On the mechanism of succinyl transfer from aryl enolsuccinates to enolates of arylketones: addition–elimination *vs.* alkoxide-assisted retro-ene reaction

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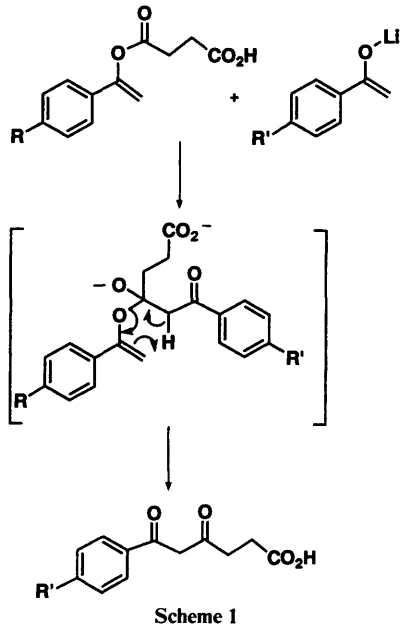
The mechanism of succinyl transfer from aryl enolsuccinates to the enolates of aryl ketones has been studied by deuterium exchange experiments and semi-empirical calculations. The calculations indicate that direct elimination is favoured over the ene mechanism. The results of a deuterium labelling study were also inconsistent with the ene mechanism.

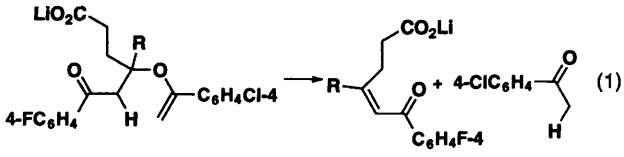
In a previous paper we described the succinyl transfer shown in Scheme 1.[1] In these reactions succinyl transfer from oxygen to carbon was achieved by forming a styryl lithium enolate at −78 °C and treating it with an enol succinate ester followed by warming to room temperature and subsequent work-up. An anion accelerated retro-ene reaction was proposed as a possible mechanism to account for this transfer.[2,3]



Scheme 1

We felt it would be fruitful to examine this reaction using semi-empirical calculations. The potential for alkoxide acceleration of the ene reaction was first investigated by Gad El Karim and co-workers in a MNDO theoretical study.[4a,b] Other than these two reports, there appears to be no systematic study of the alkoxide-assisted ene or retro-ene reactions. We systematically examined the two potential pathways to product formation with semi-empirical molecular orbital calculations.

Semi-empirical calculations were performed on the lithium enolate **1a** in order to obtain transition structures and enthalpies of activation for the proposed retro-ene and elimination processes leading to products **2a** and **3** [reaction (1)].[5] The MNDO Hamiltonian[7] (in CAChe™ MOPAC 94.1 based on MOPAC 6) was chosen since it is parametrized for lithium. No attempt was made to find the global minimum in either the starting lithium alkoxide or the products. The MNDO



1a; R = OLi
1b; R = H
1c; R = OH

2a; R = OLi
2b; R = H
2c; R = OH

3

(1)

Table 1 Enthalpies of activation for the retro-ene reactions of **1a–c** calculated by MNDO

Reactant	R	$\Delta H^{\ddagger}$/kcal mol^{-1}	$\Delta_r H$/kcal mol^{-1}	$\Delta S^{\ddagger}$/eu
1a	OLi	45.8	−47.7	−2.9
1b	H	60.1	−14.5	−3.7
1c	OH	55.3	−23.9	−5.4

calculated geometry of the concerted retro-ene transition structure is qualitatively similar to that obtained from a 3-21 G *ab initio* calculation for the propene–ethene ene reaction.[8] The calculated $\Delta H^{\ddagger}$ value for the retro-ene is 45.8 kcal mol^{-1} ($\Delta S^{\ddagger}$ = 2.9 eu).

