CHAPTER III

Solvent Effects in the Stereoselectivity of Cyclic α-Ketoester Alkylations

III.1. Introduction:

Development of the knowledge in chemistry is closely associated with the knowledge of solutions\(^1\). The Greek philosophers considered all chemically active liquids under the single name "Divine water". In this context, the word "water" was used to designate everything liquid or dissolved. However, with the development of chemistry different solvents and their role in chemical reactions was increasingly recognised. The influence of solvents on the rate of chemical reactions and later, on the chemical equilibria was discovered along with the development of knowledge in chemical reactions.

Solvents can be classified on the basis of various properties such as m.p. and b.p., vapor pressure, heat of vaporization, index of refraction, density, viscosity, surface tension, dipole moment, polarizability and specific conductivity. Among these the one relevant to the present discussion is the classification based on polarizability. Solvents whose molecules possess dipoles are designated as dipolar (or simply polar) as opposed to those having no
dipole moment. The permanent dipole moment of organic solvents vary from 0 to 5.5 Debye units. The values of dipole moment increase steadily on going from hydrocarbon solvents to solvents containing dipolar groups such as C=O, C=N, N=O, S=O or P=O. Dielectric constants also play a role in the properties of solvents. Dipole moment together with dielectric constant is often used for determining the solvent polarity. Solvents are also classified on the basis of having an ionisable proton or not. For the purpose of convenience and relevance to the present study, following classification is adopted for the common organic solvents.\(^2\)

1. Non-polar or very weakly polar solvents with virtually no ability to solvate cations or anions. Examples: alkanes, benzene, methylene chloride, chloroform.

2. Weakly polar solvents which can, however, solvate cations. Examples: Ether, THF, DME, di-, tri- and tetra-glymes, aliphatic tertiary amines, pyridine, etc.

3. Polar aprotic solvents with good cation solvating power but with no ability to directly solvate anions. Examples: Hexamethylphosphorlic triamide (HMPT), dimethyl sulfoxide (DMSO), dimethylformamide (DMF), acetone, acetonitrile.

4. Polar protic solvents which can solvate both anions (hydrogen bonding) and cations. Examples: water, ammonia, methanol, ethanol.
Above classification is very broad in nature with the possibility of certain borderline cases falling into other classes depending on the particular reaction.

The role of organic solvents on the reaction rate can be understood through Hughes-Ingold rules. $S_{N2}$ reaction of the type shown in equation 1 is relevant to the present discussion as it involves an anion (enolate), and an alkyl halide, there is a dispersal of charge in the transition state (TS). For such a reaction, Hughes-Ingold rules predict that there would be small decrease in the rate of reaction with the increasing solvent polarity. This concept has been amply proved by experimental results. The rate constant for the halide exchange between iodo methane with radioactive labeled iodide ion decreases by about $10^4$ times in the solvent change from less polar acetone to highly polar water. Thus, extending Hughes-Ingold rules we can say that increased solvation of the enolate leads to decrease in the rate of alklylation reaction.

The nucleophilic reactivity of the enolate anion depends not only on the extent of solvation by the solvent but also on its association with the corresponding cation.
An ion pair associated anion is much less reactive than a free (non-associated) ion. The interactions between the anion and the counter cation can be minimized by increasing the polarity of the medium in such a way as to solvate the cation (gegenion) specifically or by increasing the inter ionic distance. Highly polar aprotic solvents solvate metal cations and thus make the anions naked. Another elegant way of removing metal cations is by means of caging them in macrocyclic ligands such as crown-ethers and cryptands. There is also a possibility of considerable amount of aggregation of the anion-cation ion pairs in the non-polar solvents, resulting in retarding the rate of reaction.

It should be noted that very small difference in standard molar Gibb's energy change ($\Delta G^\circ$) could lead to large degree of selectivity. It requires less than 3 kcal/mol of activation energy to change 10:90 to a 90:10 product mixture. Thus solvents can, potentially be made to play a greater role in the formation of products.

