

What Makes Fluorine So Special?

Comparisons of H, F and Cl

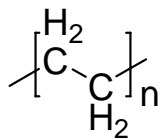
Property	H	F	Cl
Electronic Configuration	1s ¹	...2s ² 2p ⁵	...3s ² 3p ⁵ 3d ⁰
		More electrons, 7 valence electrons	
Electronegativity (Pauling)	2.1	4.0	3.0
		Profound effects on Reactivity	
Ionization Energy (kcal/mol)	315	403	300
		F+ less likely than Cl+	
Electron Affinity (kcal/mol)	17.8	83.5	87.3
		e-/e- repulsions are important to the <u>small</u> F-	
Bond Energy of C-X (kcal/mol)	99	111	78
		Strong bond = thermal stability	
Bond Length of C-X (Å) (CX ₄)	1.09	1.32	1.77
		Short bond	

$$\text{I.E.} = \text{X} \rightarrow \text{X}^+ + \text{e}^-$$

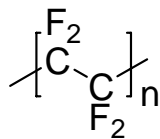
$$\text{E.A.} = \text{X} + \text{e}^- \rightarrow \text{X}^-$$

$$(1 \text{ Joule} = 4.184 \text{ cal})$$

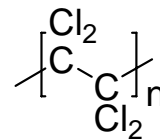
Polythenes:



stable



stable



unstable

(Shows similarity between H and F – *actually the STERICS make the Cl version unstable*)

Preference as Leaving Groups

H⁺

F⁻

Cl⁻

(Shows difference between H and F. *This is an Electronics issue*)

^1H and ^{19}F NMR

Nucleus	^1H	^{19}F
Rel. Sensitivity	1.00	0.834
Spin	1/2	1/2
Abundance	99.98%	100%
NMR Frequency in MHz for 1T field	42.576	40.055
Typical δ range /ppm	10ppm	260ppm

larger spectral width means spectra are more informative

Bond Energies for Halogens (*in kcal/mol*)

Halogen	X-X	H-X	BX ₃	AlX ₃	CX ₄
F	37.7	136.0	154.2	139.1	109.0
Cl	58.2	103.0	106.1	102.1	78.2
Br	46.1	88.0	88.0	86.0	65.0
I	36.1	71.0	65.0	68.1	57.1

The F-F bond is weak, too many electrons in a confined area.

Generally, F forms strong bonds.

Also recall $F^- < Cl^- < Br^- < I^-$
for Nucleophilicity
and Leaving Group Ability

Why Is Fluorine So Special?

There are three special characteristics that make fluorine attract so much attention.

It is the most electronegative element

It is the smallest substituent after hydrogen

It can form a stronger bond with carbon than hydrogen can.

Table 1.1 Representative physical properties of selected atoms

Atom	Electronegativity	van der Waals radius (Bondi) (Å)	Bond length (CH ₃ -X) (Å)	Dissociation energy (CH ₃ -X) (kcal/mol)
H	2.2	1.20 ●	1.09	99 ●
F	4.0 ●	1.47 ●	1.39	110 ●
Cl	3.0	1.75	1.77	85
Br	2.8	1.85	1.93	71
C	2.5	1.70	1.54	83 ●
O	3.5	1.52	1.43	86

*It is the **combination** of these three features that gives fluorinated materials their unique properties.*

Often profound effects can result from switching just one hydrogen for fluorine.

For example, recall the Citric Acid Cycle / tricarboxylic acid (TCA) cycle and the Krebs's cycle.