The experimental activation energy for the retro-ene reaction of pent-1-ene is 49.9 kcal mol^{-1},† however, this value may be as high as 63 kcal mol^{-1}.[8] The calculated activation energy for this reaction is 60.6 kcal mol^{-1} at the MP2/6-31G*//RHF/3-21G[8] level while that for the retro-ene reaction of methyl 2-methylpent-4-enoate to propene and methyl acrylate is 50.2 kcal mol^{-1} at the MP2/6-31G*//RHF/6-31G level.[9] Thus we believe that our estimate of 45.8 kcal mol for the retro-ene reaction of **1a** leading to **2a** and **3** is reasonable.[10]

In our case the alkoxide substituent is on the carbon of the breaking C–O bond in the proposed retro-ene. We have carried out further MNDO calculations on the retro-ene reaction of **1b** and **c** in order to compare the possible effect of the lithium alkoxide substituent to H and OH. The results shown in Table 1 suggest that the retro-ene reaction is accelerated significantly by the lithium alkoxide substituent in **1a** relative to **1b** ($\Delta\Delta H^{\ddagger}$ = 14.3 kcal mol^{-1}) and **1c** ($\Delta\Delta H^{\ddagger}$ = 9.5 kcal mol^{-1}). The calculated $\Delta\Delta H^{\ddagger}$ values are typical for the oxy-anion effect.[3d] The enthalpies of the reaction increase dramatically in going from **1b** to **1a** ($\Delta\Delta_r H$ = 33.2 kcal mol^{-1}). Thus the reverse (ene)

† 1 cal = 4.184 J.

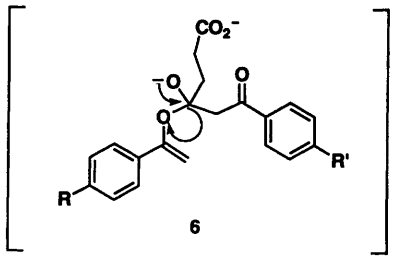
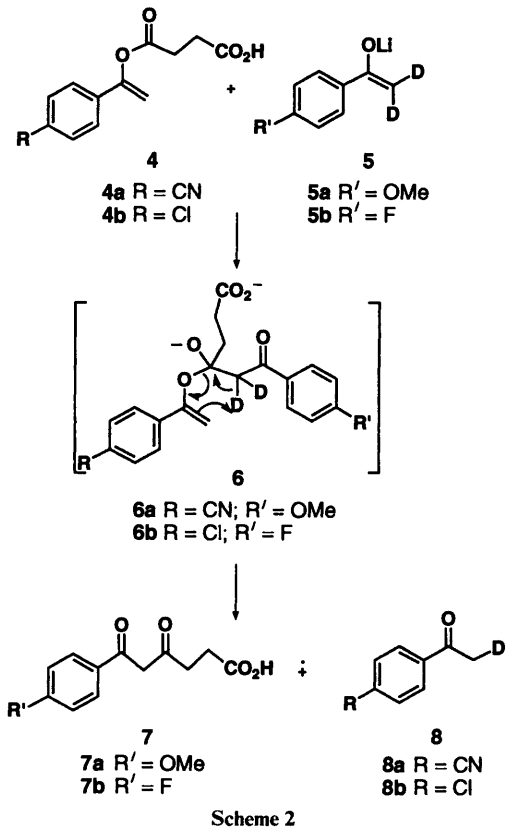


Fig. 1 Mechanism for the elimination reaction

reaction of 4-chloroacetophenone with **2a** ($\Delta H^{\ddagger}$ = 93.4 kcal mol^{-1}) is retarded by the alkoxide substituent relative to **2b** ($\Delta H^{\ddagger}$ = 79.2 kcal mol^{-1}) and **2c** ($\Delta H^{\ddagger}$ = 74.6 kcal mol^{-1}). Since electron-withdrawing groups on the ene acceptor enhance the rate of the reaction relative to H in unactivated acceptors,[12] it is likely that electron-releasing functionalities on the ene acceptor would lower the reaction rate.

The calculated $\Delta H^{\ddagger}$ value for the elimination (Fig. 1) is 5.4 kcal mol^{-1} ($\Delta S^{\ddagger}$ = 0.6 eu). This large difference in the calculated activation free enthalpies strongly suggests that the elimination mechanism is operative.

