Stereoselective Addition of Lithium Amides to Activated Triple Bonds

Ben-Ami Feit,* Shulamit Dickerman, Djamal Masrawe, and Ariela Fishman School of Chemistry, Tel-Aviv University, Tel-Aviv 69978, Israel

The nucleophilic addition of R''_2NLi to alkyl esters of $R'C \equiv CCO_2R$ (R' = H, CO_2R ; R = Me, Et) in apolar solvents, in the presence and in the absence of solvating agents, has been studied. The only or the main reaction product obtained under all experimental conditions was the corresponding (E)- $R''_2NCR'=CH-CO_2R$. It is suggested that the vinyl-lithium intermediate, which is first formed by an *anti*-type addition of R''_2NLi to the triple bond, undergoes a very fast isomerisation, owing to the highly effective configurationally destabilising R^+ effect of the electron-donating dialkylamino *trans*- β -substituent.

Vinyl-lithium compounds formed by direct lithiation of β substituted activated olefins are reactive intermediates of great interest. Their multifunctionality and synthetic versatility have been demonstrated by their conversion in stepwise reactions into valuable synthons, which are structural units of many natural products.¹ Such vinyl-lithium compounds are also the intermediates formed in the addition of negatively charged nucleophiles (e.g. lithium compounds) to activated acetylenes of the type YC=CG (G = CO_2R , CONR, CN, SO_2R , etc.; Y = H, G, R, Ar, OR, SR, NR₂, etc.).² The configurational stability of vinyl-lithium compounds is one of several factors which might affect the stereochemical result of its reaction with an electrophile, and depends, in turn, on several factors such as ionpairing characteristics, effect of the medium, and substituent effects. The greater the ion-pair contact, the higher is its configurational stability.³⁻⁶ Substituents which stabilise carbanions by delocalisation [C(O)R,^{6.7} CO₂R,⁸⁻¹² CHO¹²] decrease the configurational stability of the corresponding vinyllithium compound. a-Lithiated olefinic nitriles are relatively stable,^{10.13} as the α -substituents stabilising the carbanions by an inductive effect (OR,¹⁴ SR,^{15.16} SeR,¹⁷ NC,¹⁸ etc.) tend to stabilise the configuration of the corresponding vinyl-lithium compounds. A β -substituent could influence the configurational stability of α -lithiated activated olefins in two ways. The *trans* configuration of an α -lithic derivative of an α,β -disubstituted activated olefin of the type YCH=CHG (1) is stabilised owing to internal complexation of the Li counter-ion by the cis β -Zsubstituent. Compounds (1a-d) are some typical examples.

Li
$$G$$

(1) a; ^{15b} G = CN,Y = SEt
b; ^{15b} G = S(O)R,Y = SR
c; ¹⁹ G = Ph, Y = CO₂R
d; ²⁰ G = CN, Y = NH₂

Another relevant effect of an electron-donating β -substituent has been studied with regard to the influence of a β -substituent A (A = NR₂, OR, SR) on the relative configurational stabilities of the dimethyl esters of α -lithiated fumaric acid (2)-Li and maleic acid (3)-Li (Scheme 1).²¹

Protonation of the reaction mixture obtained from either compound (2) or (3) with methanol (for which case k_2 and $k_3 \gg k_1$ and k_{-1}), resulted exclusively in compound (3). With a relatively weak electrophile such as PhCHO, when the above relationship does not hold, the lactone derived from



compound (2)-Li resulted, for A = pyrrolidin-1-yl, morpholino, in relatively high yields. These observations confirm (a) the existence of a (2)-Li=(3)-Li equilibrium, by which the two isomeric vinyl-lithium compounds are capable of interconversion, and (b) that $k_1 \ge k_{-1}$. It was concluded²¹ that the configurational stability of a vinyl-lithium compound having a *trans*-substituent of this type is lower than that of the *cis*-isomer.

