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SURFACE ENHANCED ENANTIODIFFERENTIATION IN REACTIONS OF CHIRAL ACETOACETATES.

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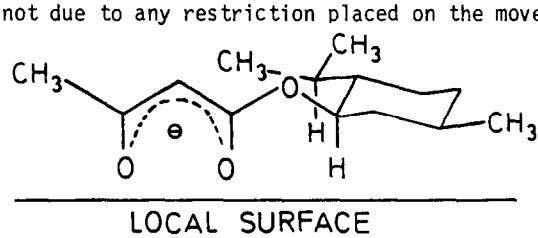
ABSTRACT: The stereoselectivity of the alkylation of chiral acetoacetates by racemic secondary alkyl halides changes when the reaction is carried out on a solid support; the change can be interpreted in terms of a model involving surface imposed conformational restrictions.

The use[1] of solid supports such as alumina as media for routine organic reactions has increased to the extent that reagents such as sodium borohydride, tetrabutylammonium fluoride, potassium permanganate etc., are now commercially available in an adsorbed form. The process of adsorption should result in a molecule with reduced rotational and translational mobility and thus one might expect a pattern of reactivity in appropriate molecules which could be attributed to one, or both, of these factors. Disappointingly however, few attempts[2] have been made to exploit such behaviour and in general the justification for the use of a supported reagent is based on the simplification of an experimental procedure, or a change in reactivity with respect to solution which is not due to any restriction placed on the movement of the substrate molecule

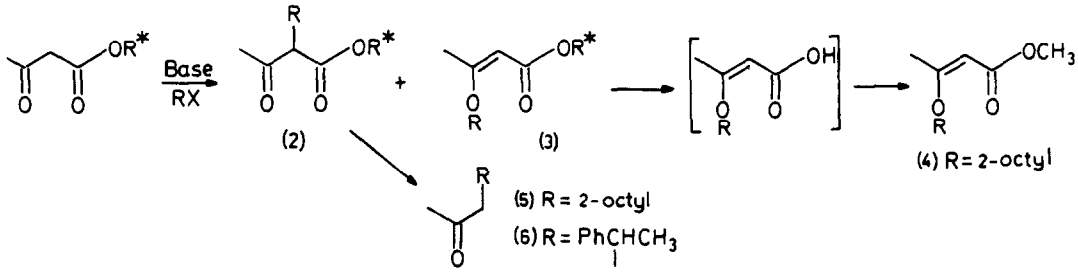


(1)

Reactions of chiral acetoacetates such as those involving extraannular chirality transfer[3] and those studied here,would be expected to result in poor stereoselectivity due to the lack of control of transition state geometry which results from the unrestricted relative movement of the chiral group and the reaction centre. Thus such processes should be excellent probes for the effectiveness of surfaces in usefully restricting the conformational freedom of a reacting molecule. However if a molecule is to be used in investigating such effects it is essential that its orientation on the surface be well defined; this again makes acetoacetates particularly useful as,in accordance with expectations, inelastic electron tunneling spectroscopy suggests[4] that on adsorption on alumina they are orientated orthogonally to the local surface. The effect of this is that the ester alkyl group (R*),which in solution would be expected to enjoy considerable rotational freedom,will be much more restricted; when R* is an essentially planar group, such as menthyl, rotation about the O-R* bond would involve particularly severe disruption of the adsorption complex and it seems reasonable to suggest that an arrangement such as (1), which involves a strong interaction between the β-ketoester enolate and the surface,and minimal internal steric interactions,is one of the major rotamers

†deceased

involved in surface reactions such as those described here.



Thus a variety of chiral acetoacetates was alkylated in solution ($DMSO/K_2CO_3$) and on a solid support (Al_2O_3/t-BuOK) with the secondary alkyl halides (±)-2-bromooctane and (±)-(1-bromoethyl)-benzene, the stereoselectivity of the process being evaluated by determination of the optical purity (o.p.) of the products following removal of the chiral auxiliary. The alkylation of acetoacetates can give both the C- and O- alkylated products,(2) and (3) respectively. However isolation, hydrolysis and esterification of the O-alkylated product on the only occasion on which it was formed in substantial amounts ($DMSO/K_2CO_3$,(±)-2-bromooctane) gave a methyl ester (4) which was essentially optically inactive. Thus in view of this result, expected because of the separation of chiral group and reaction centre,the O-alkylated product was not considered further. Dealkoxycarbonylation of the C-alkylated product, using either KOH-EtOH or LiCl-DMSO[5], gave the ketone (5)[6] or (6)[7] whose o.p. was determined following removal of the chiral alcohol by chromatography. The results of these experiments are shown in Table 1. The optical purities are very small for all reactions carried out in solution but they are reproducible and are independent of the dealkoxycarbonylation method used. In all cases no trace of the chiral inducing group could be detected (gc)in the samples used for the determinations of o.p.

