

The Effect of an Electron-donating β -Substituent on the Configurational Stability and Reactivity of Vinyl Carbanions

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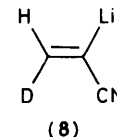
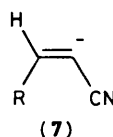
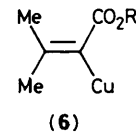
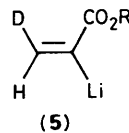
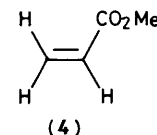
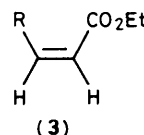
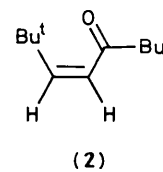
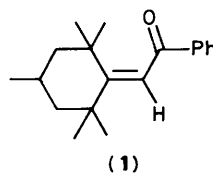
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The effect of an electron donating β -substituent A (A = $\text{N}(\text{CH}_2)_2\text{O}(\text{CH}_2)_2$, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{CH}_2$, OMe, SMe, or OPh) on the relative configurational stabilities and nucleophilic reactivities of the dimethyl esters of α -lithiated fumaric acid (**17**)-Li and maleic acid (**18**)-Li was studied in THF, by comparing their reaction products with electrophiles (MeOH, Ph_2CO , aldehydes). It was confirmed that when located at a *trans* position to the vinyl carbanion, the substituent A had two inter-related effects: decreasing the configurational stability of the vinyl carbanion and increasing its nucleophilic reactivity. The rapidly-established (**17**)-Li \rightleftharpoons (**18**)-Li equilibrium was completely on the (**18**)-Li side with A = OR, SR, NR_2 . The products formed were those derived from (**18**)-Li only (with MeOH) or from both (**17**)-Li and (**18**)-Li depending on both the relative nucleophilic reactivities of the intermediates and on the electrophilicity of the electrophile. The products derived from (**18**)-Li predominated with the more reactive electrophiles.

The information available in the literature about the factors which affect the configurational stability of vinyl carbanion salts is scattered and very incomplete. Calculated energy barriers for inversion of the configuration of methyl, ethenyl, and cyclopropyl carbanions are 20.2, 31.1, and 36.6 kcal mol⁻¹ respectively.¹

A clear correlation seems to exist between the ion-pairing characteristics of a lithiated alkene and its configurational stability;† the more contact the ion-pair the higher is its configurational stability. Full retention of the geometry was observed when *Z*-stilbene was treated with LDA and Ph_2CO or CO_2 in a benzene-pentane (1:1) mixture, but no retention at all in a benzene-DEE (1:1) mixture.² The extent of isomerization of *Z*-($\text{Ph}\bar{\text{C}}=\text{CHEt}$)Li⁺ in solution decreases when the solvating properties of the solvating additives decreases; the order is: TMEDA > DME > THF > DEE.³† Full retention of configuration of the derived vinyl carbanion was observed for the *Z*- $\text{PhCH}=\text{CHCN}$ -LDA- Ph_2CO reaction system in a DEE-hexane (3:1) mixture, while complete isomerization took place in THF, DME, or a DEE-hexane mixture (3:1) containing a crown ether.⁴ No systematic or detailed study on the effect of an α -substituent has been carried out; the relatively little data available suggest that an α -substituent which stabilizes the negatively charged carbon by delocalization, decreases the configurational stability of the corresponding lithiated alkene. Some of the activated olefins for which this observation holds are compounds (**1**),⁵ (**2**),⁶ (**3**),^{7,8} and (**4**).^{9,10} In contrast to the configurational instability of the intermediate (**5**),⁹ the corresponding cuprate (**6**) is stable¹¹ in THF, due to the relatively high covalent nature of the C-Cu bond. The species (**7**)¹² and (**8**)⁹ were relatively stable. α -Substituents stabilizing carbanions by an inductive effect, tend to stabilize the configuration of the derived vinyl carbanions. Thus, for example, vinyl carbanions derived from vinyl ethers $\text{BuOCH}=\text{CHCH}_2\text{OBu}$,¹³ vinyl sulphides (**9**),¹⁴ (**10**),¹⁵ and

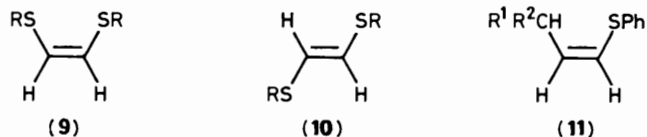


(**11**)¹⁶, vinyl selenides¹⁷ (**12**) and vinyl isocyanides (**13**)¹⁸ were configurationally stable. Vinyl carbanions having an α -alkyl substituent, such as those derived from propene¹⁹ or but-2-ene²⁰ are configurationally stable. Recently calculated values of the difference of energies of the linear and bent forms ($E_{\text{linear}} - E_{\text{bent}}$) of vinyl carbanions of the type $\text{CH}_2=\bar{\text{C}}-\text{R}$, were +36.6, +10.3, +5.0, and -5.7 kcal mol⁻¹ for R = H, CN, CO_2R , and CHO, respectively.²¹ These figures are consistent with the experimentally observed

† Thermodynamic configurational stability.

‡ TMEDA = Tetramethylethylenediamine; DME = dimethoxyethane; DEE = diethyl ether.

relative configurational stabilities of the various α -substituted lithiated alkene described above.



