B: Organic Chemistry

Paper IV - Physical and organic Chemistry

B.Sc. Part II

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Active methylene compounds

Active methylene compounds:

$Z\text{-}CH_2\text{-}Z^1$

where Z and Z^1 can be $-CO_2R$, COR, $CONR_2$, CN, NO_2, COR, SO_2R, SO_2OR, SO_2NR_2

Example:

- Ethyl acetoacetate; Z = $CH_3C(O)-$ and Z^1 = $-CO_2Et$

  $CH_3\text{-}C(O)\text{-}CH_2\text{-}CO_2Et$

- Diethyl melonate ester; Z, Z^1= CO_2Et

  $CH_2(-CO_2Et)_2$

Active methylene compounds

Ethyl acetoacetate (EAA)

Discovery

Reaction

Na + EtOAc →Ethyl acetoacetate (EAA) or acetoacetic ester

Speculation about structure of EAA

Geuther (1863)

$CH_3C(OH)=CHCO_2Et$ (β-hydroxycrotonic ester)

Evidences for unsaturated hydroxyl group

EAA + Na → H_2(↑) presence; of hydroxyl group

EAA+ Br_2 → Decolourization; presence of unsaturation

EAA + $FeCl_3$ → reddish violet colour; -C(OH)=C- similar to phenolic group

Frankland and Dupa (1865)

$CH_3COCH_2CO_2Et$ (β-ketobutyric ester)

Evidences for ketonic group

EAA + $NaHSO_3$ → Bisulphite addition product

EAA + HCN → Cyanohydrin product

Active methylene compounds

Structure of EAA (continued)

Both formulae are right (1910).

There is equilibrium between enol and keto form.

$CH_3COCH_2CO_2Et \rightleftarrows CH_3C(OH)=CHCO_2Et$

Knorr (1911)

Isolation of two different form.

1) Cooled EAA to -78℃. Keto form crystallized.

2) Sodium derivative of EAA cooled to -78℃. Neutralized with equivalent HCl. Enol form in solidified as glassy solid.

Solid state:

No equilibrium. only one state exists.

Liquid and gaseous state:

equilibrium exists but stability differs.

it is sensitive to temperature, solvent, pH, catalyst, pressure etc.

Active methylene compounds

Tautomerism

Laar (1885) (*Greek*: same parts)

Tautomers or tautomerides:

Structurally different compounds in rapid equilibrium

Example:

Keto-enol tautomerism	>CH-C(=O)< $\rightarrow\leftarrow$	>C=C(-OH)<
Three carbon system;	>CH-C=C< $\rightarrow\leftarrow$	>C=C-CH<
Nitoso-oxime;	-CH-N=O $\rightarrow\leftarrow$	C=N-OH
Nitro-aci;	-CH-NO_2 $\rightarrow\leftarrow$	C=N(O)OH
Imine-enamine;	-CH-C=N- $\rightarrow\leftarrow$	-C=C-NH-
Amido-imidol	NH-C=O $\rightarrow\leftarrow$	N=C-OH
azo-hydrazone	N=N-CH $\rightarrow\leftarrow$	NH-N=C
diazo- amino	N=N-NH $\rightarrow\leftarrow$	NH-N=N
Diazo-nitrosamine	Ar-N=NOH $\rightarrow\leftarrow$	Ar-NH-N=O

Active methylene compounds

Evidences of tautomerism

Direct separation

keto enol equilibrium is very sensitive to pH and even to soft glass.

Enol is more volatile than keto.

Meyer (1920) separated these in aseptic condition by fractional distillation.

Indirect evidence

Deuterium exchange in CH_3COCH_3 in D_2O

Active methylene compounds

Tautomerism

Estimation of equilibrium

Two types; physical and chemical

Physical methods:

non- interfering, preferred

- Refractive index (RI);
  - If isolable, then independent RI is compared with the RI of the equilibrium mixture, i.e. EAA, or
  - From table of atomic refraction, independent refractive indices of both forms are calculated and equilibrium estimated with the observed RI.
- Conductivity measurement; If two forms differ in conductivity then conductivity measurement is measured i.e. nitromethane
- Optical activity; If two forms have different optical activity then optical rotation is measured. mutaroration
- Proton NMR.

Active methylene compounds

Tautomerism

Estimation of equilibrium

Chemical methods:

Reaction should be faster than the interconversion

two types; direct and indirect methods

Direct method

Br_2 reacts rapidly with enol form. Fast Titration with Br_2 at 0°C.