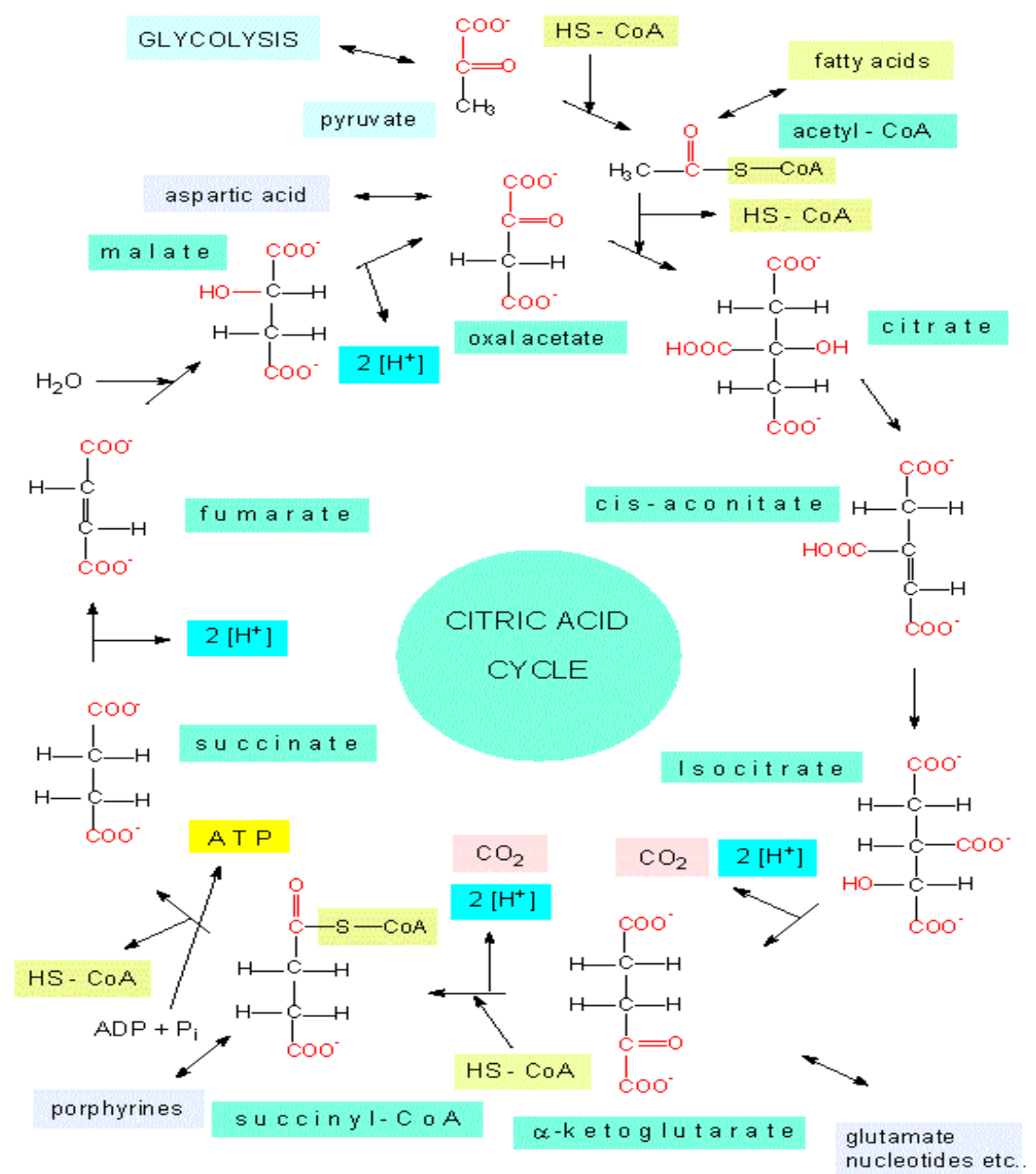
It is the final common catabolic pathway for the oxidation of fuel molecules →energy.

Two carbons enter the citric acid cycle as acetyl CoA and two carbons leave as CO₂.