- (14) a: $^{15}\text{Y} = \text{CN}$, $\text{Z} = \text{SEt}$
 b: $^{15}\text{Y} = \text{S(O)R}$, $\text{Z} = \text{SR}$
 c: $^{10}\text{Y} = \text{S(O)Ph}$, $\text{Z} = \text{CH}_2\text{OMe}$
 d: $^{22}\text{Y} = \text{CN}$, $\text{Z} = \text{NH}_2$
 e: $^{23a}\text{Y} = \text{SPh}$, $\text{Z} = \text{OEt}$
 f: $^{23b}\text{Y} = \text{CO}_2\text{R}$, $\text{Z} = \text{MeNCOSEt}$

It has been suggested that one factor determining the site of the deprotonation of 1,2-disubstituted activated alkenes $\text{ZCH}=\text{CHY}$ (Y and $\text{Z} =$ electronegative substituents), is stabilization of the derived vinyl-lithium compound by the neighbouring substituent. This stabilization is affected by an internal complexation of the positive counterion by the β -substituent as in (14). A direct consequence of this mode of influence of the β -substituent, was a preferred stabilization of the *E*-configuration of the vinyl-lithium compound, resulting in regioselective deprotonation of the parent alkenes. Compounds (14a–f)^{15,10,15,22,23a,23b} are some representative examples.

There is evidence indicating that both kinetically- and thermodynamically-controlled deprotonations are affected by internal complexation.^{23b} Calculations done for *E*- β -aminoacrylonitrile²² have shown that intramolecular complexation (which leads to α -deprotonation) is energetically equivalent to the combined inductive and mesomeric effects, which are in favour of β -deprotonation. Even deprotonation of a non-activated vinylic C–H bond could be accomplished due to internal complexation, such as in (15)²⁴ or (16).²⁴ An additional

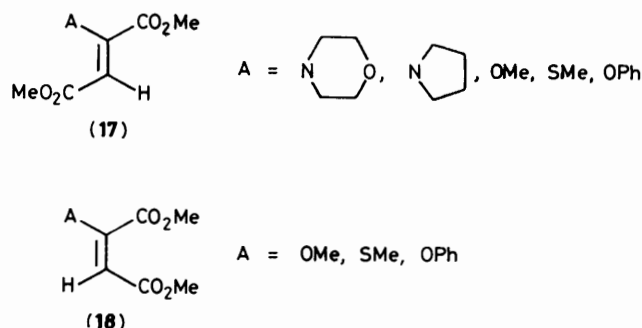


effect of an electron-donating β -substituent (besides coordination), which has not been hitherto described, was studied in the present work.

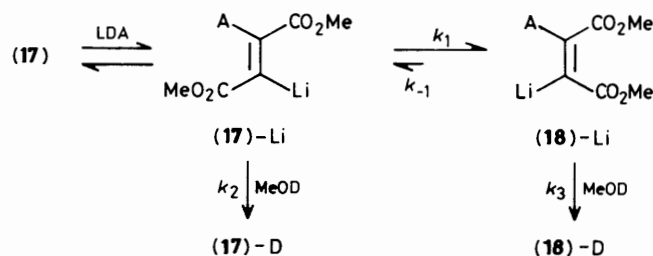
Results and Discussion

α -Substituted derivatives of the dimethyl esters of fumaric (17) and maleic (18) acids were treated with electrophiles in the presence of LDA in THF, at low temperatures (-90°C), by adding an excess of the electrophile to the alkene–base solution.

The electrophiles used were MeOD(H), Ph₂CO, PhCHO, EtCHO, MeCHO. The results obtained in the (17)–LDA–MeOD(H) reaction system (with $\text{A} = \text{NR}_2$, OMe, SMe) imply that the (17)–Li isomerized completely into (18)–Li in a very rapidly established equilibrium reaction (Scheme 1). The only product isolated was (18)–D, the β -deuteriated derivative of the

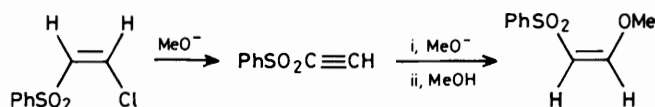
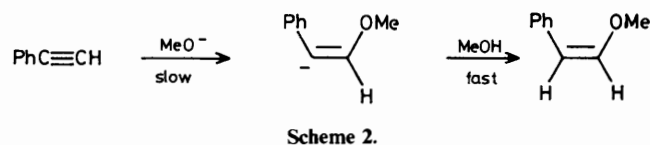


Z-isomer (18) (Table 1, Entries 3, 6, and 16–18, 23). The same results were obtained on treating compound (17) with LDA for 5 min or for 60 min before adding the MeOD (Entries 16, 17, 18,



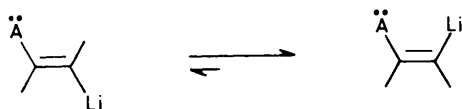
Scheme 1.

and 23). It might be well assumed that the product(s) obtained by quenching the (17)–LDA reaction mixture with the very reactive electrophile MeOD, reflect the exact position of the (17)–Li \rightleftharpoons (18)–Li equilibrium, since both k_2 and k_3 are obviously much larger than k_1 and k_{-1} . It follows that for the substrates used $k_1 > k_{-1}$. The observed retention of configuration of the derived vinyl carbanion intermediates in the $\text{PhC}\equiv\text{CH}-\text{MeO}^- - \text{MeOH}$ ²⁷ and in the $\text{Z}-\text{PhSO}_2\text{CH}=\text{CHCl}-\text{MeO}^- - \text{MeOH}$ ²⁸ reaction system (Schemes 2 and 3) might be regarded as support for the above assumption that



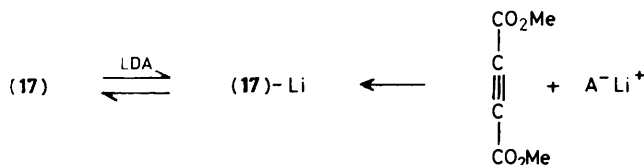
k_2 and $k_3 \gg k_1$ and k_{-1} . For $\text{A} = \text{OPh}$, a mixture of the two β -deuteriated isomers in almost equal amounts was obtained, indicating that $k_1 \approx k_{-1}$ in this case. A by-product (5%) isolated from this reaction mixture was dimethyl di-

isopropylaminomaleate. The very pronounced configurational instability* of (17)-Li in the case of A = OMe, SMe, NR₂, and to a lesser extent with A = OPh, suggests that the configurational stability of the vinyl-lithium compound is greatly reduced by the presence of an *E*-β-substituent due to its R⁺ effect (Scheme 4).