III.2. Solvent effects in regioselectivity of enolate alkylations

Enolate anion is an ambident anion having two reactive ends viz. $\mathcal{C}$ and $\mathcal{O}$ with a substantial fraction of negative charge distribution over both these centers (Fig.III.1). If the substitution reaction is kinetically controlled, the regioselectivity of attack on the carbanion and the oxyanion
is determined by the relative nucleophilicity by each of the donor atoms in the ambident anion in relation to the given electrophilic reactant. Among the factors influencing the mode of the reaction (counter cation, additives, concentration, temperature, pressure, leaving group, structure of the alkylating agent) solvent plays a major role in the C vs. Q alkylation. Several authoritative and exhaustive reviews have appeared on this subject.\textsuperscript{2,5-6} In protic solvents C-alkylation competes significantly with Q-alkylation because of preferential deactivation (solvation) of the more electronegative atom viz., Q through hydrogen bonding. When dipolar aprotic solvents (DMSO, DMF) are employed, due to lack of specific solvation of the anion and preferential solvation of counter cation, a significant amount of Q-alkylation results. Greatest yields of C alkylated products are obtained when poorly electron solvating solvents such as DME, THF are used (Scheme III.1) because of the ion pairing between oxygen atom and the counter cation.\textsuperscript{7-9} (except lithium enolate). An alternative
explanation for the solvent effects of regioselectivity is based on the well known concept of hard and soft acid base (HSAB) theory.\textsuperscript{10}

III.3. Solvent effects on the stereochemistry of organic reactions

Two configurations $Z,Z$ and $Z,E$ (Fig.III.2 A & B) are possible for the enolate ion generated from a cyclic $\beta$-ketoester. These arrangements are frequently found to exchange slowly on a NMR time scale and therefore, sometimes, regarded as conformation rather than configuration. This rate of interconversion, however, is rapid compared to the reactions with electrophiles. Further only $Z,Z$ (Fig.III.2 A) can form bidentate chelate with metal cation\textsuperscript{11,12,13}. When under chelation there is some degree of aggregation of the ion-pair depending upon the solvents. For e.g., Zaugg et al.\textsuperscript{14,15} have shown that sodio-diethyl n-butyl malonate exists as an reverse micelle comprised of some 40-50 monomer units in class 1 solvents (benzene and cyclohexane).\textsuperscript{2} By contrast, the chelate appears to be monomeric in dimethoxy
A dissociated ion pair of β-ketoester is expected to be high in polar aprotic solvents such as DMF and polar protic solvents, CH₃OH. In the present study we have used β-ketoesters embedded in a large hydrophobic molecules, trans-decalones and trans-hydrindanones. Therefore, the degree of aggregation, based on purely steric reasons, is expected to be very less.