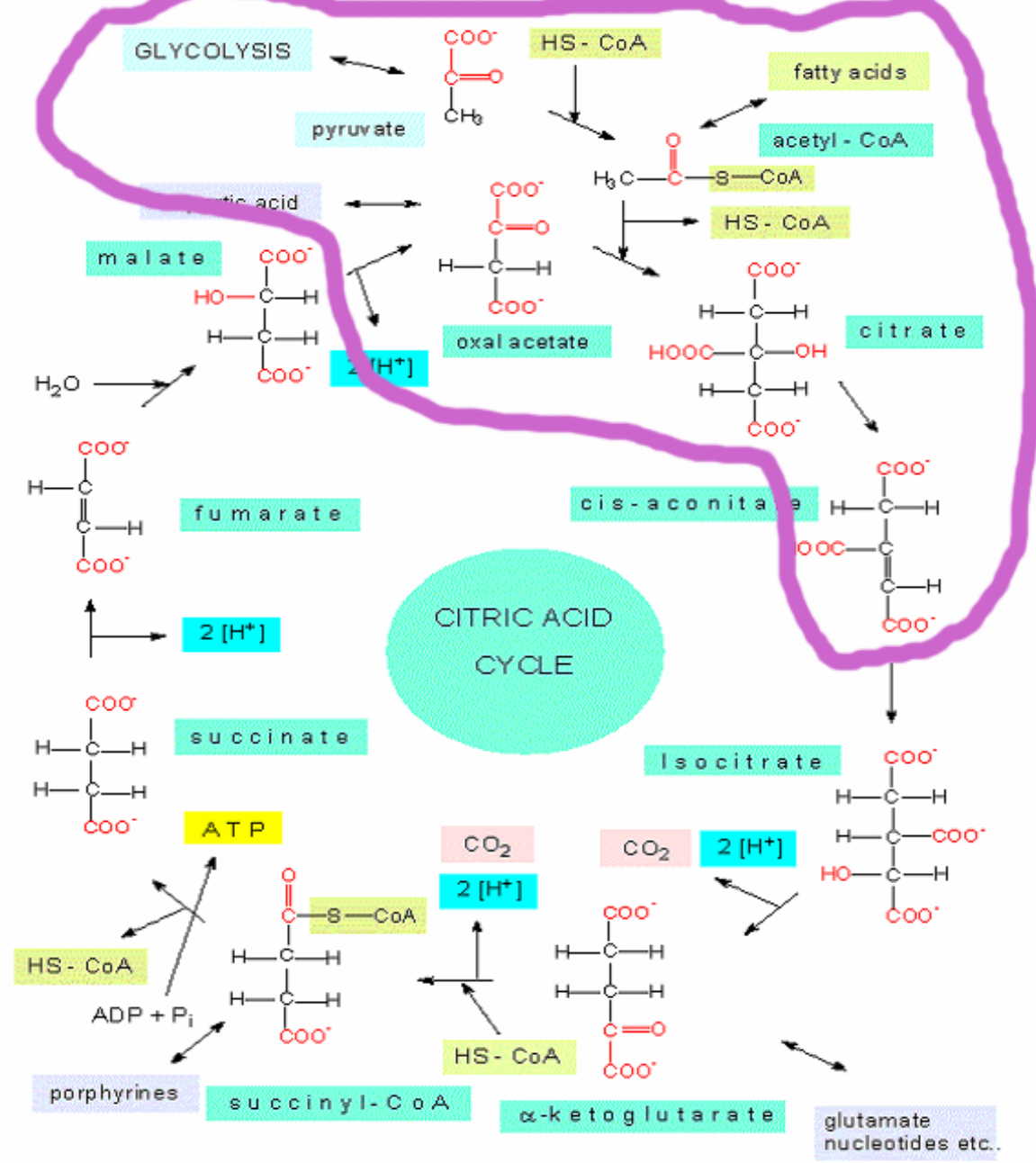
In the course of the cycle, four oxidation-reduction reactions take place to yield reduction potential in the form of three molecules of NADH and one molecule of FADH₂.

A high energy phosphate bond (GTP) is also formed.