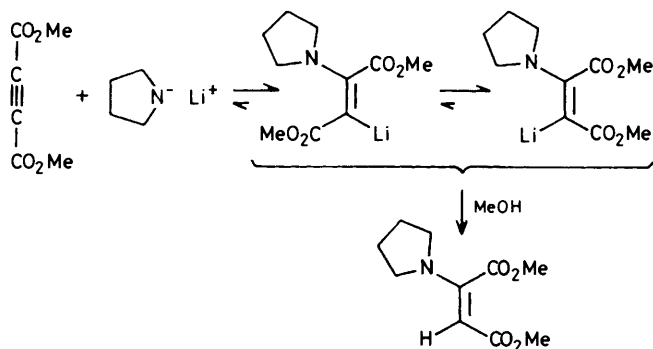
Scheme 4.

As expected, this destabilizing effect was smaller with A = OPh (as compared to A = NR₂, OMe, SMe) owing to conjugation to the benzene ring. This resulted only in a partial isomerization of (17; A = OPh)-Li to the corresponding (18)-Li (*cf.* entries 26 and 27 Table 1). The results obtained are consistent with the Hammett σ values of these substituents.²⁹ The addition of negatively charged nucleophiles to activated acetylenes is a reversible *trans*-addition reaction.^{30a} The vinyl-lithium compound (17)-Li could therefore be obtained either by deprotonation of (17) or by addition of A⁻Li⁺ (Scheme 5).



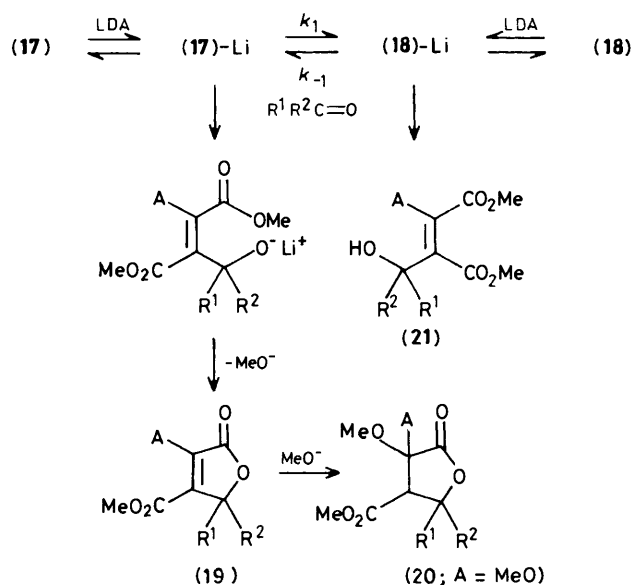
Scheme 5.

Protonation of the reaction mixture of each of these two reactions should yield the same product(s). The reaction of lithium pyrrolidide with compound (17) in THF at -90 °C, followed by quenching with MeOH, resulted (as expected) in the dimethyl α -pyrrolidinomaleate.



Scheme 6.

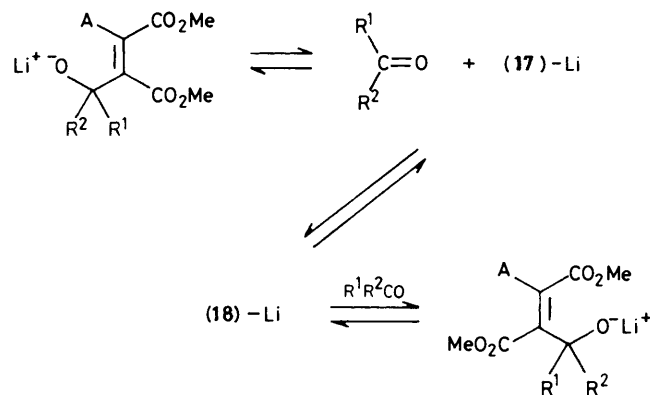
The main products isolated in the reaction of either (17) or (18) with several carbonyl compounds R¹R²C=O (Ph₂CO, PhCHO, EtCHO, MeCHO) are presented in the following general reaction Scheme 7. The lactone (20) was formed *in situ* by the addition of MeO⁻ to the dihydrofuran (19). The products formed were those derived from (17)-Li only, or from both (17)-Li and (18)-Li. This was in contrast to the results



Scheme 7.

obtained with MeOD where one product—that derived from (18)-Li—was formed (except in the case of A = OPh).

An alternative reaction pathway for the *in situ* formation of at least part of the lactone (19) from the carbinol (21) might be possible as follows (Scheme 8):



Scheme 8.

This alternative was ruled out by treating each of several carbinols (21) with LDA in the presence of the corresponding carbonyl compound. In no case was the lactone (19) formed, and most or all of the carbinol was recovered (Table 1, Entries 28–30).

The results summarized in Tables 1 and 2 suggest that the type of products formed (see Scheme 7), their yields, the substituent A, the nucleophilic reactivities and the configurational stabilities of (17)-Li and (18)-Li, and the electrophilic reactivities of the electrophiles—all these are interrelated. A clear trend was observed of an increase of the yield of the carbinol (21) on account of the lactone (19), on either increasing the electrophilic reactivity of the electrophile or on decreasing the nucleophilic reactivity of the vinyl-lithium compound, derived from the alkenic substrate, under comparable conditions. Compound (19), derived from (17)-Li was the only or the main product on treating the relatively weak electrophiles Ph₂CO and PhCHO with either (17) or (18) having A =

* All reactions were carried out under thermodynamically-controlled conditions.

