INTERNATIONAL COLLEGE OF PHARMACEUTICAL INNOVATION
国际创新药学院

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|---|---|
| **Class** | Pharm, BioPharm |
| **Course** | Fundamentals of Medicinal & Pharmaceutical Chemistry |
| **Code** | FUNCHEM.8 |
| **Title** | Covalent bonding in physiologically important ions and molecules |
| **Lecturer** | Prof. Xinchen Teng |
| **Date** | 2024-10-25 |

# RECOMMENDED READING

- General Chemistry - The Essential Concepts by Chang and Goldsby (7th edition)
  - Section 9.1, 9.2, 9.4 - 9.9

# Learning outcomes

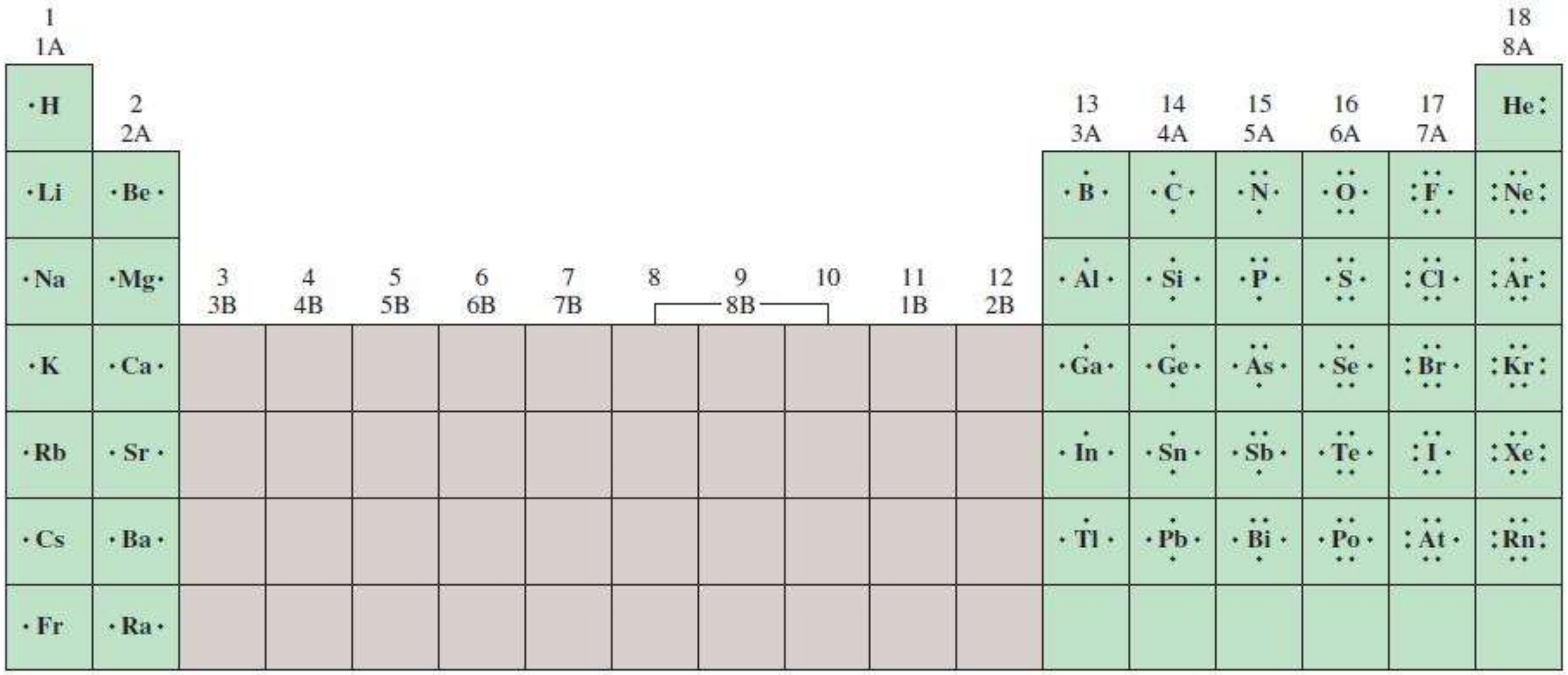
- Construct Lewis dot structures for diatomic and triatomic molecules using a set of simple rules.
- Define resonance.
- Define bond order and its relation to bond strength/length.
- Define free radical.
- Identify nitric oxide and superoxide ion and hydroxyl radical as free radicals.
- Define disproportionation (dismutation) reaction.
- Outline equation for the disproportionation of superoxide and state the role of superoxide dismutase in this.
- Outline equation for the reaction of nitric oxide and superoxide ion to give peroxynitrite.
- Recall the neurotoxicity of peroxynitrite.