Citric Acid Cycle

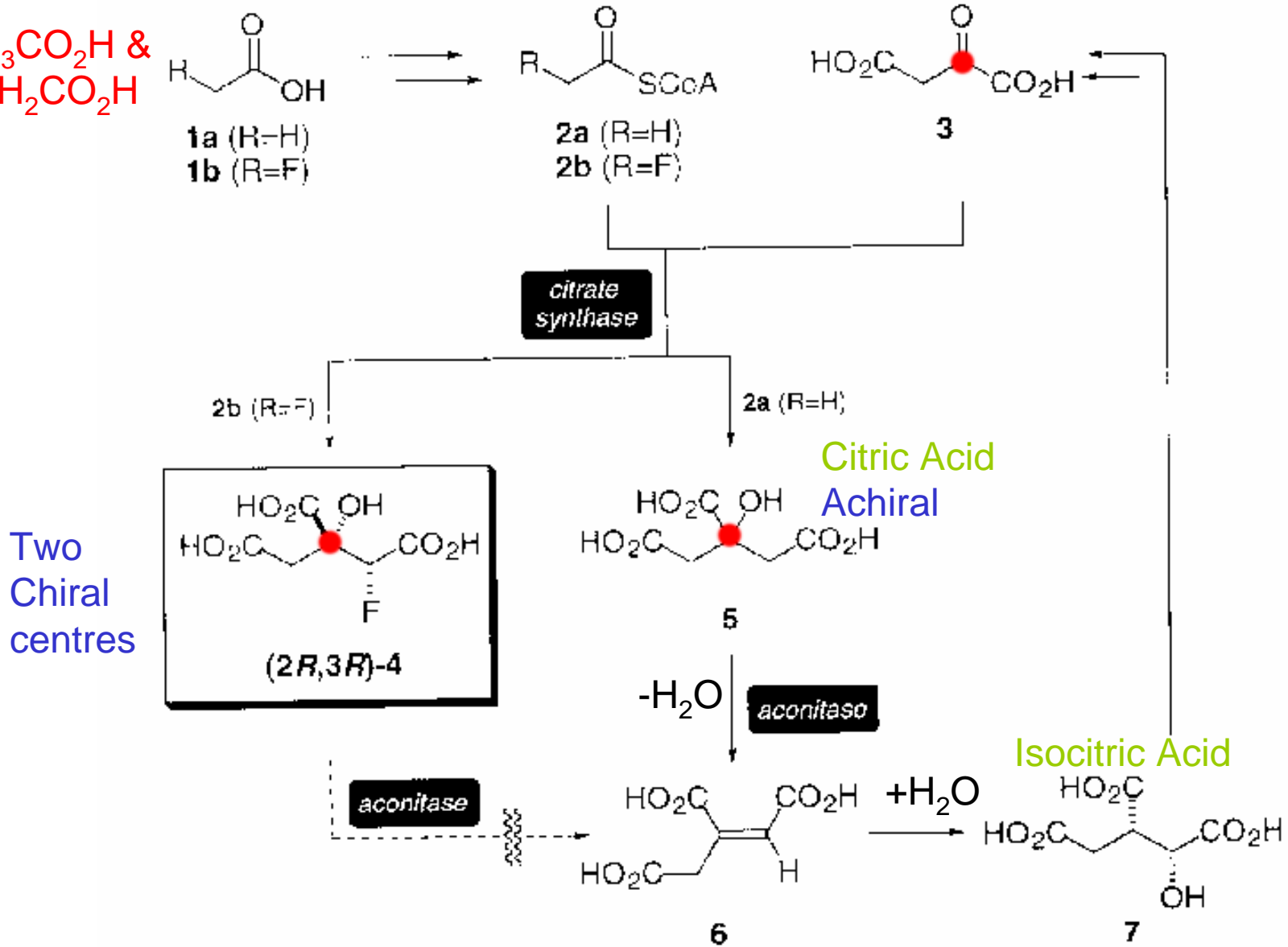


Citric Acid Cycle



Let us consider what happens when fluoroacetic acid becomes involved in the acetic acid metabolism system:

$\text{CH}_3\text{CO}_2\text{H}$ &
 $\text{FCH}_2\text{CO}_2\text{H}$



Due to the similar steric effect of fluorine and hydrogen, the fluoroacetic acid is “mistakenly” recognized as acetic acid and ends up being converted into fluorocitric acid via combination of fluoroacetyl-CoA and oxaloacetic acid with citrate synthase.

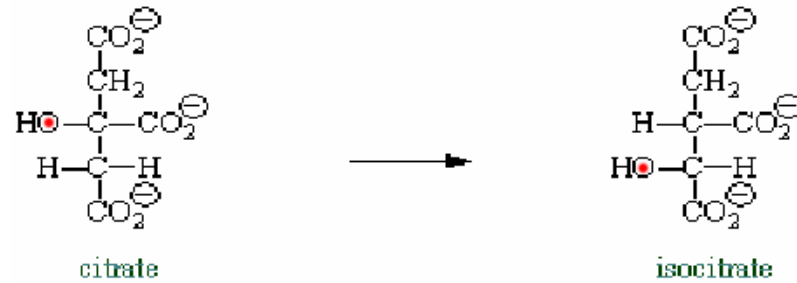
Interestingly this reaction is **enantiospecific**, yielding the (2R, 3R) isomer.

The (2R, 3R) diastereomer has been shown to be extremely poisonous, causing convulsions and ventricular fibrillation.