Table 1. Reaction of compounds (17) and (18) with electrophiles in presence of LDA^a

| Entry | Alkene | Amount (mmol) | LDA (mmol) | Electrophile | Amount (mmol) | t_1 t_2 (min) | | Reaction products (g, %) |
|-----------------|-------------------------------|---------------|------------------|-----------------------|------------------|----------------------|-----|--|
| | | | | | | | | |
| 1 | (18)-morpholino | 2.2 | 4.4 | PhCHO | 7.3 | 30 | 75 | (19) (0.64, 93) |
| 2 | (18)-morpholino | 2.2 | 4.4 | MeCHO | 7.3 | 45 | 60 | (19) (0.18, 34); (21) (0.07, 11.6) |
| 3 | (18)-morpholino | 2.2 | 4.4 | MeOD | 21.2 | 90 | 60 | (18)-D (0.50, 100) |
| 4 ^b | (18)-pyrrolidino | 2.17 | 2.4 | PhCHO | 4.35 | 60 | 120 | (19) (0.44, 70) |
| 5 ^b | (18)-pyrrolidino | 2.17 | 2.4 | MeCH ₂ CHO | 4.35 | 60 | 180 | (19) (0.43, 83) |
| 6 ^b | (18)-pyrrolidino | 2.17 | 2.4 | MeOD | 4.35 | 60 | 0 | (18) _{total} = (18) + (18)-D (0.50, 100); (18) (0.075, 15); (18)-D (0.425, 85) |
| 7 | (18)-D, MeO | 1.5 | 3.0 | Ph ₂ CO | 5.0 | 30 | 90 | (20) (0.51, 95); Ph ₂ CHOH (0.23, 42) |
| 8 | (17)-MeO | 1.5 | 3.0 | | 5.0 | 0 | 60 | (20) (0.31, 58) |
| 9 | (17)-MeO | 1.5 | 3.0 | | 1.0 ^c | 35 | 30 | (19) (0.134, 54); (20) (0.026, 5); Ph ₂ CHOH (0.100, 54) |
| 10 | (17)-MeO | 1.5 | 3.0 ^m | Ph ₂ CO | 1.5 ⁿ | 15 | 30 | (18) (0.79, 30); (20) (0.201, 53) ^o |
| 11 | (18)-D, MeO | 1.5 | 3.0 | | 5.0 | 0 | 60 | (20) (0.18, 30); (18)-D (0.026, 10) ^d |
| 12 | (17)-MeO | 1.5 | 3.0 | PhCHO | 5.0 | 15 | 60 | (19) (0.065, 17.6); (21) (0.12, 28.6); PhCH ₂ OH (0.095, 29) |
| 13 ^e | (17)-MeO | 1.5 | 3.0 | | 5.0 | 15 | 60 | (19) (0.104, 28.1); (21) (0.11, 26.2); PhCH ₂ OH (0.028, 8.5) |
| 14 ^b | (17)-MeO | 2.9 | 3.2 | | 5.0 | 30 | 60 | (19) (0.115, 16); (21) (0.130, 16) |
| 15 ^b | (17)-MeO | 2.9 | 3.2 | MeCHO | 5.0 | 15 | 120 | (19) (0.081, 15); (21) (0.171, 27) |
| 16 | (17)-MeO | 2 | 4 | MeOD | 21.2 | 5 | | (18)-D (0.270, 77) |
| 17 | (17)-MeO | 1.5 | 3 | | 21.2 | 60 | 60 | (17)-D (0.184, 70) |
| 18 ^f | (17)-MeO | 2 | 4 | | 21.2 | 5 | | (18)-D (0.270, 77) |
| 19 | (17)-MeS | 1.5 | 3 | Ph ₂ CO | 5.0 | 30 | 60 | (19) (0.300, 59); (21) (0.19, 36) |
| 20 | (17)-MeS | 1.5 | 3 | | 5.0 | 0 | 60 | (19) (0.19; 37.5); ^g (21) (0.22, 39.4); (17) + (18) ^g (0.064, 22.5) |
| 21 | (17)-MeS + (18)-MeS | 2.6 | 2.6 | PhCHO | 5.0 | 30 | 180 | (19) (0.275, 40); (21) (0.156, 21) |
| 22 | (17)-MeS | 1.5 | 3.0 | MeCH ₂ CHO | 5.0 | 30 | 60 | (19) (0.19, 58.6); (21) (0.15, 40) |
| 23 | (17)-MeS | 1.5 | 3.0 | MeOD | 21.2 | 5 | 30 | (18)-D (0.285, 100) |
| 24 | (17)-PhO | 1.06 | 2.12 | Ph ₂ CO | 5.0 | 0 | 60 | (21) (0.34, 77); ^j Ph ₂ CHOH (0.09, 23) |
| 25 | (17)-PhO | 1.06 | 2.12 | MeCH ₂ CHO | 5.0 | 30 | 60 | (19) (0.03, 10.8); (21) (0.18, 58); ⁱ (17) + (18) (0.10, 40) |
| 26 | (17)-PhO | 1.06 | 2.12 | MeOD | 21.0 | 30 | 60 | (17) + (18) ^k _{total} (0.13, 52); (17) (0.003, 1.1); (17)-D (0.088, 35.3); (18) (0.009, 3.6); (18)-D (0.03, 12); (18)-NPr ₂ (0.03, 12) |
| 27 | (18)-PhO | 1.06 | 2.12 | MeOD | 21.0 | 30 | 60 | (17) + (18) ^k _{total} (0.13, 52); (17)-D (0.062, 24.8); (18)-D (0.068, 27) |
| 28 | (18)-MeO, PhCH(OH) | 0.72 | 2.4 | PhCHO | 2.45 | 180 | | (21) (0.15, 75) ^q |
| 29 | (18)-MeS, Ph ₂ COH | 0.27 | 0.54 | Ph ₂ CO | 0.81 | 60 | | (21) (0.10, 100); Ph ₂ CHOH (0.03, 30.3); Ph ₂ CO (0.05, 36) |
| 30 | (18)-MeS, EtCH(OH) | 0.36 | 0.73 | | 1.09 | 60 | | (21) (0.090, 100) |

