The Chemistry of Heterocycles

Mohammad Jafarzadeh Faculty of Chemistry, Razi University

The Chemistry of Heterocycles, (Second Edition).

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5 Five-Membered Heterocyles

With this large group of heterocycles, ring strain is of little or no importance. Ring-opening reactions are, therefore, rarer than in three- and four-membered heterocycles. The crucial consideration is rather whether a compound can be regarded as a heteroarene or whether it has to be classified as a heterocycloalkane or heterocycloalkene.

Various aromaticity criteria apply to heteroarenes, and as a consequence, different opinions have been expressed on this matter.

5.1 Furan

[A] Formerly, the positions next to the heteroatom were indicated as α and α '. The univalent residue is known as furyl. All ring atoms of furan lie in a plane and form a slightly distorted pentagon.





Structure of furan (bond lengths in pm, bond angles in degrees) The structural representation follows from the fact that the bond length between C-3 and C-4 is greater than that between C-2 and C-3 and between C-4 and C-5. The ionization potential is 8.89 eV, the electron being removed from the third π -MO.

The dipole moment is 0.71 D, with the negative end situated on the O-atom. In contrast, the dipole moment of tetrahydrofuran is 1.75 D. The small dipole moment of furan confirms that one electron pair of the O-atom is included in the conjugated system and therefore delocalized.

Furan has the following UV and NMR data:

UV (ethanol)	¹ H-NMR (DMSO-d ₆)	¹³ C-NMR (DMSO-d ₆)
λ (nm) (ε)	δ (ppm)	δ (ppm)
208 (3.99)	H-2/5: 7.46	C-2/5: 143.6
	H-3/4: 6.36	C-3/4: 110.4

The signals in the region typical for benzenoid compounds indicate that a diamagnetic ring current is induced in the furan molecule. Thus, furan fulfils an important experimental criterion for aromaticity in cyclic conjugated systems.

A description of the electronic structure of the furan molecule is based on the assumption that all ring atoms are sp²-hybridized. The overlap of the five $2p_z$ atomic orbitals yields delocalized π -MOs, three of which are bonding and two antibonding.



Electronic structure of furan

(a) sp^2 -hybridization of the ring atoms

(b) energy level scheme of the π -MO (qualitative) and occupation of electrons

(c) π -MO (the O-atom is situated at the lowermost corner of the pentagon)

(d) π -electron densities calculated by ab initio MO methods [2]

MOs π_2 and π_3 , as well as π_4^* and π_5^* , are energetically inequivalent, contrary to the fact that the carbocycles benzene and the cyclopentadienyl anion are iso- π -electronic with furan. Because the nodal plane of π_3 passes through the heteroatom, in contrast to that of π_2 , the degeneracy is lost.

Every C-atom contributes one electron and the O-atom two electrons to the cyclic conjugated structure. The six electrons occupy the three bonding π -MOs in pairs.

As there are six electrons distributed over five atoms, the π -electron density on each ring atom is greater than one. Furan is thus a π -electron excessive heterocycle.

Resonance energy has been used for many years as the criterion for quantifying aromaticity in cyclic conjugated systems. It is defined as the deficiency in the energy content of a system when compared with nonconjugated or aliphatic reference structures and, therefore implies greater stability.

Resonance energy can be theoretically calculated or experimentally determined. The latter is known as *empirical resonance energy*.

The values of the empirical resonance energy for furan are reported to lie between 62.3 and 96.2 kJ mol⁻¹, the value varying from laboratory to laboratory using different methods.

The energy of the furan π -system is less than the sum of the π -electron energies of the localized fragments C(sp²)-C(sp²) and O(sp²)-C(sp²) multiplied by two in each case. This difference may be viewed as the energy liberated by delocalizing the π -electrons in the furan molecule.

The empirical resonance energy of benzene was calculated to be 150.2 kJ mol⁻¹. As the value for furan is 80 kJ mol⁻¹, its aromaticity is less than that of benzene.

The so-called DEWAR resonance energy is based on a corresponding aliphatic polyene which is the hexa-1,3,5-triene in the case of benzene, and the divinyl ether in the case of furan.

The value found for benzene was 94.6 kJ mol⁻¹ and that for furan 18.0 kJ mol⁻¹. These values also show that furan is less aromatic than benzene.