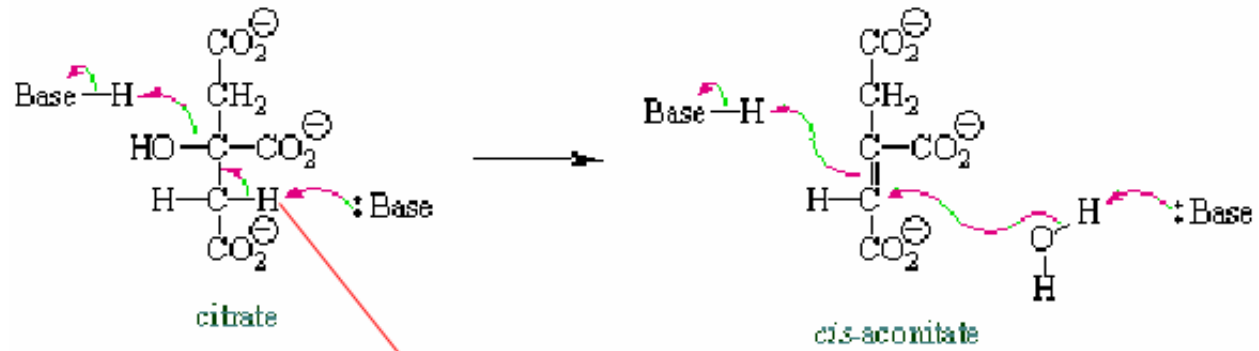
The other three diastereomers of this fluorocitric acid have been found to be non-toxic. (2R, 3S); (2S, 3S); (2S, 3R).

Normally the citric acid undergoes the aconitase catalyzed dehydration, and subsequent hydration to yield isocitric acid.

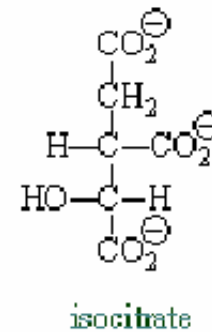
Isomerisation reaction



However it turns out that the Fluorine atom in (2R, 3R) fluorocitric acid is in the position where the Hydrogen would normally be removed.



When this H = F, get no reaction



Cleavage of the much stronger C-F bond cannot be achieved, and thus fluorocitric acid does not progress along the citric acid cycle.

This leads to an inhibition of the citric acid cycle, and an accumulation of this fluorinated material.

This type of behavior is often referred to as the “mimic effect”.

It is a direct effect of the similar steric size of F and H, and the fact that C-F is stronger than C-H (points 2 and 3 from before).

Very often molecules with a single fluorine atom display profound changes biological activity due this “mimic effect”.

(So it behaves the same, behaves the same, does something different)

Rat Poison

Extracts from selected Rodenticide / Environmental Sources.

a) 1080 - Sodium Fluoroacetate $C_2H_2FO_2Na$

It is tasteless and odorless, biodegrades quickly in contact with soil and in water, but is residual and remains fully active in mammalian tissue. It can be readily taken up into vegetable tissue by leaf absorption or root uptake and into fish tissue.

In appearance it is a fluffy colorless to white powder, which may be dyed black (for safety reasons).

It is totally soluble in water.

It is lethal to all mammals, both placental and marsupial (with certain very restricted exceptions) with dosages generally less than 1mg/kg (poison to bodyweight), and most avian species with dosages up to 10mg/kg.

Entry routes are via inhalation; ingestion; dermal and ocular contact and absorption.

There is no antidote to 1080 poisoning

1080 works by interfering with the Krebs's cycle. Toxicity is delayed by up to several hours while the body converts the fluoroacetate to fluorocitric acid, which in turn disrupts the Krebs's cycle.

Death by 1080 is not painless. It is prolonged and distressing.

Animals stagger around, frightened, disoriented and convulsing until they succumb to central nervous system collapse, coronary failure, or are attacked by predators that they cannot fend off.

Death can take up to 20 hours.

Compound 1080 is also known as 'the poison that keeps on killing'. In other words, the cat that ate the rat that was poisoned by 1080 has forfeited all its nine lives.

For a time, 1080 was banned in the United States. It can only be used by licensed exterminators, but environmentalists continue to oppose its use.

b) Fluoroacetate is a natural form of the slightly more toxic sodium fluoroacetate.