^a The general procedure for the reaction is described in the Experimental section. ^b Results published by R. R. Schmidt, J. Kast, and H. Speer.²⁵ ^c A solution of Ph₂CO in THF (40 ml) was added into the alkene-LDA solution during 15 min. ^d Calculated from the ¹H n.m.r. spectrum of the crude product mixture. ^e The solvent used was diethyl ether. ^f The base used was KDA instead of LDA. ^g Calculated from the ratio of the integrations of the SMe absorption bands in the ¹H n.m.r. spectrum of the crude product mixture: δ 2.07 [SMe of (21)]; δ 2.83 [SMe of (19)]; δ 2.37, 2.35 [SMe of (17) and (18)] = 37.5:40:22.5. ^h Using either (17) or (18) or a mixture of these two makes no difference since the same equilibrium mixture of the corresponding vinyl carbanions lithium salts is reached in presence of the base. ⁱ A solution of (17) and Ph₂CO in THF was added into the cooled LDA solution during 20 min. ^j The lactone (19) was not obtained. ^k ¹H N.m.r. spectroscopy and t.l.c. of the crude product show no presence of (19). ^l [(17) + (18)]_{total} = (17) + (17)-D + (18) + (18)-D the yield of each of these was calculated from the ¹H n.m.r. spectrum of [(17) + (18)]_{total} mixture. ^m No lactone could be detected. ⁿ The base used was lithium tetramethylpiperidide (LTMP), prepared by addition of the required amount of Bu^tLi into a solution of tetramethylpiperidine in THF at -90 °C. ^o A solution of Ph₂CO in THF (45 ml) was added dropwise during 75 min into the (17)-LDA solution at -90 °C. ^p Ph₂CHOH was not formed in presence of LTMP.²⁶ ^q A solution of the electrophile and the carbinol in THF was added in one portion into the cooled LDA-THF solution (details in the Experimental section).

morpholino, pyrrolidine, or OMe (Table 1, Entries 1, 4, 7, and 9). Reaction of (17) or (18) having A = OMe with Ph₂CO gave one product—compound (19) [which was further converted *in situ* to compound (20)], but its reaction with the relatively more reactive electrophile PhCHO resulted in a mixture of the corresponding products (19) and (21) (compare Entries 7, 11, and 12–14). On the other hand, reaction of compound (18) (A = morpholino), with PhCHO gave one product—the corresponding lactone (19) (Entry 1). When substrate A has a smaller R⁺ effect (A = SMe instead of OMe), mixtures of (19) and (21) were obtained not only on reaction with the relatively reactive electrophiles (PhCHO and EtCHO) (Table 1, Entries

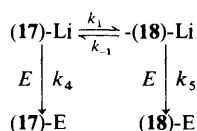
21 and 22), but also with the weak electrophile Ph₂CO (compare Entries 21 and 22 to Entries 19 and 20). Accordingly, on treating the weak electrophile Ph₂CO with the substrate (A = OPh) compound (19) was not obtained at all, the only product obtained being the corresponding carbinol (21) (77%) (Table 1, Entry 24).

The relative yields of the products formed on reacting either (17)-Li or (18)-Li with an electrophile E should depend on the magnitude of the rate constants involved, k_1 , k_{-1} , k_4 and k_5 (Scheme 9), and on the relation between the ratios k_1/k_{-1} and k_4/k_5 : The (17)-Li \rightleftharpoons (18)-Li equilibrium was in favour of (18)-Li for the substrates (17) and (18) used, which all had an A

Table 2.^a

| Alkene | Electrophiles and products | | | | |
|------------------|--|--|--------------------------|-------------------------|---------------------------------|
| | Ph ₂ CO | PhCHO | EtCHO | MeCHO | MeOD |
| (18)-morpholino | | e-1: (19) 93 | | e-2: (19) 34, (21) 11.6 | e-3: (18-D) 100 |
| (18)-pyrrolidino | | e-4: (19) 70 | e-5: (19) 83 | | e-6: (18) 15, (18-D) 85 |
| (18)-D, MeO | e-7: (20) 95 ^b | | | | |
| (17)-MeO | e-8: (20) 58 | e-12: (19) 17.6, (21) 28.6 e-13: (19) 28.1, (21) 26.6 e-14: (19) 16, (21) 16 | | | |
| (17)-MeS | e-19: (19) 59, (21) 36 e-20: (19) 37.5, (21) 39.4 | | e-22: (19) 58.6, (21) 40 | | e-23: (18-D) 100 |
| (17)-PhO | e-24: (21) 77 | | e-25: (19) 10.8, (21) 58 | | |
| (18)-PhO | | | | | e-27: (17-D) 24.8, (18-D) 27 |

^a Table 2 summarizes some of the results presented in Table 1 in a way that makes it convenient to compare the products obtained in the reactions of the various alkenes with the same electrophile, for each of the electrophiles used. ^b e- Stands for entry; the second and third figures are those of the product(s) and the yield, respectively.



Scheme 9.

group for which $R^+ > I^-$. The experimental results suggest however, that the nucleophilic reactivity of (17)-Li is larger than that of (18)-Li. Two borderline cases might be possible depending on the electrophile used and on the substituent A, under comparable conditions. (a) If for a certain E k_4 and $k_5 \gg k_1$ and k_{-1} (Scheme 9), it might be well assumed that in spite of $k_4 > k_5$ there will be no shift in the pre-established (17)-Li \rightleftharpoons (18)-Li equilibrium during the reaction with E. The yield of the reaction products will therefore represent the composition of this pre-established equilibrium mixture.

(b) For a certain relatively less reactive electrophile, for which the conditions of $k_1 > k_{-1}$ and $k_4 > k_5$ still hold, but the condition of k_4 and $k_5 \gg k_1$ and k_{-1} does not, the equilibrium will be shifted in the direction of formation of the product derived from (17)-Li.