An **aromaticity index** for heteroarenes was proposed based on experimentally determined bond lengths.

[B] By analogy with benzene, furan undergoes reactions with electrophilic reagents, often with substitution. However, it can also react by addition and/or ring-opening depending on reagent and reaction conditions.

Electrophilic substitution reactions

Furan undergoes electrophilic substitution about 10¹¹ times faster than benzene under similar conditions. The reasons for this are:

- The resonance energy of furan is less than that of benzene
- The furan ring has a π -electron excess, while in benzene, the π -electron density is one on each ring atom

The electrophilic substitution reactions of furan, like those of benzene, take place by an additionelimination mechanism.



The substitution is regionelective to the α -position; when these positions are occupied, the β -position is substituted. There are two reasons for this:

• The delocalization of the positive charge in the σ -complex II is more efficient, as it is not impaired by the heteroatom.

• The HOMO coefficient is greater on the α -C-atoms than on the β -C-atoms.

The importance of the resonance energy for the reactivity of the substrate clearly emerges from the mechanism. The π -system of furan contains more energy than that of benzene. Less energy is, therefore, required in the case of furan to interrupt its cyclic conjugation by way of π -complex \rightarrow transition state $\rightarrow \sigma$ -complex.

Chlorination of furan at -40 °C yields 2-chlorofuran and 2,5-dichlorofuran. Bromination with the dioxane-Br₂ complex at -5 °C gives 2-bromofuran.

Nitration is best carried out with fuming nitric acid in acetic anhydride at -10° to -20 °C, and yields 2nitrofuran. Pyridine-SO₃ or dioxane-SO₃ complex converts furan into furan-2-sulfonic acid and then further into furan-2,5-disulfonic acid. Alkylation and acylation are also possible. The action of mercury(II) chloride and sodium acetate in aqueous ethanol brings about mercuration of furan:

Metalation

n-Butyllithium in hexane metalates furan in the 2-position, while excess of reagent at higher temperature produces 2,5-dilithiofuran. This is principally an acid-base reaction, as furan is deprotonated by the strong base butylate:

$$-$$
 + n-BuLi ----- $-$ Li + n-BuH

Addition reactions

Furans yield the corresponding tetrahydrofurans by catalytic hydrogenation.

In some addition reactions, furans behave as 1,3-dienes. For example, furan reacts with bromine in methanol in the presence of potassium acetate to give 2,5-dimethoxy-2,5-dihydrofuran by a 1,4-addition:

$$Me - \overline{OI} + H + Br - Br - HBr MeO - HBr + MeO - HBr MeO - MeO - HBr MeO - M$$

The analogy of the reactivity of furan with that of butadiene is further underlined by the fact that furan undergoes a DIELS-ALDER reaction with dienophiles such as maleic anhydride:



As with butadiene, a 'normal' DIELS-ALDER reaction occurs, i.e. the HOMO of furan interacts with the LUMO of maleic anhydride. The reaction is **diastereoselective**. ALDER'S *endo*-rule applies to the stereochemistry of the cycloadducts **1**/**2**; thus in acetonitrile at 40 °C, the *endo-adduct* **1** is formed 500 times faster than the *exo*-adduct **2** owing to **kinetic control**.

However, with a sufficiently long reaction time, product formation becomes subject to thermodynamic control; the initially formed *endo*-compound is completely converted via the educts into the *exo-* **compound, which is more stable by 8 kJ mol**⁻¹.

With acetylenic dienophiles, e.g. acetylenedicarboxylic ester, adducts are formed (e.g. **3**) which are isomerized by acids to phenols. The selective hydrogenation of **3** to **4** followed by a [4+2] cycloreversion yields the 3,4-disubstituted furan **5**:



There are even reactions which involve one olefinic π -bond of furan. Furan reacts with ketones under conditions of the PATERNO-BÜCHI reaction to give 2a,5a-dihydro-2*H*-oxeto[2,3-b]furans **6**:



Ring-opening reactions

Furans are protonated in the 2-position, and not on the O-atom, by BRÖNSTED acids:



Concentrated sulfuric or perchloric acids induce polymerization of the cations, while dilute acids, e.g. perchloric acid in aqueous DMSO, cause hydrolysis to 1,4-dicarbonyl compounds.