Stereochemical outcome of a nucleophilic substitution reaction, on a saturated carbon can also depend on the nature of the solvent. In contrast to dipolar aprotic (e.g., DMF) solvents, the protic solvents diminish the nucleophilicity of anions and simultaneously favor the ionization of polarized bonds. This factor makes it possible to displace a given reaction toward either the $S_N^1$ or $S_N^2$ type. A remarkable
example in which varied mechanisms operate in different solvents leading to the formation of different products is found in the nucleophilic substitution of cholesteryl tosylate (Scheme III.2). The nucleophilic substitution of cholesteryl tosylate in dipolar aprotic solvents (DMF, DMSO) results in the 3α-derivative 5 with concomitant inversion of configuration. In contrast, in protic solvents (e.g., CH₃OH) a mixture of the 3β- and 3,5-cyclo-6β-derivatives 6,7 are formed, corresponding to an SN1 mechanism. A publication which had profound influence on the initiation of the present study, reported in this chapter, was by Nakanishi et al. They found remarkable and dramatic solvent effect on the di-enolate alkylation diastereoselectivity of the steroidal enone 8 (Scheme III.3) and decalenone 11 (Scheme III.4). They found that when the
di-enolate anion of 11 β-acetoxy-4-methyl-19-nor-testosterone generated with Et(Me)2OK-in benzene was treated with deuterated methyl iodide resulted in the predominant formation of Z (E)-alkylated product. This result is in contrast with the earlier result of Permutti and Mazur18 who carried out the same alkylation in the presence of t-BuOH and showed that alkylation ratio of 9:91 favoring E-alkylation. Thus a preferential α (E) attack has taken place in t-BuOH and preferential β (Z) attack occurred in benzene. The results were rationalized on the basis of product like TS (SP3 configuration at the alkylating site in non polar
solvent benzene and/or specific solvation of t-BuOH on the β-face of the di-enolate resulting in the α-attack of the alkylating agent, when protic solvent t-BuOH was used. The preferential degree of aggregation of the di-enolate and as well as the structure of aggregate may also contribute to the observed stereochemistry. Recent theoretical work by Cieplak and Wiberg\textsuperscript{19} also emphasize the importance of considering solvent effects in determining the stereoselectivity. They found that stereoselectivity can be different during the addition of nucleophile across carbonyl group on going from gas phase to solution phase. Finally, Jackman\textsuperscript{2} in his authoritative review article states that "a systematic study of this problem seems highly desirable in order to confirm the reported experimental findings and delineate the precise role of cation and solvent in the apparent stereoselective control of alkylation of these β-ketoesters".

III.4. Results and discussion

We have studied the methylation and benzylation of the enolate ion generated from trans-6-methoxycarbonylhydrindan 5-one (14, Scheme III.5) and trans-C\textsubscript{10}-substituted 2-methoxycarbonyldecal-3-ones 15, 16, 17 (Scheme III.6) using five solvents. The solvents chosen for the present study are

(1) a highly polar protic solvent MeOH (2) a moderately polar protic solvent t-BuOH (3) a moderately polar aprotic solvent, acetone (4) a highly polar aprotic solvent DMF, and (5) a
non-polar solvent benzene (along with 18-crown-6). The properties of these solvents particularly the ones related to their polarity are given in the Table III.1.

Potassium carbonate was used as base for generating the anion in acetone (medium). Care was taken to make potassium carbonate anhydrous by keeping it in a preheated oven at 180°C for 3-5 h. However, we can't rule out the possibility of the presence of trapped water molecules present in K₂CO₃. These water molecules may also play a role in the stereoselectivity of the alkylation reaction. Details of stereochemical assignment for the alkylated products obtained in this reaction has been described in Chapter I (acetone as solvent).
TABLE III.1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Dipolemoment M(10⁻³₀cm)</th>
<th>Dielectric constant (Eₜ)</th>
<th>Polarity (Eₜᴺ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Methanol</td>
<td>5.7</td>
<td>32.66</td>
<td>0.762</td>
</tr>
<tr>
<td>2</td>
<td>t-Butanol</td>
<td>5.8</td>
<td>17.51</td>
<td>0.389</td>
</tr>
<tr>
<td>3</td>
<td>Acetone</td>
<td>9.0</td>
<td>20.56</td>
<td>0.355</td>
</tr>
<tr>
<td>4</td>
<td>N,N-Dimethyl Formamide</td>
<td>10.8</td>
<td>36.71</td>
<td>0.404</td>
</tr>
<tr>
<td>5</td>
<td>Benzene</td>
<td>0.0</td>
<td>2.27</td>
<td>0.111</td>
</tr>
</tbody>
</table>


The ratios of the alkylated products (Z vs. E) obtained in the above solvents are gathered in Table III.2 (Fig.III.3).

The present study clearly shows that the polarity of the solvent does not play a major (dramatic) role in determining the stereoselectivity of the alkylation reaction. However, the following points could be noted from the Table III.2.