The purpose of the present work was to verify this conclusion with regard to vinyl-lithium intermediates formed in the addition reaction of lithium amides to activated triple bonds.

Results and Discussion

Nucleophilic addition of lithium amides derived from secondary amines, to alkyl esters of propiolic (4a) and acetylenedicarboxylic (4b) acids, $R' \subseteq CCO_2 R$ [(4a; R' = H) (4b; $R' = CO_2 R$)] was carried out in apolar solvents [tetrahydrofuran (THF), diethyl ether (DEE), DEE-hexane, hexane] at -78 °C with and without solvating agents (TMEDA, 18crown-6). The only or the main reaction product obtained on quenching the reaction mixture with water or methanol was the corresponding (E)- $R''_2NCR'=CHCO_2R$ (8). The nucleophilic

		Amount			Reaction	
Entŗy	Alkyne	(mmol)	R_2N^-* (mmol)	Solvent	products (g, %)	¹ H N.m.r. data ^{<i>a</i>}
1	(4b)	1.5	P (3.0)	THF	(7b) (0.040, 12)	1.96 (m, 4 H), [3.25—3.87 (m); ^c 3.74 (s), 3.80 (s)] (10 H), 5.18 (s, 1 H)
					(8b) (0.220, 69)	1.97 (m, 4 H), 3.27 (m, 4 H), ^c 3.65 (s, 3 H), 3.96 (s, 3 H), 4.53 (s, 1 H)
2	(4b)	2.0	P (1.5)	THF	(8b) (0.32, 100)	
3	(4b)	2.0	M (2.2)	THF	(8b) (0.442, 86)	1.24 (t, 3 H), 1.37 (t, 3 H), ^c 3.15 (t, 4 H), 3.74 (t, 4 H), 4.10 (q, 2 H), 4.38 (q, 2 H), 4.80 (s, 1 H)
4	(4b)	2.0	M (2.2)	DEE	(8b) (0.216, 42)	
5	(4b)	2.0	M (2.2)	Hexane	(8b) (0.295, 57)	
6	(4b)	2.0	M (2.2)	THFTMEDA	(7b) (0.070, 14)	
					(8b) (0.407, 80)	
7	(4b)	2.0	M (2.2)	MeO(CH ₂ CH ₂ O) ₂ CH ₃	(7b) (0.066, 13)	
					(8b) (0.444, 87)	
8	(4b)	2.0	M (2.2)	THF18-Crown-6	(7b) (0.061, 12)	
					(8b) (0.444, 87)	
9	(4b)	2.0	Pr ⁱ ₂ N ⁻	DEE	(7b) (0.032, 6)	
			-		(8b) (0.508, 94)	
10	(4b)	2.0	$Pr_{2}^{i}N^{-}$ (2.2)	DEEhexane (2:1)	(8b) (0.421, 77)	0.97—1.45 (m, 18 H), 3.58 (h, 2 H), 3.88 (q, 2 H), ^b 4.13 (q, 2 H), 4.13 (q, 2 H), 4.48 (s, 1 H)
11	(4a)	3.0	PP (3.0)	THF	(8a) (0.477, 82)	1.15 (t, 3 H), 1.38–1.78 (m, 6 H), 2.98–3.30 (m, 4 H), 3.98 (q, 2 H), 4.35 (d, 1 H, <i>J</i> 14 Hz), 7.09 (d, 1 H, <i>J</i> 14 Hz)
12	(4a)	2.0	$Pr_{2}^{i}N^{-}$ (1.0)	THF	(8a) (0.160, 40)	1.00–1.40 (m, 15 H), 3.55 (h, 2 H), ^b 3.95 (q, 2 H), 4.45 (d, 1 H, J 13.8 Hz), 7.30 (d, 1 H, J 13.8 Hz)
13	(4a)	2.0	ТМР	THF	(8a) (0.306, 64)	1.23 (t, 3 H), 1.39 (s, 12 H), 1.62 ('s', 6 H), 4.02 (q, 2 H), 4.75 (d, 1 H, <i>J</i> 14.2 Hz), 7.53 (d, 1 H, <i>J</i> 14.2 Hz)

