, 2004. Full reference provided in Supporting Information.

Table 1. Key Geometrical Parameters for the Stationary Points of **2** and **2**(THF).[a]

species	$R_{\mathrm{Li-C1}}$ (Å)	$R_{\mathrm{Li-C2}}$ (Å)	$R_{\mathrm{Li-C6}}$ (Å)	$R_{\mathrm{C2-C6}}$ (Å)	$R_{\mathrm{C1-C2}}$ (Å)	Φ (deg)[b]
cis reactant	2.33 (2.37)	2.36 (2.39)	2.03 (2.06)	3.32 (3.19)	1.35 (1.35)	16.4 (9.4)
trans reactant	2.33 (2.36)	2.36 (2.37)	2.03 (2.05)	3.27 (3.17)	1.35 (1.35)	−12.2 (−13.8)
cis TS (chairlike)	2.03 (2.08)	2.12 (2.10)	2.04 (2.05)	2.27 (2.33)	1.41 (1.40)	0.5 (36.0)
trans TS (chairlike)	2.10 (2.06)	2.13 (2.15)	1.99 (2.06)	2.42 (2.27)	1.42 (1.41)	−1.2 (−5.0)

[a] The numbers in parentheses are for the complex with THF. [b] Φ gives the dihedral angle between the C2−C1−Li and C1−Li−C6 planes.

results, which should be more reliable. Specifically, the discussion will employ MP2 results with the aug-cc-pVTZ basis set (aug-cc-pVDZ, for the complex with a single THF molecule), with vibrational ZPE and thermal contributions to the free energies being calculated at the B3LYP/6-31+G(d) level of theory.

The geometries of the optimized minima and transition states of **2** and **2**(THF) are depicted in Figures 2 and 3, respectively, and the key geometrical parameters are summarized in Table 1. The calculated free energies of the various stationary points are summarized in Table 2. Additional structural parameters and energetic information are reported in the tables in Supporting Information.

The stabilities of the cyclohexane-like reactant structures depicted in Figure **2** derive from the interaction of the Li^+ ion with the π bond.[3,21] Both *cis*- and *trans*-coordinated complexes are located in the optimizations. The MP2 calculations predict the *cis* and *trans* reactants to be nearly isoenergetic, with the energy difference being only 0.1 kcal/mol with the aug-cc-pVTZ basis set (Table 2). On the other hand, the *trans* product of **2** is calculated to be 1.2 kcal/mol more stable than the *cis* product as a consequence of steric effects involving the proximity of the methyl and $\mathrm{CH_2Li}$ substituents on the cyclopentane ring in the latter. In the *cis* product, the C7−C1 and C7−Li distances are 3.07 and 2.54 Å, respectively; in the *trans* product the corresponding distances are 3.26 and 2.98 Å.

For **2**, the transition state on the *cis* reaction path has a chairlike structure. Two transition states, one with a chairlike structure and the other with a twisted structure, leading to the *trans* product were located, with the former being predicted to be about 1.4 kcal/mol more stable. In the twisted transition state structure, the methyl group connected to C6

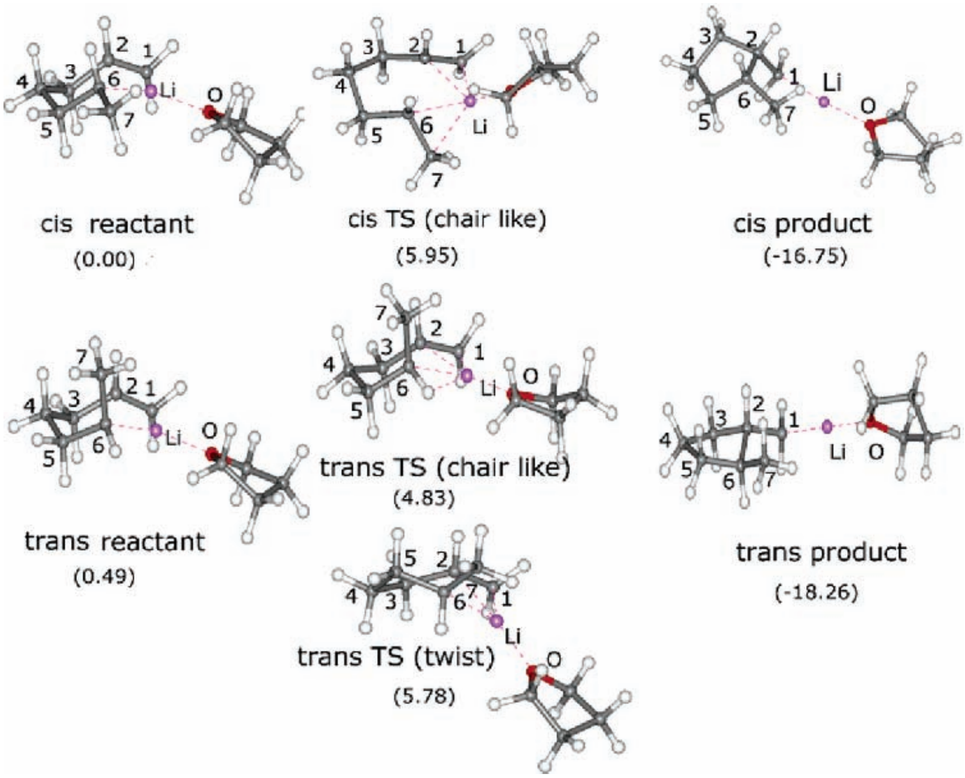

Figure 3. Calculated stationary points of **2** complexed with a molecule of THF. The numbers within parentheses denote the relative free energies (kcal/mol) calculated using the MP2/aug-cc-pVDZ method.