Stereoselectivity observed in methanol or t-BuOH for the alkylation of all the substrates 14-17, are similar within the experimental errors (column 6 & 7, Table III.2). These ratios are also comparable with the results of acetone.
FIG.III.3. Representative mixture $^1$H NMR Spectra of alkylated products from which ratios of the isomers formed were calculated.
**TABLE III.2**

![Chemical Structures](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>n</th>
<th>R</th>
<th>R¹</th>
<th>Sub. No.</th>
<th>Product</th>
<th>Distribution</th>
<th>Z: E</th>
<th>MeOH</th>
<th>t-BuOH</th>
<th>Acetone</th>
<th>DMF</th>
<th>Benzene/18-Crown-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>H</td>
<td>CH₃</td>
<td>14</td>
<td>84:16 81:19</td>
<td>71:29</td>
<td>84:16</td>
<td>89:11</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>H</td>
<td>C₆H₅CH₂</td>
<td>14</td>
<td>45:55 40:60</td>
<td>16:84</td>
<td>28:72</td>
<td>30:70</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>H</td>
<td>CH₃</td>
<td>15</td>
<td>70:30 69:31</td>
<td>69:31</td>
<td>83:17</td>
<td>81:19</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>CH₃</td>
<td>CH₃</td>
<td>16</td>
<td>17:83 15:85</td>
<td>15:85</td>
<td>18:82</td>
<td>17:83</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>CH₃</td>
<td>C₆H₅CH₂</td>
<td>16</td>
<td>00:100 00:100</td>
<td>02:98</td>
<td>04:96</td>
<td>03:97</td>
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<td></td>
<td></td>
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<tr>
<td>7</td>
<td>2</td>
<td>COOC₂H₅</td>
<td>CH₃</td>
<td>17</td>
<td>68:32 69:31</td>
<td>64:36</td>
<td>72:28</td>
<td>70:30</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>2</td>
<td>COOC₂H₅</td>
<td>C₆H₅CH₂</td>
<td>17</td>
<td>03:97 10:90</td>
<td>17:83</td>
<td>11:89</td>
<td>11:89</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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a. All reactions were conducted at rt under dry N₂ atmosphere until the β-Ketoesters were fully consumed (TLC).

b. Ratios are based on the salient signals in ¹H NMR (400 MHz/200 MHz) spectra (± 5%) of the total reaction mixture.

219
differential aggregation of the enolate ion in methanol, t-butanol and acetone. It is also possible that the exact position of transition state on the reaction co-ordinate may be responsible for these interesting results. It may also be possible that the alkylation ratios in these solvents reflect differential electrophilicity of the alkylation agents involved.

The alkylation ratios in DMF point to greater Z-alkylation. In fact in all the cases studied, a marginal increase of Z-attack on going from acetone to DMF can be noticed. This can arise from the formation of naked anion due to solvation of gegenion, K⁺, by DMF. The naked anion would preferentially project itself in the axial side leading to greater Z-attack. However, all the other factors responsible for the stereoselectivity as discussed in detail in Chapter I are applicable. As expected, in addition to Q-alkylated products, minor amounts of the Q-alkylated products were also formed when DMF was employed as solvent. Ratios of Q vs. Q-alkylated products are given in Table III.3.

The alkylation reaction conducted in benzene containing 18-crown-6 as additive resulted in products wherein the stereoselectivity observed was comparable to that of DMF as solvent. However, unlike in DMF, as expected there were no Q-alkylated products. 18-Crown-6 a phase transfer catalyst had to be used because Potassium carbonate is insoluble in
benzene. In the absence of this catalyst the reactions were either not taking place or were taking very long periods. Since the enolate formation had to take place at the interface. Therefore, 18-crown-6, which is a specific ligand for solvating $K^+$ was used (in 5 % molar ratio) to carry out this reaction. Due to specific solvation of $K^+$ by 18-crown-6, reactions in benzene also result in the formation of naked anion$^{20}$ where the electron pair is projected towards axial side preferentially in comparison with other solvents leading to increased $Z$-alkylation.

Alkylation ratios were determined on the basis of integration of diagnostic signals in $^1H$ NMR spectra. In one case (entry 8, Table III.3) the $Q$-benzylated product was isolated and characterized. The assignment for various protons present in the molecule is given in the spectrum ($^1H$ NMR, Fig.III.5).