## Lewis dot structures

- A Lewis dot symbol consists of the symbol of an element and one dot for each valence electron in an atom of the element.
- Valence electrons are the electrons that occupy the outmost shell of the atom or ion.
- Valence electrons are capable of participating in bonding between atoms and ions.
- You can use Lewis dot structures to represent the bonding in molecules and ions.

# Lewis electron dot symbols

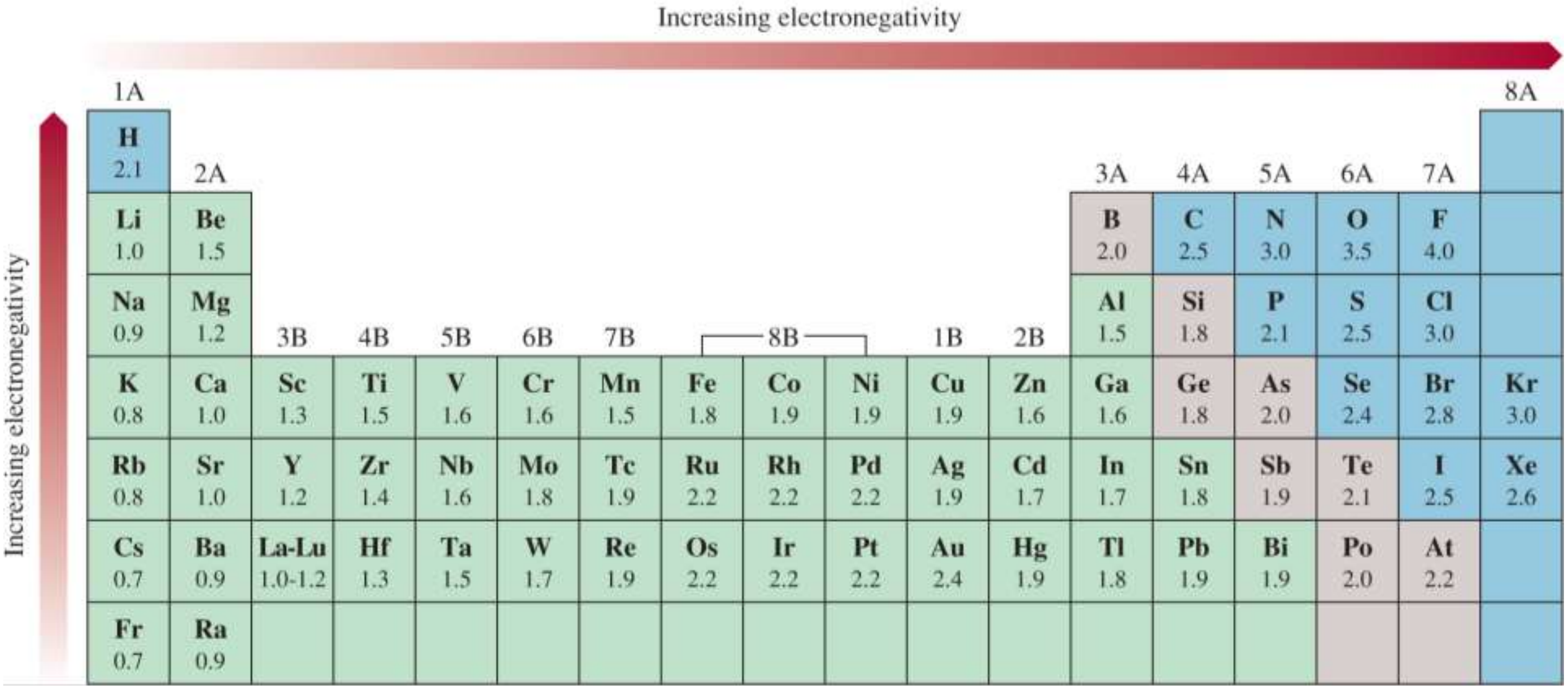
Lewis symbols are used mainly for *s*- and *p*-block elements