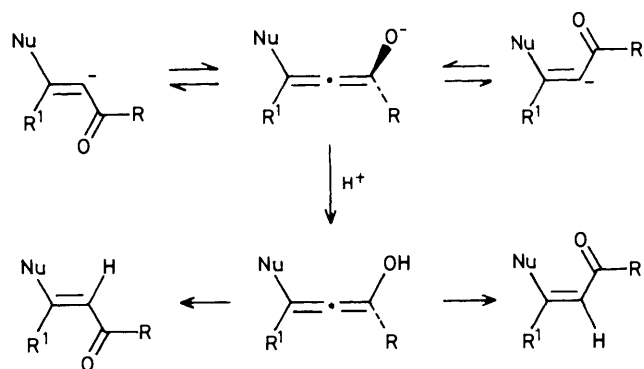
Case (a) is exemplified by the reaction of MeOD with substrates having A = pyrrolidino, morpholino, OMe, and SMe, for which the only product obtained was (18)-D (Entries 6, 3, 16, and 23). Case (b) is exemplified by the reactions of the following substrate-electrophile pairs: pyrrolidino-PhCHO; pyrrolidino-EtCHO; morpholino-PhCHO; OMe-Ph₂C=O (Table 1, Entries 4, 5, 1, 7, 8, and 10). In between are all other cases originating from A having a relatively small R^+ effect [(17)-SMe-Ph₂CO; (17)-OPh-MeOD], or from the electrophile being less reactive than MeOD and more reactive than Ph₂CO [(17)-OMe-PhCHO; (17)-morpholino-MeCHO], or from a combination of both these factors [(17)-SMe-PhCHO; (17)-SMe-EtCHO; (17)-OPh-PhCHO]. For these intermediate cases, mixtures of the two main products resulting from the simultaneous reactions of (17)-Li and (18)-Li with E are expected. The yields will then be affected by the relation of the two ratios k_1/k_{-1} and k_4/k_5 .

It is clear from the results of the present work that a substituent A having an R^+ net effect and located at a β -position *trans* to the C-Li bond, has two inter-related effects which are in direct correlation to each other: decreasing the configurational stability (increasing k_1/k_{-1}) of the vinyl-lithium compound and increasing its nucleophilic reactivity. Based on this dual effect of A on the results obtained (Tables 1 and 2), it was possible to

rank the A substituents with regard to their effect of decreasing the configurational stability of a vinyl-lithium compound of the type $AC^{\ominus}CLi$ in the following order: morpholino > pyrrolidino > OMe > SMe > OPh. This is also the decreasing order of the nucleophilic reactivity of the corresponding lithiated alkene depending on A.

A certain difficulty is involved in these interpretations and in the derived conclusions, which are based on the types of the products obtained and their yields. This is due to the difficulty of sorting out the relative contributions of each of the two factors operating on the reactivity, *i.e.* the configurational stability and the nucleophilicity of the lithiated alkene. Thus, for example the yield of the configurationally inverted product could have been controlled by either the configurational instability of the *E*-carbanion or by its greater nucleophilicity. Both these properties are constitution-variable on one hand, whereas the nucleophilicity is also electrophile-variable on the other. As a result the conclusion drawn as to the effect of the electron-donating *trans*- β -substituent on the configurational stability and the nucleophilic reactivity of a lithiated alkene, should be regarded to some extent as a tentative one.

It has been suggested in connection with addition reactions of charged nucleophiles to activated acetylenes $R'C\equiv CY$, that vinyl carbanion intermediates bearing charge-delocalizing α -substituents ($Y = COR, SO_2R, NO_2, Ar, etc.$) have relatively low isomerization barriers, and are expected to isomerize to an allenic-type intermediate.^{30b} It is claimed^{30b} that reaction of



such an equilibrium mixture with an electrophile, which preferentially attacks the oxygen, requires that a stereoconvergent product becomes probable. This, as a matter of fact, has been regarded as evidence for the involvement of the allenic