Table. Addition of lithium amides $(R_2N^-Li^+)$ to RC=CCO₂R

928

* P = pyrrolidinide, PP = piperidinide, M = morpholinide, TMP = 2,2,6,6-tetramethylpiperidinide. ^{*a*} Chemical shifts are reported in δ values with Me₄Si as internal reference, using 60 and 340 MHz spectrometers. ^{*b*} Solvent for n.m.r., CCl₄. ^{*c*} Solvent for n.m.r., CDCl₃.

addition of negatively charged nucleophiles to activated acetylenes is an *anti*-type addition. This was confirmed $^{22-24}$ by carrying out the reaction in a protic medium in which the initially formed vinyl anion intermediate could be rapidly protonated. The only or the major olefinic product obtained under such conditions was the (Z)-olefin. It might be therefore suggested that the highly favoured formation of (E)- $R''_2NCR'=CHCO_2R$ (8) in an aprotic medium, observed in the present work (Table), is due to an *anti*-type nucleophilic addition of $R''_2N^-Li^+$ to the activated triple bond, yielding first compound (5)-Li, which then undergoes a relatively fast isomerisation to give (6)-Li (Scheme 2).

The formation of high yields of compound (8) as the main reaction product on quenching of the (5)-Li=(6)-Li equilibrium mixture indicates that $k'_2 \gg k'_{-2}$. As the reverse elimination reaction should take place via the (Z)-intermediate (5)-Li, it is also obvious that $k'_2 \gg k'_{-1}$.

Internal co-ordination of the Li atom takes place to a different extent with each of the two isomeric vinyl-lithium compounds, so their ion-pairing characteristics, steric factors, and the (configurationally) destabilising effect of the *trans* β -electron-donating substituent (NR"₂) are all influencing simultaneously the k'_2/k'_{-2} ratio. However, the same result was obtained under conditions where contact ion pairs (reaction medium: DEE, DEE-hexane, hexane; Table, entries 4,5,9,10), solvent-separated ion pairs (reaction medium: THF, diethylene glycol-dimethyl ether; Table, entries 1—3,7,11—13), and free ions (reaction medium: THF with TMEDA or 18-crown-6 as solvating agents; Table, entries 6,8) were the intermediates involved in the addition reaction. Furthermore, compound (**8b**) was also the only or the main product formed on protonation of



either the methyl ester ^{21.25a,b} or the bulky t-butyl ester ^{25b} of the intermediate (**5b**)-Li ($\mathbf{R'} = \mathbf{CO}_2\mathbf{R}$, $\mathbf{R} = \mathbf{Me}$, $\mathbf{Bu'}$; $\mathbf{R''N-} =$ pyrrolidin-1-yl) obtained by deprotonation of the corresponding olefins. This indicates that the steric interaction which could affect the shifting of the (**5**)-Li=(**6**)-Li equilibrium towards (**5**)-Li (decreasing the k'_2/k'_{-2} ratio) is not sufficient to counteract the effect of the *trans*- β -NR''₂ group. It should, however, be mentioned that protonation of the t-butyl esters (in contrast to the methyl esters) of the (**5b**)-Li=(**6b**)-Li equilibrium mixture for the case of R''_2N = morpholino and 4-methylpiperazin-1-yl, resulted in mixtures of the corresponding products (**7b**) and (**8b**), in the ratio 1:4 and 1:3, respectively.^{25b}