# Six step procedure to Lewis dot structure

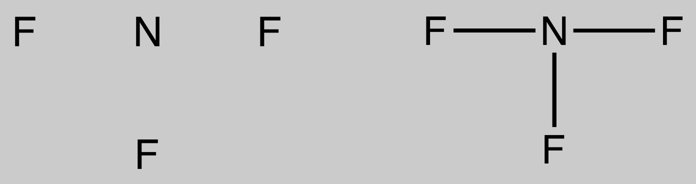
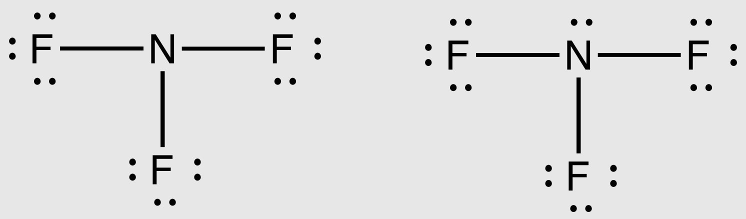
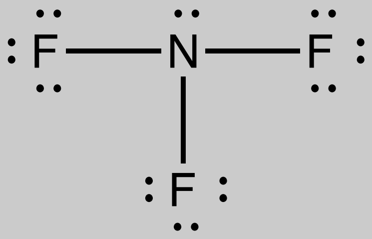
1. Count the number of valence electrons on each atom. This is the same as the group number. Add electrons for negatively charged ions. Subtract electrons for positively charged ions.
2. Arrange the atoms within the molecule. The atom with the lowest electronegativity (usually) is generally the central atom. Exclude hydrogen when choosing central atom.
3. Connect the centre atom with the other atoms using a single bond. Single bond is 1 pair of electrons.
4. Then complete the octet rule on the most electronegative atoms first by adding lone pairs of electrons. Hydrogen can only have 2 electrons (duet rule). Check to see how many electrons are left from the original total. Add these to central atom.
5. If the central atom has an incomplete octet, use the electrons from surrounding atoms to make double or triple bonds. Only C, N, O, P, and S form multiple bonds.
6. Indicate the structures of any resonance forms.

# Electronegativity trends

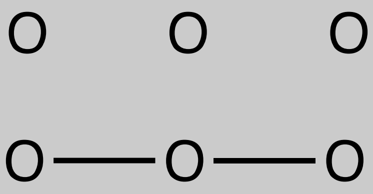
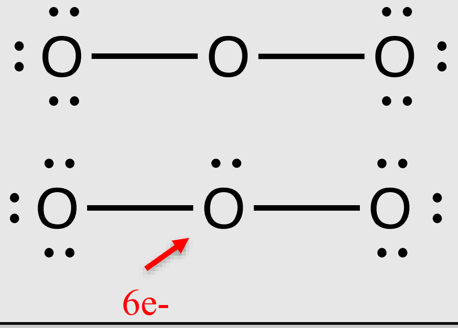
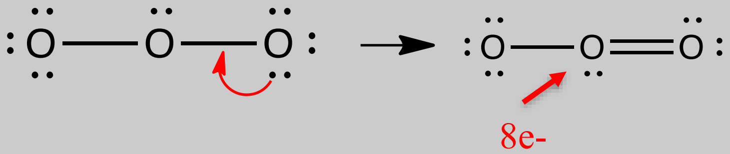
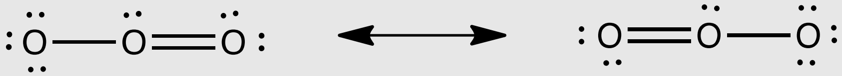



Pauling scale of relative electronegativity values

# Lewis dot structure of $NF_3$

| | |
|---|---|
| 1. Count the number of valence electrons on each atom | 26 valence electrons<br>3x F $(2s^22p^5)$ + N $(2s^22p^3)$<br>21 + 5 |
| 2. Arrange the atoms within the molecule. The central atom is generally less electronegative than the ones surrounding it.<br>3. Connect the centre atom with the other atoms using a single bond |  |
| 4. Complete the octet rule on the most electronegative atoms first. Then the other atom. |  |
| 5. Check central atom<br><br>N satisfies octet rule. No action |  |
| 6. Show any resonance forms | No resonance structures required |

# Lewis dot structure of $O_3$

| | |
|---|---|
| 1. Count the number of valence electrons on each atom | 18 valence electrons i.e. 3x O ($2s^2 2p^4$) |
| 2. Arrange the atoms within the molecule.<br>3. Connect the centre atom with the other atoms using a single bond |  |
| 4. Complete the octet rule on the most electronegative (outer) atoms first. Then add electrons to the other atom (central). |  |
| 5. Check central atom for octet |  |
| 6. Show any resonance forms |  |

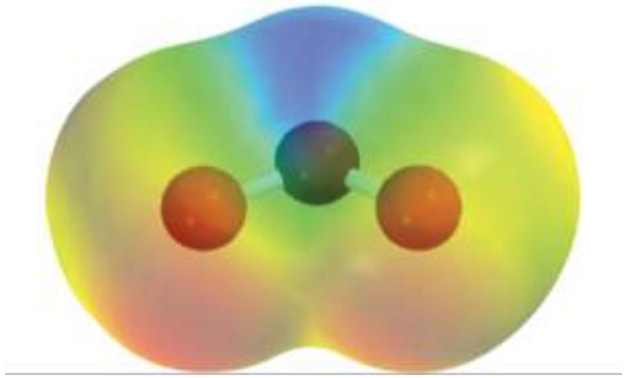
# Resonance and resonance structures

- The term **resonance** itself means the use of two or more Lewis structures to represent a particular molecule.
- A resonance structure is one of two or more Lewis structures for a single molecule that cannot be represented accurately by only one Lewis structure.
- The double-headed arrow indicates that the structures shown are resonance structures.
- In resonance structures, all atoms must be shown in the same position, and only the positions of the electrons are different.