In summary, results from the present study show that there are no dramatic influences by the solvent in determining the stereoselectivity of alkylation reaction, in contrast to their profound role in the regioselectivity of alkylation.

The rates of the alkylation reactions as expected, differed considerably with the change of the solvent. The reactions (methyllations) were complete within 2 h in DMF and in
Fig. III.5. $^1$H NMR (400 MHz) Spectrum of trans-3-benzyl oxy
10 β-ethoxycarbonyl-2-methoxycarbonyldecal-2-ene
about 8 h in benzene/18-Crown-6, acetone and t-BuOH, whereas in MeOH reaction needed 18 h. This result may reflect solvation of the anion by the solvent (methanol) through hydrogen bonding. We found that, generally all benzylations needed additional 4 h for completion, possibly due to lower electrophilicity of the benzyl cation.

In the course of present study of alkylation of β-ketoesters, we had conducted initially benzyla- 
tion of trans-2-methoxycarbonyl 10-methyldecal-3-one (16) using 2 moles of potassium t-butoxide/t-butanol. From this reaction C₂ and C₄-dibenzylated product was isolated along with monobenzylated product. The structure for this compound was arrived on
Fig. III.4  
A. $^1$H NMR (90 MHz) Spectrum  
B. $^{13}$C NMR (22.5 MHz)  
C. EI (70 CV) mass spectrum of trans 2α, 4α-dibenzyl-2β-methoxycarbonyl-10-methyldecal-3-one.
the analysis of $^1$H and $^{13}$ NMR spectral data (Fig. III.4). As expected second benzylation also took place on the α-face of the enolate generated from the monobenzylated product.

III.5. Experimental

For General, See Chapter I experimental section.

General Procedures for alkylation reactions:

III.5.1. Potassium Carbonate/methanol

The β-ketoester (0.1 mmol) in methanol (5 ml) was added to potassium carbonate which was taken in methanol (5 ml) under alkylating agent (methyl iodide, benzyl bromide, 0.5 mmol) was added in methanol (5 ml) during 10 min. and stirred at rt. for 15 h. Benzylation needed little more time (18-24 h). After the usual work up viz. filtration, removal of the solvent, spectra were obtained on crude products to fix the relative isomeric ratio (Z vs E).

III.5.2. Potassium Carbonate/t-Butanol

To a suspension potassium carbonate (0.5 mmol) taken in t-butanol (5 ml), β-ketoester (0.01 mmol) in t-butanol (5 ml) was added under magnetic stirring in $N_2$ atmosphere. The reaction mixture was stirred at ambient temperature for 15-30 min. and alkyl halide (methyl iodide benzyl bromide, 0.5 mmol) in t- butanol (5 ml) was added dropwise during 10 min. Reaction progress was monitored by TLC (hexane: EtOAc 9:1). It was found that methylation was complete in 12 h. Whereas
alkylation with benzyl bromide needed 15-24 h. The reaction mixture was filtered through Celite pad and processed by the earlier (Chapter I) described procedure. As mentioned earlier $^1$H NMR spectra on crude products were recorded routinely before separating individual isomers to obtain relative isomeric ratios.

### III.5.3. Potassium Carbonate/Acetone

The β-Ketoester (0.1 mmol) in acetone (3 ml) was added to potassium carbonate (0.5 mmol) which was dispersed in dry acetone (5 ml) under magnetic stirring and N$_2$ atmosphere. After stirring at rt. for about 20 min. alkylating agent (methyl iodide/benzyl bromide 0.5 mmol) in acetone (5 ml) was added over a period of 10 min. After 12 h. by which time reaction complete (TLC, solid particles ($K_2CO_3$, potassium iodide/potassium bromide) were filtered and processed due work up. The method which was followed earlier to obtain isomeric ratio ($Z$ and $E$) holds good in this case also.

