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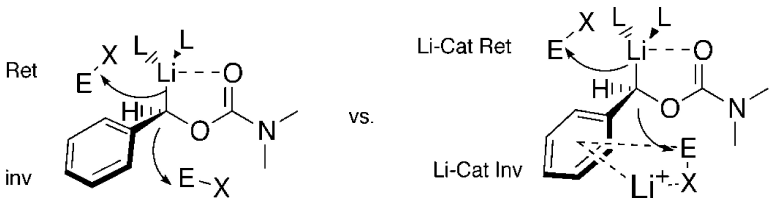

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A DFT Computational Study on Electrophilic Substitutions upon α-Oxy-Substituted Benzylorganolithium Compounds: Lithium Catalysis Is the Hidden Piece of the Puzzle

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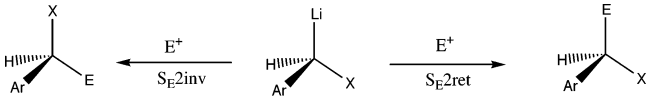
Experimental results on electrophilic substitutions (S_E2) undergone by configurationally stable organolithium compounds have been piling up so as to constitute a rather puzzling issue. Most conflicting examples refer to the behavior of not only α-oxy- or α-amino- but also other α-heteroorganolithium compounds.[1] Thus, the former, as described by Hoppe,[2] protonate with retention ($S_E2$ret), although inversion ($S_E2$inv) has been observed as well.[3] The general rule for acylations when reacted with acid chlorides or CO_2 calls for inversion ($S_E2$inv), but when reacted with esters or anhydrides, calls for retention ($S_E2$ret). Nevertheless, Hoppe reported an unexpected retention with acid chlorides,[4] and Beak[5] described that α-aminoorganolithium compounds behaved analogously. Alkyl halides, which usually lead to inverted products (S_{E2}inv), reacted with retention in intramolecular alkylations;[6] carbonyl compounds, which generally lead to retention of configuration, have also been reported by Beak[7] and Toru[8] to yield inverted products. In addition, enantioselection appears to be sensitive to a number of other factors.[9] Unexpected racemizations have also been reported;[10a] in one particular case racemization was assigned to a predominance of SET vs polar mechanisms.[10b] In trying to rationalize these results, Hoppe advanced a promising idea: hard electrophiles capable of anchoring to the lithium atom should lead to retention of configuration, whereas those having a low LUMO might rather prefer to react with inversion.[2] Other authors[11,8] have also adhered to this proposal.



X = OR, NRR', SR, etc

We planned a comprehensive computational analysis to approach the problem.[12] For this purpose one should address (a) the study of the barrier for inversion of the C−Li bond[13] and (b) the study of all competitive routes for significant electrophilic substitutions (S_E2). Herein, we report the results of a detailed DFT (B3LYP/6-31+G*) study aimed at providing a coherent picture of electrophilic substitutions upon α-oxybenzylorganolithium compounds (part b above). The relevant conclusion resulting from this work is that lithium catalysis plays a key role in the electrophilic substitutions upon α-oxybenzylorganolithium compounds, thereby determining their stereochemical output. To the best of our knowledge this is the first call upon lithium catalysis in electrophilic substitutions undergone by α-oxybenzylorganolithium compounds.[14,15] In contrast, Reich et al. found that added lithium salts do not catalyze the S_N2 displacement of lithiated dithianes upon alkyl halides in the presence of HMPA.[16]

The extensive experimental details available from the work of Hoppe and Hoffmann led us to choose **1**, the monomeric lithium derivative of O-benzyl-*N*,*N*-dimethylcarbamate, as model for our study. In accordance with X-ray data,[17] we included two dimethyl ether molecules as discrete solvation ligands. Nevertheless, due to the importance of solvation in organolithium chemistry,[18] we first evaluated the significance of discrete solvation and aggregation upon **1**. Although some benzyllithium oligomers are known,[19] dimerization of **1cip-2e** was found (HF/6-31G*) to be a costly process; accordingly, dimeric species were discarded as likely intermediates.[20] On the solvation issue we learned (B3LYP/6-31+G*) that the monomeric contact ion pair **1cip-2e** is highly polarized and thus amenable for further solvation even at the face opposite to that occupied by lithium (**1cip-2e1e** is 8.16 kJ mol^{-1} more stable than **1cip-2e** itself). This kind of solvation of the π system[21] was suggestive of a plausible mechanism for electrophilic substitutions, namely that involving initial complexation of electrophiles or ions at the rear of the C−Li bond (see below). The computed energies of solvent-separated ion pairs **1ssip** solvated by up to four solvent molecules were found to be higher (>84 kJ mol^{-1}) and were therefore rejected for further study.[22] Accordingly, we restricted our study to the contact ion pair **1cip-2e** (see the Supporting Information for optimized structures).