Nucleophilic attack by water probably takes place at the 2-position of protonated furan.

Finally, in a reversion of the PAAL-KNORR synthesis, 2-hydroxy-2,3-dihydrofuran gives rise to the 1,4-dicarbonyl compound hexane-2,5-dione as shown.

[C] Several methods exist for the preparation of furan. The method of retrosynthetic analysis (COREY and WARREN) is used as a guiding principle for the heterocyclic synthesis of the most important target systems. This procedure leads to 'logical' starting materials and methods for constructing the required heterocycles which can then be compared with existing and preparatively important methods.

When furan is considered in the light of a *retrosynthetic analysis*, it can be seen to derive from a double enol ether and can, therefore, be dissected retroanalytically in two ways (I, II):



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If the retrosynthesis follows route I (addition of water to the furan C-2/C-3 bond followed by bond opening O/C-2, i.e. an enol ether hydrolysis according to steps **a-c**), then the 1,4-dicarbonyl system **8** is obtained as the first suggested adduct.

Starting from **8**, the furan system should be formed by a cyclic dehydration. Further retroanalysis of **8** leads via f to the α -halocarbonyl compound **10** and to the enolate of the carbonyl compound **11**. The latter should be convertible into the 1,4-dicarbonyl system **8** by alkylation with **10**.

Following route II, it can be seen that the primary H₂O addition to the furan C-2/C-3 bond can also occur in an opposite direction to a, i.e. according to the retrostep **d**. This leads to the intermediate **7** for which the bond cleavage O/C-2 (**e**) is retroanalytically rationalized and leads to the γ -halo- β -hydroxycarbonyl system **9**.

A retroaldol operation (g) provides the same starting materials **10** and **11** as the retrosynthesis I; route II, however, suggests as the first step aldol addition of **10** and **11** to give **9** followed by intramolecular S_N cyclization of the enolate **9** to the dihydrofuran **7** and conversion into furan by dehydration.

As is shown by the following syntheses, the results of the retrosynthesis can be applied in practice.

(1) 1,4-Dicarbonyl compounds, especially 1,4-diketones, undergo cyclodehydration when treated with coned H_2SO_4 , polyphosphoric acid, $SnCl_2$ or DMSO, providing 2,5-disubstituted furans **12** (*Paal-Knorr synthesis*):



In an acid-base equilibrium, the BRÖNSTED or LEWIS acid adds to one of the carbonyl groups in the 1,4-dicarbonyl system (13) enabling a nucleophilic intramolecular attack by the second carbonyl group, to form 14; finally, the β -elimination, which is also acid-catalyzed, occurs (14 \rightarrow 12).

(2) α -Halocarbonyl compounds react with β -keto carboxylic esters to yield derivatives of 3-furoic acid 15 by cyclocondensation (*Feist-Benary synthesis*):



The FEIST-BENARY synthesis requires the presence of a base, e.g. aqueous Na_2CO_3 . It proceeds as a multistep reaction involving at least two intermediates (16/17) of which 3-hydroxy-2,3-dihydrofurans 17 can be isolated in some cases. The formation of 16 results from an aldol addition, that of 17 from an intramolecular nucleophilic substitution.

Cyclic 1,3-diketones also react with α -halocarbonyl compounds according to the FEIST-BENARY synthesis to produce furans:



In the reaction of β -keto esters with α -halo ketones, the possible competition between C-alkylation (followed by reaction of the PAAL-KNORR type) and aldol addition (followed by reaction of the FEIST-BENARY type) can result in mixtures of isomeric furans.

Regioselectivity can, however, sometimes be controlled by the reaction conditions, as for instance in the interaction of chloroacetone with an acetoacetic acid ester, leading to the furan-3-carboxylates **18/19**:



(3) A furan synthesis which cannot easily be deduced from retrosynthetic considerations is the ring transformation of oxazoles by a DiELS-ALDER reaction with activated alkynes. 4-methyloxazole 20 reacts with dimethyl acetylenedicarboxylate to provide furan-3,4-dicarboxylic ester 22 via a nonisolable adduct 21:



The first step is a [4+2] cycloadditon and the second a [4+2] cycloreversion. The fact that cycloreversion is **not a retroaction** of the first step is due to the formation of thermodynamically very stable acetonitrile, as well as furan.