### III.5.5. Potassium Carbonate/ N,N-Dimethyl Formamide (DMF)

To potassium carbonate (0.5 mmol) in DMF (2 ml) was added β-ketoester (0.1 mmol) in DMF (5 ml) dropwise manner over a period of 10 min. while stirring magnetically under dry nitrogen atmosphere. After 5 min. alkylating agent (methyl iodide/benzyl bromide, 0.5 mmol) in DMF was added
during 15 min. Alkylations were complete within 2 h. Reaction mixture was passed through filter paper and the filtrate was concentrated under reduced pressure. The residue of the reaction mixture was taken in water (50 ml) and extracted with diethyl ether (25 ml X 5). After usual work up and on removal of the solvent obtained the spectra as usual to afford the epimeric ratio.

III.5.5. Potassium Carbonate/ Benzene/18-crown-6

Potassium carbonate (0.5 mmol) taken in dry benzene (5 ml) with catalytic amount of 18-crown-6 (2 mg) and to that β-ketoester (0.1 mmol) in dry benzene (5 ml) was added while stirring under a blanket of nitrogen atm. After 15 min. alkylating agent (methyl iodide/benzyl bromide, 0.5 mmol) in dry benzene (5 ml) was added dropwise during 15 min. and stirred for 15 h by which time reaction was complete, mixture filtered and washed with dry benzene (25 ml X 2). The filtrate was taken in water (50 ml) and layers separated. The aqueous layer was again extracted with diethyl ether (25 ml X 3) and concentrated. Final traces of benzene was removed under reduced pressure. From the crude reaction mixture traces of 18-crown-6 was separated by column chromatography (hexane : ethyl acetate 95 : 5) before obtaining the epimeric ratio (Z and E) in usual way.
III.5.6 Potassium tertiary butoxide/t-butanol

To a solution of a β-ketoester (0.1 mol) in dry t-butanol (5 ml) added potassium t-butanol (0.11 mmol) in t-butanol (2 ml) under a blanket of dry nitrogen and constant stirring at ambient temperature (25-30°C). After 15 min. during which time the solution turned light yellow, an excess of the alkyl halide methyl iodide/benzyl bromide (0.5 mmol) in t-butanol (5 ml) was added dropwise with a syringe during 10 min. and allowed to stir overnight (12h). Usually colorless solution and white precipitate was observed during this period. The reaction mixture was added to brine (25 ml) and extracted with diethyl ether (20 ml X 5). The crude alkylated (methylated or benzylated) products isolated after due work up and on removal of solvent as light yellow oil, found negative to the ferric chloride color test. The $^1$H NMR spectrum of this crude material was recorded and relative ratios of peaks characteristic to each isomer were calculated. The individual isomers were separated by chromatography (TLC, column and chromotron) and characterized.

Analytical samples were obtained by repeated column chromatography by using different solvent system as eluants. The alkylated products obtained were colorless solids or light yellow oils.
trans-2α,4α-Dibenzyl-28-methoxycarbonyl-10-methyldecal-3-one

IR (Neat) $\nu_{\text{max}}$: 1712, 1600 cm$^{-1}$

$^1$H NMR (90 MHz): $\delta$ 0.97 (3H, s), 1.01 - 1.85 (10H, m), 2.15 - 3.35 (6H, m), 3.40 (3H, s), 7.05 (10H, m).

$^{13}$C NMR (100 MHz): $\delta$ 17.61 (q, C$_{10}$-CH$_3$), 20.93 (t, C-8), 25.57 (t, C-7), 26.12, (t, C-6), 31.65, 35.08 (s, C-10), 41.05, 42.04, 51.88, 52.07, 61.39, 96.08, 125.62, 126.73, 127.95, 128.17, 129.05, 131.04, 136.90, 141.43, 173.57.

MS (EI, 70ev) M/e (relative intensity): 405 (M$^+$, 68), 346 (35), 314 (100), 282 (75), 254 (42), 228 (55), 145 (35), 131 (30), 117 (40), 109 (35), 91 (100), (81) (30), 67 (29), 55 (26), 41 (20).

229
III.6. References