B3LYP/6-31+G* calculations on carboxylation (CO_2), alkylation (MeCl), and acylation (MeCOCl) upon **1cip-2e** all coincide in one clear-cut point: retentive electrophilic substitutions ($S_E2$ret) are the favored processes (Supporting Information, Table 1). Thus, the transition structures for the retentive (**CO_2ret-ts**) and invertive (**CO_2inv-ts**) carboxylations were separated ($\Delta\Delta E^*$) by only 1.38 kJ mol^{-1}, the former being lower in energy. Therefore, provided that carboxylation conforms to the non-Curtin−Hammett profile, one would expect a small preference for retention, in complete disagreement with experiment. Furthermore, the alkylation of **1cip-2e** by methyl chloride with retention (**MeClret-ts**) was calculated to lie at lower energy ($\Delta\Delta E^* = 36.19$ kJ mol^{-1}) than that with inversion (**MeClinv-ts**) in clear opposition to experimental facts. Computations on the acylation of **1cip-2e** by acetyl chloride predicted predominant retentive acylation as **MeCOClret-ts** was found to be under **MeCOClinv-ts** ($\Delta\Delta E^* = 1.72$ kJ mol^{-1}), once again opposing experiment (see the Supporting Information for optimized structures).

In examining the above transition structures for electrophilic substitutions occurring with inversion at the carbon-bearing lithium we noticed the lack of appropriate assistance to the electrofugal group. Thus, the following question arose: could it be possible that external lithium salts catalyze electrophilic substitutions with inversion?[16,17]

DFT calculations (B3LYP/6-31+G*) have shown that monomeric, unsolvated lithium chloride or solvated lithium ions (both $Li(OMe_2)_2^+$ or LiCl were used as models) catalyze the carboxylation of **1cip-2e** with inversion at the C−Li bond (Supporting Information, Table 2). The existence of catalysis is proven by the fact that transition structures **LiCl·CO_2inv-ts** and **LiCl·CO_2ret-ts** were

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respectively 3.93 and 32.30 kJ mol^{-1} above the ground-state complex (Table 2, entries 1 and 2), whereas the barriers for the uncatalyzed reactions were found at 33.93 kJ mol^{-1} (S_E2ret) and 35.31 kJ mol^{-1} (S_E2inv) above their corresponding ground state (Table 1). Moreover, the barrier for inversion **LiCl·CO$_2$inv-ts** lies at lower energy (3.93 kJ mol^{-1}) than that for retention **LiCl·CO$_2$ret-ts** (32.30 kJ mol^{-1}), thus proving the decisive influence of lithium catalysis on the stereochemical outcome of the reaction. For a better assessment we examined also the carboxylation reaction catalyzed by solvated lithium ions $^+$Li(OMe $_n$)$_n$. Again, the barrier for the lithium ion-catalyzed carboxylation represented by **$^+$Li(OMe$_2$)$_2$·CO$_2$inv-ts** was much easier to overcome (ΔE^{*}= 17.36 kJ mol^{-1}; Table 2, entry 4) than those of the uncatalyzed reactions (ΔE^{*}= 33.93 and 35.31 kJ mol^{-1}; Table 1, entries 1 and 2). Since the solvation/desolvation of lithium ions is fast and takes place with scarcely any energy cost,[23] it can be stated that the catalyzed process leading to invertive carboxylation clearly has an advantage over the uncatalyzed ones. Therefore, it can be stated that the carboxylation of α-oxybenzylorganolithium compounds should give rise to inverted products because (1) it likely fits into a non-Curtin−Hammett profile and (2) either the LiCl or the lithium ion-catalyzed routes prevail over the noncatalyzed ones (see the Supporting Information for optimized structures).

