Chapter 3
3. Chemistry of Aromatic Degradation

In the nineteenth century it was recognized that aromatic compounds differ from unsaturated aliphatic compounds, but for many years chemists were hard pressed to arrive at a mutually satisfactory definition of aromatic character.

In 1925 Armit and Robinson (1) recognized that the aromatic properties of the benzene ring are related to the presence of a closed loop of electrons, the aromatic sextant (aromatic compounds are thus the arch examples of delocalized bonding), but it was still not easy to determine whether rings other than the benzene ring possessed such a loop. With the advent of magnetic techniques, most notably nuclear magnetic resonance (NMR), it was possible to determine experimentally whether or not a compound had a closed ring of electrons; aromaticity can now be defined as the ability to sustain an induced ring current. A compound with this ability is called diatropic.

3.1 Stability of the benzene ring

Stability of the benzene ring depends on the following facts

(a) That, Heats of hydrogenation and combustion of benzene are lower than expected. Heat of hydrogenation is the quantity of heat evolved when one molecule of unsaturated compound is hydrogenated. In most cases the value is 28-30 K.cal.mol\(^{-1}\) for each double bond of the compound (2). Cyclohexene has heat of hydrogenation of 28.6 K.cal.
mol\(^{-1}\) and cyclohexadiene has about twice that (55.4 K.cal.mol\(^{-1}\)). It is reasonable to expect cyclohexatriene to have a heat of hydrogenation about three times as large as cyclohexene, that is, about 85.8 K.cal.mol\(^{-1}\). Actually, the value for benzene (49.8 K.cal.mol\(^{-1}\)) is 36 K.cal.mol\(^{-1}\) less than this expected value. In other words, benzene is more stable than we would have expected cyclohexatriene to be. The heat of combustion of benzene is also lower than that expected, and by about the same amount.

(b) Carbon-carbon double bonds in a wide variety of compounds are found to be about 1.34 Å long. Carbon-carbon single bond, is 1.53 Å in ethane (2). Benzene possesses three single and three double bonds, hence there should be three short bonds (1.34 Å) and three long bonds (1.48 Å). X-ray diffraction studies show that the six carbon-carbon bonds in benzene are equal and have a length of 1.39 Å, and are thus intermediate between single and double bonds.

(c) Benzene has resonance structure: structures that differ only in the arrangement of electrons. Benzene is a hybrid of I and II. Since I and II are exactly equivalent, and have the same stability, they make equal contributions to the hybrid (2).
In the earlier chapter we have discussed that two hydroxyl groups are the prerequisite for the aerobic microbial degradation and ring cleavage. The processes involved in the dearomatisation of aromatic compounds are hydroxylation, ring opening by introduction of two atoms of oxygen.

3.2 Dearomatisation reactions under aerobic conditions

3.2.1 Hydroxylation

Both the hydroxylation and the ring cleavage of aromatic compounds are of widespread occurrence in nature, whereas such processes are relatively uncommon in the laboratory and are of little value in organic synthesis. Nevertheless, a number of chemical systems which bring about these reactions are now known with detailed information about their mechanisms in some cases.

The reagents used for hydroxylation are Fentons’s reagent, Peracids, Hamilton’s System, Oxidation by Cupric-Amine-oxygen and Udenfriend’s and related systems.

The best known and most extensively studied system, which brings about the hydroxylation of aromatic compounds is Fenton’s reagent and hydrogen peroxide. The system is complex, but there is now strong evidence that hydroxylating species is the hydroxyl radical.

Chemical composition of these hydroxylating system are as follows

(a) Fenton’s System (3) Ferrous iron and $\text{H}_2\text{O}_2$

(b) Hamilton’s System (4) $\text{H}_2\text{O}_2$ in aqueous solution at pH 4.0
(c) Cupric amine oxygen (5) Cupric ion and oxygen
(d) Udenfriend's System (6) Ferrous ion, EDTA and ascorbic acid

Of all the systems mentioned above Udenfriend's system is nearest to being a suitable model for the biological processes.

3.2.2 Ring opening

There have been comparatively few investigations for the mechanisms involved in the cleavage of benzenoid systems. Benzene itself can be split under fairly vigorous conditions, e.g., by catalytic oxidation in the vapor phase to maleic anhydride and naphthalene can be opened by a molybdate catalyzed reaction with hydrogen peroxide (7). Phenolic compounds can be cleaved under much milder conditions. Phenol gives cis, cis-muconic acid with peracetic acid at room temperature (8), and since the well-studied biological ring openings involve phenols, discussion will be focussed on these reactions.

