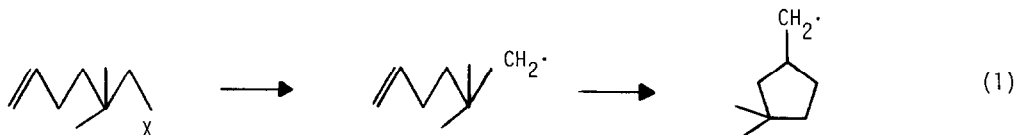EVIDENCE FOR SINGLE ELECTRON TRANSFER IN THE REACTION OF
A LITHIUM ENOLATE WITH A PRIMARY ALKYL IODIDE

E. C. Ashby* and J. N. Argyropoulos
School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332 USA

Abstract: Evidence for a radical process in the reaction of the lithium enolate of pro-
piophenone with a primary alkyl iodide was obtained by the observation of cyclization of
an appropriate radical probe, by the trapping of the radical intermediate and by the com-
parison of the relative rates of reactions of the probe alkyl iodide with the correspon-
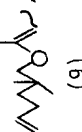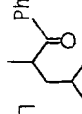ding bromide and tosylate.

The alkylation reaction of enolate anions is an important synthetic reaction whose
mechanism is generally recognized to be S_N2 in nature.[1] Nevertheless, radical intermediates
have been reported when enolates were allowed to react with ketones,[2,3] esters,[4] nitro-
benzene[2] and 2-chloro-2-nitropropane.[5] Furthermore, Zook observed small quantities of
alkanes when primary and secondary halides were allowed to react with enolate anions.[6]
Recently, we have reported that typical nucleophiles, e.g. OR^-, SR^-, NR_2^-, $LiCuR_2$ and metal
hydrides[7-10] which previously were thought to react with alkyl halides via an S_N2 process
actually proceed in some cases by a one electron transfer process. Hence, we embarked on
a detailed mechanistic study of the reaction of a typical enolate, lithiopropiophenone,
with cyclizable primary alkyl halide and tosylate probes in order to establish the extent
of radical formation in the reaction.

The radical probe chosen was 2,2-dimethyl-1-iodo-5-hexene and its bromo and tosylate
derivatives.[7,10] The compounds all contain a 5-hexenyl group which has been found previ-
ously to be a good probe for SET by exhibiting characteristic radical cyclization (eq. 1).[11]
An added feature of this probe is that it cannot undergo elimination.

$$(1)$$

The results of reacting 2,2-dimethyl-1-iodo-5-hexene (1) with lithiopropiophenone (2)
are shown in exps. 1-2 of Table I. The products of the reaction are the cyclic hydrocarbons
(7 and 8) as well as the O-alkylation compound (9) and the C-alkylation compounds (10 and 11).
The formation of the cyclic hydrocarbons (7 and 8) is highly suggestive of a radical inter-

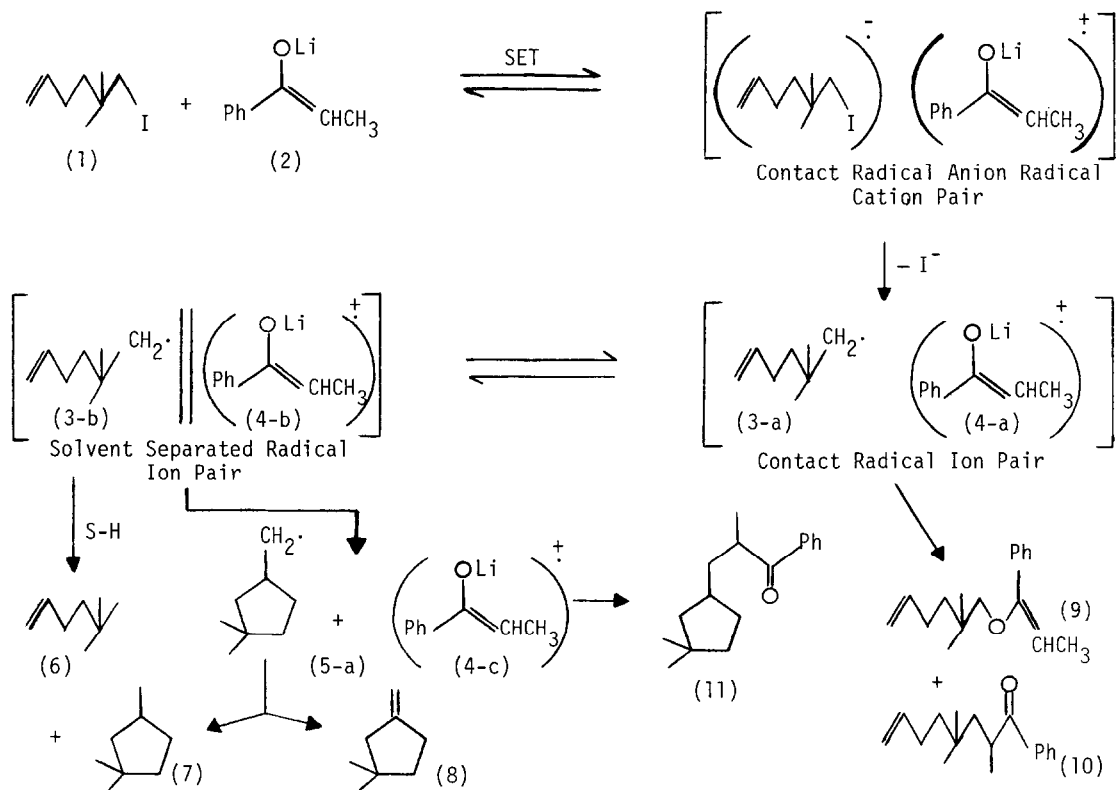Table I: Reaction of /\/\/\X with Lithiopropiophenone[a] in HMPA at 24°C.