Table 1. Solution[a]

R*	RBr	Reaction Time (h)	% Yield[b]	%C[c]	$[\alpha]^{d,e}$	o.p.[d,e]	Configuration
(-)-menthyl	2-octyl	72	89	0.9	-0.86	4.8(3.4)[f]	S
(-)-menthyl	1-phenylethyl	70	82	6.5	+2.8	3.7(3.4)	S
(-)-phenylmenthyl	2-octyl	160	96	1.0	-0.56	3.1(2.4)	S
(-)-phenylmenthyl	1-phenylethyl	164	70	1.37	+3.04	4.0(-)	S
(+)-menthyl	2-octyl	76	82	0.95	+0.72	3.3(2.4)	R

Table 2. Surface[g]

R*	RBr	Reaction Time (h)	% Yield[b]	%C[c]	$[\alpha]^{d,e}$	o.p.[d,e]	Configuration
(-)-menthyl	2-octyl	148	30	No"O"	-2.33	13.0(13.11)[f]	S
(-)-menthyl	1-phenylethyl	78	32	No"O"	-1.67	2.3(2.1)	R
(-)-phenylmenthyl	2-octyl	168	79	4	-6.21	34.5(28.4)	S
(-)-phenylmenthyl	1-phenylethyl	156	55	3.9	-10.2	13.7(12.8)	R
(+)-menthyl	2-octyl	162	38	No"O"	+2.41	13.4(13.7)	R

Notes : (a) K_2CO_3-DMSO; acetoacetate: base: RBr, 1:1.05:2.5

(b) % yield of crude alkylated product.

(c) by ^{1}H-n.m.r.

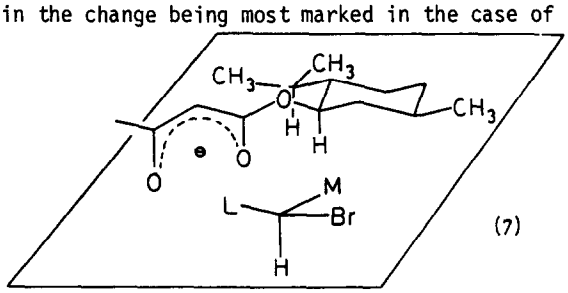
(d) R-(+)-4-methyldecan-2-one, $[\alpha]_{546}^{22}$ 16° ($CHCl_3$)[6]

(e) S-(+)-4-phenylpentan-2-one, $[\alpha]_D$ 74.5° (C_6H_6)[7]

(f) Result of duplicate experiment in parentheses.

(g) t-BuOK-Al_2O_3; t-BuOK:RBr : acetoacetate, 0.06 (90g Al_2O_3): 0.09:0.02.

Alumina was chosen as a support for the adsorbed phase alkylations as it had been shown[8] to be most effective in promoting anionic reactions; t-BuOK was used as a base to minimise the possibility of transesterification. The supported base was prepared as previously described[8] for NaOMe-Al_2O_3 and was activated at 120° and 3 mm Hg. To ensure that the reaction did actually take place on the surface it was carried out in the complete absence of solvent. The ester and the alkylating agent were added sequentially to the support and the mixture was shaken until homogeneous following each addition. The progressive formation of the alkylated products and disappearance of the starting material was monitored by NMR, samples of alumina withdrawn at intervals being eluted with chloroform. When starting material was no longer detected the solid was exhaustively eluted with chloroform to give a product containing the C-alkylated ester, which was converted as before to the corresponding ketone whose o.p. was measured (Table 2). The alkylations on the surface of alumina are characterised by a substantial increase in the C/O ratio, an observation which supports the contention that the β-ketoester is adsorbed in an orientation such as is shown in (1), in which the O-atom is hydrogen bonded to the surface and is thus less accessible to the alkylating agent. When (-)-menthyl and (-)-phenylmenthyl acetoacetate are alkylated with (±)-2-bromooctane there is a substantial enhancement of the stereoselectivity shown by the system in solution: the o.p. of the ketone (5) obtained from (-)-phenylmenthyl acetoacetate on alumina, for example, was 6½ times that obtained in DMSO. When (±)-(1-bromoethyl)-benzene is used as alkylating agent there is a reversal of the selectivity shown in solution, with again the change being most marked in the case of the phenylmenthyl ester.