The conversion of phenol into cis, cis-muconic acid might be expected to proceed via catechol and o-benzquinone, equation (i). The oxidation of catechol to o-benzoquinone by peracetic acid may well be by two electron process equation (ii), but such reactions can be brought about also by one electron oxidizers e.g., 3-aminocatechol and protocatechuric acid have been oxidized to the corresponding o-quinones with silver
oxide (9,10). The peracid oxidation of o-quinones to muconic acids may follow the path established for the cleavage of benzils (11), equation (iii).

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\begin{align*}
\text{HO} & \quad \rightarrow \quad \text{HO} \quad \rightarrow \quad \text{O} \quad \rightarrow \quad \text{CO}_2\text{H} \\
\text{HO} & \quad \rightarrow \quad \text{H} \quad \rightarrow \quad \text{COCH} \quad \rightarrow \quad \text{CO}_2\text{H} \\
\text{O}_2\text{H} & \quad \rightarrow \quad \text{COCH}_3 \\
\end{align*}
\]

3.3 Dearomatisation reaction under anaerobic conditions

In anaerobic conditions carboxyl group is incorporated followed by reduction of the aromatic compounds. In microbial degradation enzymes attack a specific position and one particular compound is formed whereas in chemical reaction different isomers of the same compound are formed.

3.3.1 Carboxylation and Reduction

Phenol carboxylation is industrially used. Treatment of the salt of a phenol with carbon dioxide brings about substitution of the carboxyl group, \(-\text{COOH}\), for hydrogen of the ring. Sodium phenoxides can be
carboxylated, mostly in the ortho position by CO₂. This reaction is known as Kolbe-Schmitt reaction. Potassium phenoxide, which is less likely to form such complex, is chiefly attacked in the para position.

It is the most important application in the conversion of phenol itself into o-hydroxybenzoic acid, as salicylic acid.

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\text{Sodium salicylate} \quad \text{Salicylic acid}
\]

After carboxylation the first step in the biochemical reduction of benzoate is its activation through conversion into benzoyl-CoA by an inducible ligase. The thioesterification of α-β unsaturated acids increases their reactivity towards reducing agents owing to the resonance effect between the double bond and S-Co group. The resonance stabilization of the aromatic ring is great (≈ 160 KJ mol⁻¹); chemical considerations require that for additions to an aromatic nucleus to occur, the system of bonding characterized by very extensive delocalization of the π-electrons must be converted to one in which little of the delocalization energy remains. The critical step in the reduction of the benzene is the addition of the first two hydrogen atoms, since the reaction is endergonic \( \Delta G_{\circ} (2H=H_2) + 60kJ \text{ mol}^{-1} \). Nature probably overcomes this problem by binding the reaction product and reducing it further. The reductions of the second and third double
bonds are exergonic reactions \( \Delta G^\circ \ 2H = H_2 \) -90 and -70 kJ mol\(^{-1}\) respectively and are therefore thermodynamically favored (12).

The well known Birch reduction of benzene (13) uses sodium as electron donor in the liquid ammonia serving as solvent for solvatised electrons. Normally, alcohol serves as a proton donor. Reduction to a cyclohexadiene proceeds in a distinct, alternating electron transfer and protonation steps (Fig 3.1). The reduction of benzene (1a) to the radical ion (1b) has been determined by cyclic voltametry to have mid-potential of -3.15 V versus the hydrogen electrode (14). To measure this step, which represents the principal barrier in ring reduction, water and other protic impurities must be totally excluded. Subsequent protonation of the radical anion (1b) to the neutral radical (1c) favors reduction. The cyclohexadienide anion (1d) is formed from the neutral radical (1c) by transfer of another electron. This reaction occurs at -0.25 V (measured for reoxidation of the carbanion) and is greatly favored by protonation of the carbanion (1d) to the stable product cyclohexadienide (1e). The biological reduction has to solve several major problems: (a) generating a reduced enzyme species with superreductive activated electron; (b) preventing the reduced active site from reacting with undesired partners e.g., water \( (\text{H}^+) \); (c) transferring an electron to the substrate and stabilizing the resulting radical anion;
Fig 3.1 Mechanism of chemical Birch reduction of benzene and biological Birch reduction of benzoyl-CoA
(d) providing H⁺ for protonation and another electron for further reduction to ensure quick removal of the reactive radical anion; (e) preventing the activated carboxyl group from being reduced to aldehyde.

The CO-ScoA group greatly lowers the mid-point potential of the first electron transfer step and of whole process. For example, mid-potential of the reduction of benzonitrile is 1.3 V less negative than that of benzene (-3.15 V) (14). Although reduction of benzoyl-CoA is facilitated by the CoA-thioester, the only benzoyl CoA reducing enzyme studied so far requires input energy to overcome this considerable activation energy (15).
References