It seems reasonable to assume that the reverse order of the configurational stabilities of the vinyl-lithium compounds (5b)-Li and (6b)-Li observed^{25b} for R''_2N = morpholino and 4methylpiperazin-1-yl, as compared to the other R"2N substituents used in the present work, is not due solely to the relatively larger steric interaction of the t-butyl ester groups in (6b)-Li. This assumption is based on the fact that compound (8b) was the main product of the protonation reaction of both the methyl (Table, entries 1,2) and the t-butyl^{25b} esters of the (5b)-Li \rightleftharpoons (6b)-Li equilibrium mixture for $R_2^{"N}$ = pyrrolidin-1yl. It might therefore be that an additional factor, which decreases significantly the R⁺ effect of the conjugated amino nitrogen atom (and the related k_2'/k'_{-2} ratio), is effective only in the case of the morpholine and the *N*-methylpiperazine groups, and not in the case of the other \mathbb{R}'_2 N-groups involved. This factor is revealed because of the steric interaction of the bulky tbutyl ester groups.

The results of a recent study on the ion-pair basicities of lithium amides in THF²⁶ are fully in line with the above assumption of a relatively smaller R⁺ effect associated with the morpholine and *N*-methylpiperazine substituents. It was reported²⁶ that the pK_a of di-isopropylamine (34.4) is much larger than that of morpholine (28.8). A shift similar to that of the (5)-Li=(6)-Li equilibrium towards (5)-Li, presumably for the same reason, was observed for the RO, rather than R["]₂N, derivatives of the corresponding methyl esters, when using phenyl ethers instead of the methyl ether.^{25a}

In summary, the results of the present study favour the conclusion that a *trans* β -NR["]₂ group (with the exception of such secondary amino groups as the morpholinyl and *N*-methylpiperazinyl groups) decreases the configurational stability of a vinyl-lithium compound, and that this effect, for the reaction system studied, is by far the dominant factor affecting the k'_2/k'_{-2} ratio.

It seems that the observed effect of a *trans* electron-donating (by I⁺ or R⁺) β -substituent on the configurational stability of α lithiated olefinic intermediates formed by the addition of lithium nucleophiles to activated acetylenes, or by deprotonation,^{21.25} is probably a general phenomenon. Thus, for example, the addition of RLi (R = Me, Bu) to PhC=C(O)-NMe₂,²⁷ HOCH₂C=CPh,²⁸ and to PhC=CPh²⁹ in aprotic solvents, resulted in relatively high yields of the (*E*)-isomers of the corresponding β -substituted olefins.

Experimental

All manipulations and reactions of the acetylenic compounds with the lithium amides were carried out under nitrogen and anhydrous conditions. The required amounts of THF and DEE were directly distilled into the reaction flask from a solution of sodium diphenylketyl in the corresponding ether; hexane was distilled twice over sodium. The lithium amides were prepared by adding an equimolar amount of BuLi (dissolved in hexane) to a solution of a secondary amine in the apolar solvent.

Reaction of Secondary Lithium Amides with Alkyl Esters of Acetylenecarboxylic Acids.—A solution of BuLi in hexane was added to a cooled (-80 °C) solution of the secondary amine in the apolar solvent (40 ml). The reaction mixture was stirred for 20 min at -80 °C and a solution of the ester of the acetylenic acid in that solvent (10 ml) then added dropwise. The reaction mixture was further stirred for 60 min, and methanol (2 ml) then added. After 10—15 min, ether-water was added, and the mixture then extracted with ether. The composition and yield of product(s) was determined by g.c. of the residue recovered from the organic extract. The residue was then separated by column chromatography (eluant: light petroleum–ethyl acetate). Amounts of reactants, yields, and ¹H n.m.r. data of the products obtained are given in the Table.