In conjunction with these calculations we endeavoured to examine this mechanism in a systematic way. Initially, we considered the possibility of deuterium exchange at room temperature from the enolate of [α,α,α-$^2H_3$]4-methoxyacetophenone **5a** to 4-cyanoacetophenone. This completely scrambled the deuterium atoms between the two arylketones. We then tried the same experiment at 0 and −78 °C. At −78 °C there was no detectable exchange at 6 h. We then attempted to rerun the reaction described in Scheme 2 at −78 °C for 6 h. No diketo-acid **7a** was detected. It was clear at this point that we required the acyl transfer to occur at low temperature. This being the case we chose the mixed system which afforded the fastest transfer in our previous studies.[1] We found that the reaction of the enolsuccinate **4b** where R = Cl and the enolate of [α,α,α-$^2H_3$]4-fluoroacetophenone **5b** gave complete O to C transfer in 6 h at −78 °C. We also determined that no scrambling of deuterium occurred when **5b** and 4-chloroacetophenone were kept at this temperature for 6 h.[13] The final experiment (shown in Scheme 2) showed no formation of the key mono α-deuterio-4-chloroacetophenone **8b** leaving group.[14] These data, coupled with the MNDO calculations, are not consistent with the anion accelerated ene reaction and strongly favour the direct elimination (Fig. 1).



Scheme 2

Experimental

Low temperature deuterium transfer

To a 200 ml round-bottom flask equipped with a thermometer, addition funnel and an N_2 inlet, lithium bis(trimethylsilyl)-amide (LHMDS) [1 M in tetrahydrofuran (THF), 6.8 ml, 6.8 mmol] and 15 ml THF were added and cooled to −78 °C. Under stirring, a precooled solution (−78 °C) of the [α,α,α-$^2H_3$]acetophenone **5** (6.9 mmol) in 10 ml THF was added rapidly. The resulting solution was stirred at −78 °C for 20 min. A precooled solution of **4** (3.4 mmol) in 50 ml THF was added at once. The solution was stirred for 6 h at −78 °C and without being allowed to warm, partitioned between diethyl ether (100 ml) and 2 M HCl (250 ml). A sample of the ether layer was then injected into the GCMS and monitored for the production of the diketo acid **7** and the [α-^{2}H]acetophenone **8** using the appropriate acetophenone and diketo acid as standards. The ether layer was then worked up as in ref. 1 to determine the yield of **7**.

Deuterium scrambling in acetophenone enolates

To a 200 ml round-bottom flask equipped with a thermometer, addition funnel and an N_2 inlet, LHMDS (1 M in THF, 6.8 ml, 6.8 mmol) and 15 ml THF were added and cooled to −78 °C. Under stirring, a precooled solution (−78 °C) of the [α,α,α-$^2H_3$]acetophenone (6.9 mmol) in 10 ml THF was added rapidly. A precooled solution (−78 °C) of the acetophenone (6.9 mmol) in 10 ml THF was added rapidly. In the low temperature experiment the reaction mixture was stirred at −78 °C for 6 h and partitioned without warming as above. In the experiment at room temp. the reaction mixture was allowed to warm to room temp. and kept at room temp. for 6 h before partitioning. Deuterium transfer was monitored by GCMS using the appropriate acetophenone as a standard.

Acknowledgements

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5 All geometries were fully optimized and transition structures were located with the SADDLE[12a] option. They were refined by minimizing the gradient norm using the eigenvector following technique[12b] and are characterized by calculating force constants.[12c] Only one negative (imaginary) frequency corresponding to the reaction coordinate was found for each transition structure.

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10 AM1 [13a] and PM3 [13b] calculations on **1** using a generic monovalent cation in place of lithium (sparkle option in MOPAC 6) provide results similar to the MNDO calculations.
11 (*a*) M. J. S. Dewar, E. G. Zoebisch, E. F. Healy and J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3902; (*b*) J. J. P. Stewart, *J. Comput. Chem.*, 1989, **10**, 221.
12 D. F. Taber, *Intramolecular Diels–Alder and Alder Ene Reactions*, Springer-Verlag, New York, 1984, pp. 64–65. This author proposed an alkoxide activated intramolecular ene reaction, p. 67.
13 We also examined this mechanism by a room temperature deuterium transfer study. The anion of [α,α,α-$^2H_3$]4-methoxyacetophenone **5a** was generated at −78 °C and treated with the enolsuccinate of 4-cyanoacetophenone **4a**. The reaction was allowed to warm to room temperature and was complete after 6 h. The reaction mixture was quenched with 5% HCl and the products extracted into diethyl ether. GCMS analysis indicated that we had obtained deuterium transfer to the 4-cyanoacetophenone although some [α,α-$^2H_2$] 4-cyanoacetophenone was detected. The production of the dideuterio material indicated that the deuterium transfer was due to scrambling rather than the ene mechanism.
14 Hewlett-Packard GC model 5890 and mass selective detector model 5971. were observed. No M + 1 above isotopic abundance was noted.

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