| | | | | | | | | | |
|--|---------------|---|-----------------------|------------------|------------------------|-----------------------|------------------------|------------------|-------------------|
| $\overline{\text{OCOC(MeS)=C(CO}_2\text{Me)CPh}_2}$ | 91 | C ₁₉ H ₁₆ D ₄ O ₅ S | 2.83 (s, 3 H) | 3.83 (s, 3 H) | 7.20—7.55 (m, 10 H) | | | | |
| $\text{MeS(MeO}_2\text{C)C}\equiv\text{C(CO}_2\text{Me)CPh}_2$ | 71 | C ₂₀ H ₂₀ O ₅ S | 2.07 (s, 3 H) | 3.47 (s, 3 H) | 3.87 (s, 1 H) | 4.59 (s, 1 H) | 7.15—7.85 (m, 10 H) | | |
| $\overline{\text{OCOC(MeS)=C(CO}_2\text{Me)CH(CH}_2\text{Me)}}$ | | C ₉ H ₁₂ O ₄ S | 0.95 (t, 3 H) | 1.70 (m, 1 H) | 2.17 (m, 1 H) | 2.77 (s, 3 H) | 3.87 (s, 3 H) | 5.08 (m, 1 H) | |
| $\text{MeS(MeO}_2\text{C)C}\equiv\text{C(CO}_2\text{Me)CH(OH)CH}_2\text{Me}$ | | C ₁₀ H ₁₆ O ₅ S | 0.98 (t, 3 H) | 1.70 (m, 1 H) | 1.83 (m, 1 H) | 2.29 (s, 3 H) | 3.18 (d, 1 H) | 3.77 (s, 3 H) | 3.85 (s, 3 H) |
| $\overline{\text{OCOC(MeS)=C(CO}_2\text{Me)CHPh}}$ | | C ₁₃ H ₁₂ O ₄ S | 2.82 (s, 3 H) | 3.72 (s, 3 H) | 5.83 (s, 1 H) | 6.00—7.60 (m, 5 H) | | | 4.61 (dd, 1 H) |
| $\text{MeS(MeO}_2\text{C)C}\equiv\text{C(CO}_2\text{Me)CHPh}$ | | C ₁₄ H ₁₆ O ₅ S | 2.35 (s, 3 H) | 3.65 (s, 3 H) | 3.88 (s, 3 H) | 5.89 (d, 1 H) | 7.15—7.50 (m, 5 H) | | |
| $\text{PhO(MeO}_2\text{C)C}\equiv\text{CHCO}_2\text{Me}$ | 48 | C ₁₂ H ₁₂ O ₅ | 3.72 (s, 3 H) | 3.75 (s, 3 H) | 6.60 (s, 1 H) | 6.80—7.50 (m, 5 H) | | | 61.47 (61.01) |
| $\text{PhO(MeO}_2\text{C)C}\equiv\text{CHCO}_2\text{Me}$ | | C ₁₂ H ₁₂ O ₅ | 3.65 (s, 3 H) | 3.93 (s, 3 H) | 5.17 (s, 1 H) | 7.00—7.58 (m, 5 H) | | | 4.78 (5.12) |
| $\text{PhO(MeO}_2\text{C)C}\equiv\text{C(CO}_2\text{Me)CPh}_2$ | | C ₂₃ H ₂₂ O ₆ | 3.52 (s, 3 H) | 3.58 (s, 3 H) | 4.20 (s, 1 H) | 6.50—6.77 (m, 2 H) | 6.95—7.75 (m, 13 H) | | |
| $\text{PhO(MeO}_2\text{C)C}\equiv\text{C(CO}_2\text{Me)CH(OH)CH}_2\text{Me}$ | | C ₁₅ H ₁₈ O ₆ | 1.04 (t, 3 H) | 1.72 (m, 2 H) | 2.25 (m, 1 H) | 3.63 (s, 3 H) | 3.83 (s, 3 H) | 4.70 (t, 1 H) | 61.42 (61.22) |
| $o\text{-CNC}_6\text{H}_4\text{O(MeO}_2\text{C)C}\equiv\text{CHCO}_2\text{Me}$ | 70 | C ₁₃ H ₁₁ NO ₅ | 3.73 (s, 3 H) | 3.78 (s, 3 H) | 6.79 (s, 1 H) | 6.89—7.71 (m, 4 H) | | | 59.73 (59.77) |
| $o\text{-CNC}_6\text{H}_4\text{O(MeO}_2\text{C)C}\equiv\text{CHCO}_2\text{Me}$ | 51 | C ₁₃ H ₁₁ NO ₅ | 3.73 (s, 3 H) | 3.90 (s, 3 H) | 5.41 (s, 1 H) | 7.19—7.70 (m, 4 H) | | | 4.25 (4.24) |
| $\text{Morpholino(MeO}_2\text{C)C}\equiv\text{CHCO}_2\text{Me}$ | 52 (PE-EA) | C ₁₀ H ₁₅ NO ₅ | 3.00—3.25 (m, 4 H) | 3.60—3.85 (m) | 3.65 (s) | 3.91 (s) | 4.80 (s, 1 H) | | 5.30 (5.36) |

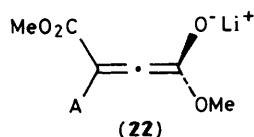
(10 H)

Table 3. (continued)

| Compound ^a | M.p. (°C) | Formula | H ^{A,B} | H ^B | H ^C | H ^D | H ^E | H ^F | Analysis (%) Found (required) | | | m/z |
|---|-----------|--|-----------------------|------------------------|------------------|-----------------------|------------------|----------------|----------------------------------|----------------|----------------|-----|
| | | | | | | | | | C | H | N | |
| Morpholino(MeO ₂ C)C≡C(DCO ₂ Me) _C A, B D | | C ₁₀ H ₁₄ NDO ₅ | 3.00—3.30 (m, 4 H) | 3.60—3.88 (m) | 3.70 (s) | 3.92 (s) | | | 63.58 (63.36) | 5.59 (5.65) | 4.58 (4.62) | 303 |
| OCOC(morpholino)=C(CO ₂ Me)CHPh B A C D | 132 | C ₁₆ H ₁₇ NO ₅ | 3.57 (s, 3 H) | 3.76—3.84 (m, 8 H) | 5.97 (s, 1 H) | 7.23—7.35 (m, 5 H) | | | | | | |
| OCOC(morpholino)=C(CO ₂ Me)CHMe B C A | | C ₁₁ H ₁₅ NO ₅ | 1.47 (d, 3 H) | 3.52—3.90 (m, 11 H) | 6.12 (q, 1 H) | | | | | | | |
| Pr ₂ N(MeO ₂)C≡CHCO ₂ Me A, B D E C | | C ₁₂ H ₂₁ NO ₄ | 1.29 (d, 12) | 3.52 (h, 2 H) | 3.64 (s, 3 H) | 3.92 (s, 3 H) | 4.80 (s, 1 H) | | | | | |
| Pyrrolidino(MeO ₂ C)C≡CHCO ₂ Me A, B D E C | | C ₁₀ H ₁₅ NO ₄ | 1.97 (m, 4 H) | 3.27 (m, 4 H) | 3.65 (s, 3 H) | 3.96 (s, 3 H) | 4.53 (s, 1 H) | | 56.56 (56.33) | 6.96 (7.09) | 6.69 (6.57) | 212 |

^a c And t over the double bond refer to *cis*- or *trans*-displacement of the methoxycarbonyl groups. ^b Chemical shifts are reported in δ values (CDCl₃) with Me₄Si as internal reference, using a 60 MHz spectrometer. ^c M⁺ = MeOH.

intermediate in the isomeric vinyl carbanions equilibrium. In the present study, protonation (or deuteration) of the equilibrium mixture containing the lithiated derivatives (17)-Li and (18)-Li resulted in one product only—that derived from (18)-Li. We therefore suggest that the corresponding allenic-type intermediate (22) is not involved in the (17)-Li \rightleftharpoons (18)-Li



equilibrium, and does not take part in the reaction of this equilibrium mixture with methanol or with any other electrophiles used.