[D] Furan is produced by the catalytic decarbonylation of 2-furaldehyde or by decarboxylation of 2-furoic acid with copper powder in quinoline.

Furan is a colorless, water-insoluble liquid of pleasant odor, bp 32 °C. Addition of hydroquinone or other phenols inhibits polymerization, which occurs slowly at room temperature.

2-Furaldehyde (furfural; from Latin for bran) is obtained industrially from plant residues which are rich in pentoses, e.g. bran, by treatment with dilute sulfuric acid followed by steam distillation:



2-Furaldehyde is a colorless, poisonous, water-soluble liquid, bp 162 °C, which slowly turns brown in air. Like benzaldehyde, it undergoes the CANNIZZARO reaction, the PERKIN reaction, the KNOEVENAGEL condensation and the acyloin condensation. The catalytic hydrogenation of 2-furaldehyde yields 2-(hydroxymethyl)oxolane **23** (tetrahydro-2-furfuryl alcohol). This compound undergoes a nucleophilic 1,2-rearrangement to give 3,4-dihydro-2*H*-pyran **24** by the action of acid catalysts:

The preparation of the colored salt **25** of 5-anilino-l(phenylimino)penta-2,4-dien-2-ol by the action of aniline and hydrochloric acid illustrates a ring-opening of 2-furaldehyde:



2-Furaldehyde is used as a solvent in the manufacture of polymers and as a starting material for syntheses. 2-Furaldehyde could attain the importance of a raw material for the chemical industry if the trend towards the use of *'regenerative raw materials*' increases further.

5-Nitro-2-furaldehyde (5-nitrofurfural), mp 36 °C, is prepared by the nitration of 2-furaldehyde. Some of its derivatives are bacteriostatic and bacteriocidal, e.g. the semicarbazone (Nitrofural), and are used to combat infectious diseases.

5-(Hydroxymethyl)-2-furaldehyde is formed by the dehydration of saccharose, e.g. with iodine in DMSO.

Furoic acid (furan-2-carboxylic acid) is obtained by dry distillation of D-galactaric acid (mucic acid):



Furoic acid forms colorless crystals, mp 134 °C. With a p K_a value of 3.2, it is a stronger acid than benzoic acid (p K_a 4.2).

Furans are occasionally found in plants and microorganisms, e.g. carlina oxide **26**, which is obtained by steam distillation from the roots of the carline thistle (*Carlina acaulis*)'.

$$\bigcirc -C \equiv C - CH_2 - Ph$$

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Some natural products containing a furan ring have an intense odor, e.g. 2-furylmethanethiol **27**, a component of coffee aroma, rose furan **28**, a component of rose oil, and menthofuran **29**, which occurs in peppermint oil. The compounds **28** and **29** are reminiscent of terpenoid structures:



[E] Furans are of considerable importance as synthetic intermediates. Their acid-catalyzed hydrolysis, as well as their ability to undergo cycloadditions, can be utilized. For instance, the furan **30**, which is accessible from methylfuran and (*Z*)-1-bromohex-3-ene by metallation and alkylation, is cleaved by aqueous acid to give the 1,4-diketone **31**. This is then converted by a base-catalyzed intramolecular aldol condensation into (*Z*)-jasmone **32**, a naturally occurring fragrance substance:



An alternative method of ring-opening is the cleavage of 2-furylmethanols (e.g. **33**) with HCI in alcohols to give esters of 4oxopentanoic acid (e.g. **34**).



Under similar conditions, 2-furyl vinylcarbonyl systems (ketones, esters, acids) also produce keto esters. For example, 3-(2-furyl)acrylic acid **38**, which is easily accessible from 2-furaldehyde by a decarboxylating KNOEVENAGEL reaction with malonic acid, yields the 3-oxoheptanedicarboxylic ester **39** (MARCKWALD cleavage):



This transformation, which is formally an internal redox process, can be explained by an ionic mechanism involving ROH addition, isomerization and hydrolytic ring-opening $(35 \rightarrow 36 \rightarrow 37 \rightarrow 34)$.