References

- (a) R. R. Schmidt, Bull. Soc. Chim. Belg., 1983, 92, 825 and references cited therein; (b) R. R. Schmidt and R. Hirsenkorn, Tetrahedron, 1983, 39, 2043; (c) R. R. Schmidt, in 'Organic Synthesis: An Interdisciplinary Challenge, ed. J. Streit, H. Prinzbach, and G. Schill, Blackwell Scientific Publications, 1985, pp. 281–294.
- 2 (a) J. I. Dickstein and S. I. Miller, 'Nucleophilic Attacks on Acetylenes,' in 'The Chemistry of the Triple Bond,' ed. S. Patai, John Wiley & Sons, 1978, ch. 19, pp. 813—955; (b) A. Bury, S. D. Joag, and C. J. M. Stirling, J. Chem. Soc., Chem. Commun., 1986, 124.
- 3 D. Y. Curtin and W. J. Koehl, Jr., J. Am. Chem. Soc., 1962, 84, 1967.
- 4 E. J. Panek, B. L. Neff, H. Cha, and M. J. Panek, J. Am. Chem. Soc., 1975, 97, 3996.
- 5 B. A. Feit, U. Melamed, R. R. Schmidt, and H. Speer, *Tetrahedron*, 1981, 37, 2143.
- 6 J. F. Arnett and H. M. Walborsky, J. Org. Chem., 1972, 37, 3678.
- 7 H. O. Hause and P. D. Weeks, J. Am. Chem. Soc., 1975, 97, 2785.
- 8 J. Shabtai, E. N. Inger, and H. Pines, J. Org. Chem., 1981, 46, 3795.
- 9 Y. Sato and S. Takenchi, Synthesis, 1983, 734.
- 10 B. A. Feit, U. Melamed, H. Speer, and R. R. Schmidt, J. Chem. Soc., Perkin Trans. 1, 1984, 775.
- 11 H. Okamura, Y. Mitsuhira, M. Miura, and H. Takei, Chem. Lett., 1978, 517.
- 12 P. Caramella and K. N. Houke, Tetrahedron Lett., 1981, 819.
- 13 Y. Sato and K. Hitomi, J. Chem. Soc., Chem. Commun., 1983, 170.
- 14 S. U. Gould and B. D. Remilard, *Tetrahedron Lett.*, 1978, 45, 4353; *ibid.*, 1978, 45, 4537.
- 15 (a) R. R. Schmidt and B. Schmid, *Tetrahedron Lett.*, 1977, 3583; (b) R. R. Schmidt, H. Speer, and B. Schmid, *ibid.*, 1979, 4277.
- 16 R. Muthukrishnan and M. Schlosser, Helv. Chim. Acta, 1976, 59, 13.
- 17 S. Raucher and G. A. Koople, J. Org. Chem., 1978, 43, 3794.
- 18 U. Schollkopf, D. Staforst, and R. Jeutsh, Liebigs Ann. Chem., 1977, 1167.
- 19 B. A. Feit, U. Melamed, R. R. Schmidt, and H. Speer, J. Chem. Soc., Perkin Trans. 1, 1981, 1329.
- 20 R. R. Schmidt, J. Tulbiersky, and P. Russegger, *Tetrahedron Lett.*, 1979, 4273.
- 21 B. A. Feit, B. Haag, J. Kast, and R. R. Schmidt, J. Chem. Soc., Perkin Trans. 1, 1986, 2027.
- 22 C. J. M. Stirling, J. Chem. Soc. Suppl. 1, 1964, 5856.
- 23 W. E. Truce and G. J. W. Tichenor, J. Org. Chem., 1972, 37, 2391.
- 24 M. T. Omar and M. N. Basyouni, Bull. Chem. Soc. Jpn., 1974, 47, 2325.
- 25 (a) R. R. Schmidt, J. Kast, and H. Speer, Synthesis, 1983, 725; (b) D. Lafont, M. Koch, and R. R. Schmidt, J. Carbohydr. Chem., 1986, 5, 601.
- 26 H. Ahlbrecht and G. Schneider, Tetrahedron, 1986, 42, 4729.
- 27 J. Klein and N. Aminadav, J. Chem. Soc. C, 1970, 1380.
- 28 L. I. Olson and A. Claesson, Tetrahedron Lett., 1974, 2161.
- 29 J. E. Mulvaney and D. J. Newton, J. Org. Chem., 1969, 34, 1936.

Received 5th March 1987; Paper 7/408