Table 2. Calculated Relative Free Energies (kcal/mol) for the Stationary Points of **2** and **2**(THF)[a]

species	relative energy
cis complex	0.00 (0.00)
cis TS (chair)	4.47 (5.95)
cis product	−15.39 (−16.75)
trans complex	−0.10 (0.49)
trans TS (chair)	4.62 (4.83)
trans TS (twist)	5.98 (5.78)
trans product	−16.61 (−18.26)

[a] The relative energies of **2** and **2**(THF) (the latter being reported in parentheses) are from MP2 calculations using the aug-cc-pVTZ and aug-cc-pVDZ basis sets, respectively.

is in the equatorial plane, whereas in the chairlike transition state, it is in the pseudoaxial position. The chairlike transition state on the *trans* pathway is also calculated to be slightly higher in free energy than those on the *cis* pathway. Hence, the theoretical results for the gas-phase pathways do not account for the high (40:1) *trans*:*cis* ratio observed in the experiments.

At the MP2/6-31+G(d) level of theory, inclusion of solvent effects using the PCM model parametrized for THF solvent at −78 °C leads to about a 2 kcal/mol increase of the activation barrier for both the *cis* and *trans* isomerization pathways relative to those for the non-solvated ion. Thus, inclusion of solvation effects via the PCM model has almost no effect on the relative barrier heights for the *cis* and *trans* pathways.

We now turn to the results of the calculations in which one or two THF molecules are explicitly included. The net binding energy between the THF molecule and **2** is calculated at the MP2/aug-cc-pVDZ level to be 17.9 and 17.2 kcal/mol for *cis* and *trans* reactant complexes, respectively. (The binding energies include the counterpoise correction for BSSE.[22]) The optimized structures and relative free energies are reported in Figure 2 and Table 2. The complexation of **2** with a THF molecule destabilizes the transition state for the *cis* pathway relative to those for the *trans* pathways. The result is that the activation energy for the pathway proceeding through the chairlike TS and leading to the *trans* product becomes 1.12 kcal/mol lower than that leading to the *cis* product. This energy difference is consistent with a ∼90% selectivity for the *trans* product, matching reasonably well the experimental result.

In both the *cis* and *trans* reactants, the binding of the THF molecule to **2** causes sizable (0.01−0.04 Å) increases in the C1−Li, C2−Li, and C6−Li distances, weakening the interaction between the Li^+ ion with the π bond, as well as a 0.1 Å shortening of the distance between the C2 and C6 carbon atoms, between which the bond is formed upon cyclization. Moreover, the distance between C2 and C6 is increased in the *cis* transition state and decreased in the *trans* transition states compared to the corresponding distances for the isolated molecule. For the non-solvated ion, the four atoms directly involved in the reaction (C1, C2, C6, Li) essentially lie in a plane in both the *cis* and *trans* transition state structures. However, when the THF molecule is included, the Li atom is displaced out of the plane in the transition state for the *cis* pathway, whereas the C1, C2, C6, and Li atoms remain nearly coplanar in the transitions states for the pathways leading to the *trans* product. The geometrical distortions brought about by the THF molecule are largely responsible for the greater stability of the TS for the chairlike *trans* pathway compared to that for the *cis* pathway because in the latter TS the C−Li and the C═C bond to which it adds can no longer be parallel, the arrangement that leads to the most efficient orbital overlap.

The calculations reveal that the second THF molecule binds much less strongly to **2** than does the first, with a binding energy of only 6 kcal/mol, which is about one-third that found for the binding of the first THF molecule. At a temperature of −78 °C, the enthalpy of evaporation of THF is 9.05 kcal/mol.[23] Thus, it is expected that under the experimental conditions used in ref 2, only a single THF molecule is strongly bound to **2**. Furthermore, the calculated activation energies of all three pathways of **2**$(\mathrm{THF})_2$ are greater than those **2**(THF), with the lowest activation energy being 8.37 kcal/mol for the *trans* chairlike TS. This provides further evidence that the cyclization reaction of **2** probably proceeds through the complex with only a single tightly bound THF molecule.

In summary, calculations show that cyclization of **2** in the gas phase slightly favors the *cis* product **4**, in agreement with the model presented in ref 3 but contrary to the results of experiments carried out using THF solvent. The calculations also reveal that a single THF solvent molecule strongly binds to the lithium cation, causing the pathway proceeding through a chairlike TS and leading to *trans* product to be favored by about 1.2 kcal/mol over that leading to the *cis* product, qualitatively consistent with the experimentally observed 40:1 preference for the *trans* over the *cis* product. Apparently, introduction of the THF of solvation into the *cis* TS increases the repulsion between the methyl group and the Li complex so much that the Li is forced out of the C1−C2−C6 plane, thus increasing the TS energy, whereas this does not occur in the case of the *trans* TS because of the greater distance of the solvated Li from the methyl group. When the methyl group is at the 3-, 4-, or 5-position, no such crowding exists and the model of Bailey et al. is successful in predicting the stereochemistry.[3]

Acknowledgment. We thank the National Science Foundation [Grants CHE0102289 (T.C.) and CHE0518253 (K.D.J.)] for support of this work.

Supporting Information Available: Full authorship of ref 20, Supporting Tables S1−S5, MP2 coordinates, and graphic for the cyclization with two THF molecules of solvation. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Wu, Y. D.; Houk, K. N. *J. Am. Chem. Soc.* **1987**, *109*, 908−910.

(22) Boys, S. F.; Bernardi, F. *Mol. Phys.* **1970**, *19*, 553−566.

(23) *CRC Handbook of Chemistry and Physics*, 85th ed.; Lide, D. R., Ed.; CRC Press: Boca Raton, 2004; Chapter 5.