In spite of the abundance of phenomena studied in the present work, it has not been recognized or interpreted in the literature that a significant factor influencing the reaction pathways of a negatively-charged alkenic carbon atom is an effect exerted by an electron-donating *trans*- β -substituent on the configuration and reactivity of this carbanion. The following are a few of such previously described cases. H-D Exchange of (*Z*)-Ph(2-BrC₆H₄)C=CHCN³¹ and of 2,2,4,6,6-pentamethylcyclohexylidene-ethanonitrile³² in MeOD-MeO⁻ solution took place with retention of the configuration of the vinyl carbanion intermediate. However, the rates of isomerization were about the same as the rates of exchange, when a *trans* β -NR₂ group was introduced into the α,β -unsaturated nitrile, such as in R₂N(Me)C=CHCN.³³ Similarly, the sulphide formed in the MeC \equiv CCN-EtS⁻Na⁺-EtSH reaction system was that derived from *Z*-MeCH=CHCN, indicating that protonation of the initially formed intermediate EtS(Me)C \equiv CCN was slower than its isomerization to Me(SEt)C \equiv CCN.³⁴ In line with this effect the main products of the base-catalysed addition of a β -dicarbonyl compound to alkyl propiolate and to dialkyl acetylenedicarboxylate, were *E*- β -substituted alkyl acrylate and a maleic ester derivative respectively.³⁵ Also, as expected, α -lithiated *Z*-RS $\overset{\ominus}{\text{C}}\text{H}=\text{CH}-\text{S}(\text{O})\text{R}$ isomerized into the *E*-isomer, while the β -lithiation product was configurationally stable.¹⁵

It should be stated, in summary, that the observed configurational stability and nucleophilic reactivity of the α -lithiated trisubstituted activated ethylenes studied in the present work, are determined by the relative contributions of each of several factors which influence these two features. In conclusion we suggest that a stereoelectronic effect exerted by A is responsible for both the lower configurational stability and the enhanced nucleophilicity of (17)-Li as compared with that of (18)-Li. This might be due to different interactions of the lone pair orbital of A with each of the *Z*- and *E*-vinyl carbanion orbitals.

Experimental

THF was refluxed over sodium and then distilled. A solution of sodium diphenylketyl in the distilled THF was prepared, and the required amounts were directly distilled into the reaction flask. LDA was prepared by adding an equimolar amount of Bu⁻Li (dissolved in hexane) into the di-isopropylamine-THF solution. All manipulations and the reactions of alkenes with electrophiles in presence of LDA, were carried out under nitrogen and anhydrous conditions.

The α -methoxy and α -phenoxy derivatives of the dimethyl esters of fumaric acid (17) and maleic acid (18) were prepared according to the methods described by Winterfeldt and Preuss.³⁶ The mixtures of the *cis* and *trans* isomers formed were separated by column chromatography.

Dimethyl α -Morpholinomaleate [18; A = N(CH₂)₂O(CH₂)₂].—The reaction of morpholine with acetylenedicarboxylic acid dimethyl ester was carried out as described before for other secondary amines.^{36,37} A solution of the acetylenic ester (7.1 g, 0.05 mol) in absolute diethyl ether (50 ml) was added dropwise at room temperature to a stirred solution of morpholine (4.8 g, 0.055 mol) in diethyl ether (100 ml). The reaction mixture was stirred for 15 h, the ether evaporated, and the residue was distilled. The fraction boiling at 115–118 °C/0.15 mmHg was collected and recrystallized to give dimethyl α -morpholinomaleate (8.0 g, 70%), m.p. 54–55 °C (lit.,³⁷ 57–59 °C) (from 1:1 ethyl acetate–light petroleum).

Dimethyl α -pyrrolidinomaleate was similarly prepared as described previously.²⁵

The Reaction of the Alkenes (17) and (18) with Electrophiles in the Presence of LDA: General Procedure.—A solution of either (17) or (18) in THF (10 ml) was added dropwise during 5 min to an LDA-THF (25 ml) solution at –90 °C. After the reaction had been stirred for *t*₁ min the electrophile was introduced in one portion, and the reaction mixture was further stirred for *t*₂ min at –90 °C. At the end of this period water was added to stop the reaction, followed by extraction with ether. The residue recovered from the organic layer was subjected to column chromatography to give the pure products. Data concerning the reactants used and their concentrations, *t*₁ and *t*₂ values, the products obtained and their yields are given for each experiment in Table 1. The structures of the alkenic starting materials and the products obtained, ¹H n.m.r. data, results of elemental analysis and mass spectra data are given in Table 3.

Reaction of Pyrrolidine with Dimethyl Acetylenedicarboxylate in the Presence of Bu⁻Li.—A solution of Bu⁻Li (1.5 mmol) in hexane was added into a cooled (–90 °C) solution of pyrrolidine (0.13 ml, 1.5 mmol) in THF (40 ml). The reaction mixture was stirred for 20 min at –90 °C, followed by addition of dimethyl acetylenedicarboxylate (0.25 ml, 2 mmol) in one portion. The reaction mixture was further stirred for 60 min, and methanol (2 ml) added. After 15 min ether–water was added. The residue recovered from the organic layer was separated by column chromatography [eluant: light petroleum–ethyl acetate (1:1)] to give a quantitative yield of dimethyl α -pyrrolidinomaleate (18; A = NCH₂CH₂CH₂CH₂) 0.32 g as a yellow oily liquid.

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