(7)

RX=2-bromooctane : L=$CH_3(CH_2)_5$, M=CH_3 (i.e. (R)-RX)

RX=(1-bromoethyl)-benzene : L=Ph, M=CH_3 (i.e. (R)-RX)

The stereoselectivity of the surface reaction can, in all cases, be interpreted in terms of the model shown for (-)-menthyl acetoacetate in (7). If the conformations available to the adsorbate are assessed from the point of view that both disruption of the adsorption complex involving the enolate and internal steric interactions should be minimised, then the conformation proposed in (7) is the only one which offers a rationalisation of both the observed stereoselectivity and the effect of changing from menthyl to phenylmenthyl. In the case of (±)-2-bromooctane if the approach of the alkyl bromide is at right angles to the plane of the ester enolate, then reaction as shown of the (R)-(-) enantiomer at the face opposite to the isopropyl group involves the least unfavourable steric interaction of ester, halide and surface. Such a transition state geometry would explain the predominance of (S)-(-)-4-methyldecanone after dealkoxycarbonylation of the alkylated β-ketoester. In the case of (±)-(1-bromoethyl)-benzene, although uncertainty concerning the structure of the enolate does not allow any interpretation of the results in solution, the stereochemistry of the alkylation on the surface, as reflected in the configuration of the major enantiomer of (6) produced, follows the pattern established for (±)-2-bromooctane: approach of (R)-(1-bromo-ethyl)-benzene (L=Ph) to the more open face of the enolate as in (7) explaining the observed excess of (R)-(+)-4-phenylpentan-2-one after dealkoxycarbonylation. Thus both the enhancement

and the reversal of stereoselectivity can be explained on the basis of the model suggested.

The results of a number of additional experiments contribute further to an understanding of the reaction system:

(i) It is possible that the strong base involved in the surface reactions, coupled to the diastereomeric nature of the products and the long reaction times, could be responsible for the changes in stereoselectivity; however this possibility can be excluded as the o.p. of the ketone (5) obtained by alkylation of (-)-menthyl acetoacetate in DMSO, is independent of whether the product is dealkoxycarbonylated directly (o.p. 4.3%), or first adsorbed on Al_2O_3/t-BuOK for 164 h. and then converted to ketone (o.p. = 4.9%, 89% recovery from Al_2O_3).

(ii) The common technique of direct adsorption of substrate or of adsorption by evaporation of solvent can lead to adsorbate aggregation[9] on the surface and thus to an arrangement for which (7) would not be a reasonable model as it involves isolated β-ketoester molecules. In this case however the o.p. obtained (13.1%) when menthyl acetoacetate was distilled onto the surface and alkylated with (±)-2-bromooctane was identical to that obtained by the standard method (13.0%).

(iii) It has previously been shown[10] that the use of higher activation temperatures for the base/alumina system results in enhanced C-alkylation of naphthols, a result which was interpreted in terms of improved hydrogen bonding of the O-atom by residual water molecules, and ultimately surface bound hydroxyls as the surface was progressively dehydrated. The activation of the Al_2O_3/t-BuOK at higher temperatures in this case resulted in a reversal of stereoselectivity but also in a progressive decrease in the yield of product. Further, and in contrast to the control experiment described above, when some of the product from a solution alkylation was adsorbed for 100 hr. on Al_2O_3/t-BuOK activated at 340°C, the o.p. was significantly different to that of the rest of the product which was analysed directly.

Thus it is clear that changes in the stereoselectivity of the alkylation of chiral acetoacetates by racemic alkyl halides do occur when the process is carried out on a surface and that these can be interpreted in terms of a model involving conformational restrictions imposed by the surface. It is attractive to consider these results in terms of a suspension of the Curtin-Hammett Principle on the surface but such a generalisation must await additional results. If this is so then the rotamer distribution should be a function of the adsorbent and the adsorption process, and consequently a greater stereoselectivity may be achievable through a better understanding of the role played by these factors in surface reactions.

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