DFT calculations also shed light onto the alkylation of **1cip-2e**. The LiCl-catalyzed double inversion (at both C−Li and C−Cl carbon atoms) **LiCl·MeClii-ts** was found to be (a) less costly than the uncatalyzed processes shown in Table 1 and (b) the favored route of all competing routes because it requires surpassing an energy barrier of 59.79 kJ mol^{-1} (Table 2), while that involving retention at the C−Cl carbon (**LiCl·MeClir-ts**) exhibits an energy barrier of 124.47 kJ mol^{-1} above that of the ground-state complex **LiCl·MeClinv** and that involving double retention **LiCl·MeClrr-ts** exhibits an even higher energy barrier (139.87 kJ mol^{-1}). The conclusion is clear-cut that lithium catalysis should drive intermolecular alkylations to give inverted products at both the benzylic and the electrophilic carbon atoms (see the Supporting Information for optimized structures).

In summary, our DFT study on the electrophilic substitutions undergone by α-oxy-substituted benzylorganolithium compounds has revealed that lithium catalysis plays a key role on their stereochemical outcome. Likewise, closely related species might behave analogously.

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Supporting Information Available: Tables of the relevant absolute and relative energies for the uncatalyzed (Table 1) and catalyzed (Table 2) reactions and Cartesian coordinates of all stationary points. This material is available free of charge via the Internet at http://www.acs.org.