Exp.	X in /\/\/\X	Molar Ratio RX: Trap: Enolate	Time (hrs)	Products (%)[b]						
				/\/\/\X	(6)	(7)	(8)	(9)	(10)	(11)
1	I	1:0:2	10	48	0	trace[c]	trace	42	8.2	0.74
2	"	"	60	8.0	0	1.0	0.88	66	11	1.0
3	I	1:1:2 (DCPH)	1.0	49	0.84	44	1.2	2.2	trace	2.1
4	"	"	4.0	19	0.85	58	1.2	4.2	0.70	2.3
5	I	1:5:2 (⬡)	60	12	0	11	0	54	9.1	0.5
6	I	1:10:0 (DCPH)	24	99	0	0	0	-	-	-
7	I	1:1:0.1 (DCPH)	8.0	88	0	8.6	0	0	0	0
8	Br	1:0:2	60	76	0	0	0	20	0.70	0
9	"	1:1:2 (DCPH)	60	79	0	0	0	12	0.70	0
10	OTs	1:0:2	60	98	0	0	0	4.4	0	0

[a] Lithiopropiophenone was prepared by reacting 1.03 equiv. propiophenone with LDA at -78°C in THF for 30 mins, followed by removal of THF and diisopropylamine under vacuum. [b] Yields were determined by g.l.c. using internal standards. All new compounds were purified by prep. g.l.c. and gave satisfactory spectral analyses. [c] Less than 0.50%.

mediate (5-a, Scheme I) which undergoes disproportionation. Though the straight-chain alkyl-
lation compounds (9 and 10) are the major products of the reaction, the presence of cyclic
C-alkylation product (11) further suggests the formation of a radical intermediate (3-b)
which cyclizes to intermediate (5-a) before coupling with the enolate radical cation (4-c).
The observation of a much higher yield of cyclic hydrocarbon (7) when lithiopropiophenone
was allowed to react with probe (1) in the presence of the radical traps dicyclohexylphos-
phine [12,13] (exps. 3-4) and 1,4-cyclohexadiene (exp. 5) provides strong evidence for the
trapping of a radical intermediate. Interestingly, both of the radical traps decrease the
yield of straight-chain alkylation products (9-10) while increasing the amount of cyclic
hydrocarbon (7) indicating that (9 and 10) are also formed via a radical intermediate. The
fact that the cyclized hydrocarbon (7) is formed predominantly over the straight-chain hydro-
carbon (6) suggests that the radical intermediate (3-b) must be trapped by the hydrogen donors
almost exclusively via a "concerted cyclization" pathway[14] leading directly to cyclic hydro-
carbon (7).

The integrity of the iodide probe in the presence of DCPH and HMPA was examined (exp. 6)
and the probe was found to be stable. Lithiopropiophenone was also shown not to react with
DCPH in HMPA. Finally, the possibility that a radical chain process involving the alkyl

SCHEME I

iodide and DCPH was eliminated by exp. 7 which shows that 10% of the enolate produced only 10% reaction. The reaction of the bromide probe with lithiopropiophenone (exp. 8) gave almost exclusively O-alkylation product (9) and none of the radical by-products (7,8, 11) even in the presence of DCPH (exp. 9). The tosylate probe reacted very slowly with lithiopropiophenone (exp. 10) yielding compound (9) as the only product.

The effect of the leaving group on the reactivity of the probes shows that the iodide reacts at a much faster rate than the bromide while the tosylate is virtually unreactive (see Table I). It is difficult to relate the order of reactivity of all three probes based on a S_N2 process since iodide and tosylate are comparable leaving groups. A more plausible explanation can be made when one compares the reduction potentials of alkyl halides and tosylates. It has been reported recently that alkyl iodides have a considerably lower reduction potential than alkyl bromides; whereas, the C-O bond in tosylates is not broken electrochemically.[15] The reactivity of the probe compounds appears to reflect this trend in reduction potentials.

In conclusion, the reaction of the alkyl iodide probe with lithiopropiophenone appears to proceed via a radical intermediate; whereas, the bromo and tosylate probes give no evidence for an electron transfer process. Further experiments utilizing other enolate anions, radical traps and probes are planned.

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