Appearance of colour of bromine is end point.

Indirect method

Excess of ethanolic Br_2 is added. unreacted Br_2 is removed with excess of 2-naphthol.

Br_2 consumed is calculated by addition of KI and HCl and then estimation of I_2 with standard thiosulphate.

Reaction

$CH_3\text{-}C(OH)=CH\text{-}CO_2Et + Br_2 \rightarrow CH_3\text{-}C(=OH^+)\text{-}CHBr\text{-}CO_2Et + Br^-$

$CH_3\text{-}C(=OH^+)\text{-}CHBr\text{-}CO_2Et \rightarrow CH_3\text{-}CO\text{-}CHBr\text{-}CO_2Et + H^+$

Active methylene compounds

EAA: Tautomerism

Stability

Thermodynamics of equilibrium

Keto form	Enol form	
C-H, C-C, C=O	C=C, C-O, C-OH	
1500 KJ/mol	1450 KJ/mol	Stability of keto form 50 KJ/mol

Keto $\overset{\rightarrow}{\leftarrow}$ Enol; K = [Enol]/[Keto]

$\Delta G^{\ominus} = RT\ln K$

for mixture with 1% enol; $\Delta G^{\ominus} = -5.7 \log(1/99) = 11.42$ KJ/mol

for mixture with 99% enol; $\Delta G^{\ominus} = -5.7 \log(1/99) = -11.42$ KJ/mol

Total difference is 22.82 KJ/mol

Active methylene compounds

EAA: Tautomerism

Stability

H-bond

Internal H-bond is 29.3 KJ/mol in EAA; enol will be favoured.

Enolization is exhibited by methylene (-CH_2-) and methyne (>CH-) adjacent to a carbonyl.

Resonance effect

Crotonaldehyde	MeCH=CHCHO	R.E.; 10.04 KJ/mol
Ethylacetate	MeC(C=O)-OEt	R.E. 75.31 KJ/mol
Ethyl methacralate	CH_2=C(Me)-C(=O)OEt	R.E.; 75.31 KJ/mol

Double bond is not in resonance with ester group

Ester group is only having inductive effect

Ethyl methacrylate structure is similar to enol form

H-O-C(Me)=CH-C(=O)Et $\leftrightarrow$ H-O^+=C(Me)=CH-C(-O^-)Et

ketone group favours enol

Stabilization of enol Ecetylacetone (diketone) > EAA((monoketone) > DEM (No ketone)

Active methylene compounds

EAA: Tautomerism

Stability :

- **Entropy effect**

  Enol has less entropy than Keto due to double bond and cyclic structure

- **Substitution effect**

  Methyl at α position has more strain energy due to steric repulsion.

- **Solvent effect**

  Enol has internal H-bond. Protic solvent decrease enol

Active methylene compounds

EAA: Tautomerism

Acidity of keto compound

$-CH_2-C(=O)- + B \rightarrow_{\leftarrow} BH + -CH^{-}-C(=O)- \leftrightarrow -CH=C(-O^{-})-$

EAA; pK_a 10.7, DEM ; pK_a 8.24

Similar to enol content in proton accepting solvent

Stability of enol may improve, if there is

Conjugation of double bond

Aryl group $C_6H_5-CO-CH_2-CO-C_6H_5$ (96%)

internal H-Bond

fluorinated enols

If there are two symmetrical carbonyls adjacent to methelene or methyne, one will be enolized.

If unsymmetrical, one will be predominantly enolized.

Active methylene compounds

EAA: Tautomerism

Mechanism

Two step; *bimolecular reaction*

Base catalysed, enolate ion intermediate

$B + R_2CHCOR \rightarrow\leftarrow BH^+ + R_2C^-COR \leftrightarrow R_2C=C(-O^-)R$

inductive effect of alkyl group controlled

due to steric hindrance in attachment of base to proton alkyl group depresses

Acid catalysed, removal of Proton from conjugated acid of ketone

$H^+ + R_2CHCOR \rightarrow\leftarrow R_2CHC(OH^+)R \rightarrow\leftarrow R_2C=C(OH)R + H^+$

hyperconjucation by alkyl group controlled

there is no steric hindrance on attachment of proton to oxygen alkyl group has no affect

Concerted; Termolecular reaction

Water as acid and/or base

Transition state is more similar to enol than to ketone