References

(1) Basu, A.; Thayumanavan, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 717. Clayden, J. *Organolithium Selectivity for Synthesis*; Pergamon Press: Oxford, UK, 2002. *Topics in Organometallic Chemistry*; Hodgson, D. M., Ed.; Springer-Verlag: Berlin, 2003; Vol. 5.
(2) Carstens, A.; Hoppe, D. *Tetrahedron* **1994**, *50*, 6097.
(3) Hammerschmidt, F.; Hanninger, A. *Chem. Ber.* **1995**, *128*, 1069.
(4) Derwing, C.; Frank, H.; Hoppe, D. *Eur. J. Org. Chem.* **1999**, 3519.
(5) Faibish, N. C.; Park, J. S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 11561.
(6) Wu, S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 715.
(7) Basu, A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 1575.
(8) Nakamura, S.; Nakagawa, R.; Watanabe Y.; Toru, T. *J. Am. Chem. Soc.* **2000**, *122*, 11340.
(9) (a) Polarity: Schlosser, M.; Limat, D. *J. Am. Chem. Soc.* **1995**, *117*, 12342. Hoppe, I.; Marsh, M.; Harms, K.; Boche, G.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2185. Rein, K.; Goicoechea-Pappas, M.; Anklekar, T. V.; Hart, G. C.; Smith, G. A.; Gawley, R. E. *J. Am. Chem. Soc.* **1989**, *111*, 2211. (b) Leaving group: Thayumanavan, S.; Lee, S.; Liao, C.; Beak, P. *J. Am. Chem. Soc.* **1994**, *116*, 9755. Behrens, K.; Frölich, R.; Meyer, O.; Hoppe, D. *Eur. J. Org. Chem.* **1998**, 2397. (c) Temperature: Curtis, M. D.; Beak, P. *J. Org. Chem.* **1999**, *64*, 16. Pipple, D. J.; Weisenburger, G. A.; Wilson, S. R.; Beak, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 2522. Park, Y. S.; Weisenburger, G. A.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 10537. Weisenburger, G. A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 12218. (d) Other: Meyers, A. I.; Warmus, J. S.; Gonzalez, M. A.; Guiles, J.; Akahane, A. *Tetrahedron Lett.* **1991**, *32*, 5509.
(10) (a) Matulenko, M.; Meyers, A. I. *J. Org. Chem.* **1996**, *61*, 573. (b) Gawley, R. E.; Low, E.; Zhang, Q.; Harris, R. *J. Am. Chem. Soc.* **2000**, *122*, 3344.
(11) Weisenburger, G. A.; Faibish, N. C.; Pippel, D. J.; Beak, P. *J. Am. Chem. Soc.* **1999**, *121*, 9522.
(12) To be published in due course.
(13) Ruhland, T.; Dress, R.; Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1467. Reich, H. L.; Dykstra, R. R. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1469.
(14) For electrophilic catalysis by ionic salts see: Westaway, K. C.; Gao, Y.; Fang, Y. *J. Org. Chem.* **2003**, *68*, 3084. Smith, P. J.; Crowe, D. A.; Westaway, K. C. *Can. J. Chem.* **2001**, *79*, 1145. Zavada, J.; Pankova, M.; Vitek, A. *Collect. Czech. Chem. Commun.* **1981**, *46*, 3247.
(15) According to ab initio calculations lithium salts catalyze S_N2 displacements See: Harder, S.; Streitwieser, A., Jr.; Petty, J. T.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1995**, *117*, 3253. Harder, S.; van Lenthe, J. H.; van Eikema Hommes, N. J. R.; Schleyer, P.v. R. *J. Am. Chem. Soc.* **1994**, *116*, 2508. Mori. S.; Nakamura, E.; Morokuma, K. *J. Am. Chem. Soc.* **2000**, *122*, 7294.
(16) Reich, H. J.; Sanders, A. W.; Fiedler, A. T.; Bevan, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 13386.
(17) Zarges, W.; Marsch, M.; Harms, K.; Boche, G. *Chem. Ber.* **1989**, *122*, 2299. Marsch, M.; Harms, K.; Zschage, O.; Hoppe, D.; Boche, G. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 321. Boche, G.; Marsch, M.; Harbach, J.; Harms, K.; Ledig, B.; Schubert, F.; Lorentz, J. C. W.; Ahlbrecht, H. *Chem. Ber.* **1993**, *126*, 1887. Zarges, W.; Marsch, M.; Harms, K.; Koch, W.; Frenking, G.; Boche, G. *Chem. Ber.* **1991**, *124*, 543.
(18) Saá, J. M. *Helv. Chim. Acta* **2002**, *85*, 814 and references therein.
(19) Beno, M. A.; Hope, H.; Olmstead, M. M.; Power, P. P. *Organometallics* **1985**, *4*, 2117. Brooks, J. J.; Stucky, G. D. *J. Am. Chem. Soc.* **1972**, *94*, 7333. Engelhardt, L. M.; Leung, W.-P.; Raston, C. L.; Twiss, P.; White, A. H. *J. Chem. Soc., Dalton Trans*, **1984**, 321.
(20) The following dimerization process **1cip-2e** + **1cip-2e** → (*R*, *S*)-**(1cip-1e)$_2$** + **2e** was found to be highly endothermic as determined by HF/6-31G*//HF/6-31G* (63.97 kJ mol^{-1}), PCM/6-31G*//HF/6-31G* (66.96 kJ mol^{-1}), and B3LYP/6-31+G*//HF/6-31G* (59.16 kJ mol^{-1}) calculations. The barrier for invertive carboxylation upon this dimer was found (HF/6-31G*) to lie 72.63 kJ mol^{-1} above the starting materials (dimer + CO_2), i.e., higher than those found for **1cip-2e** (see the text).
(21) Ma, J. C.; Dougherty, D. A. *Chem. Rev.* **1997**, *97*, 1303.
(22) We found (B3LYP/6-31+G*) that the transition structure for the retentive alkylation of **1ssip-2e** with methyl chloride was 38.03 kJ mol^{-1} higher in energy than that involving contact ion pair species **1cip-2e**. Bulk solvation as defined by Tomasi's PCM model did not modify significantly this analysis (data not shown). See Cossi, M.; Barone, V.; Mennucci, B.; Tomasi, J. *Chem. Phys. Lett.* **1998**, *286*, 253 and references therein.
(23) Computations (B3LYP/6-31+G*) show that the relative energies for some relevant solvation/desolvation equilibria: **1cip-2e** + **$^+$Li(OMe$_2$)$_4$** + **CO$_2$** → **1cip-2e·$^+$Li(OMe$_2$)$_2$** + **CO$_2$** + **2e** → **1cip-2e·$^+$Li(OMe$_2$)$_2$·CO$_2$** + **2e** are as follows: 0, 4.56, and 9.83 kJ mol^{-1}, respectively. These data should be contrasted with that of the solvation/desolvation equilibria: **$^+$Li(OMe$_2$)$_4$** → **$^+$Li(OMe$_2$)$_3$** + **1e** → **$^+$Li(OMe$_2$)$_2$** + **2e**, as determined by B3LYP/6-31+G* computations: 0, 57.24, and 136.77 kJ mol^{-1}, respectively.

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