Watch the animation titled 'Resonance Structures' on the VLE

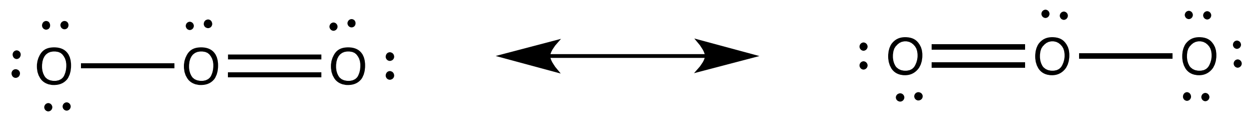
# O-O bond properties in $O_3$

- In ozone the two oxygen to oxygen bonds **are found experimentally to be identical**.
- The two O to O bond lengths are each 128 pm
- This compares with:
  - O=O (121 pm, bond order = 2)
  - H-O-O-H (149 pm, bond order = 1)
- Therefore in ozone the bonds are between single and double bonds.



# Resonance structures of $O_3$

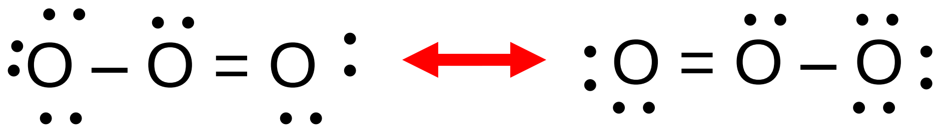
- The actual structure of $O_3$ is not represented by a single resonance structure.
- The actual structure is a hybrid of the resonance structures.
- Therefore the bond order of each oxygen to oxygen bond is 1.5.



# Bond order

- Bond order indicates the approximate strength of a bond.
- It can be used not to strictly define the strength of a bond but for purposes of comparison.
- The large the bond order the stronger the bond.

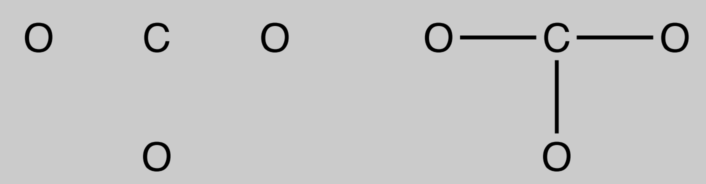
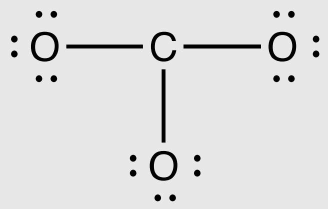
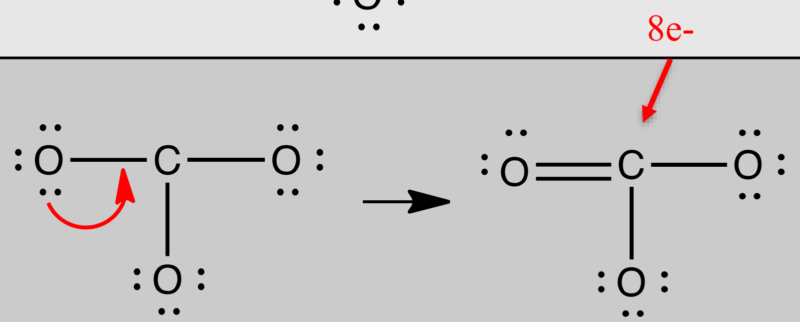
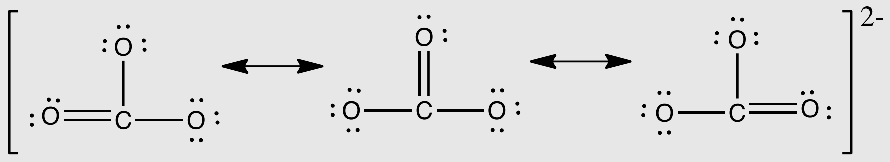
$$\text{Bond Order}_{\text{(in a small molecule)}} = \frac{\text{Number of Bonds}}{\text{Number of connections between atoms}}$$



$$\frac{3 + 3}{2 + 2} = \frac{6}{4} = \frac{3}{2}$$

Note the definition of bond order above it appropriate for use in this course. Do not refer to the definition of calculation of bond order in recommended text, General Chemistry, The Essential Concepts.

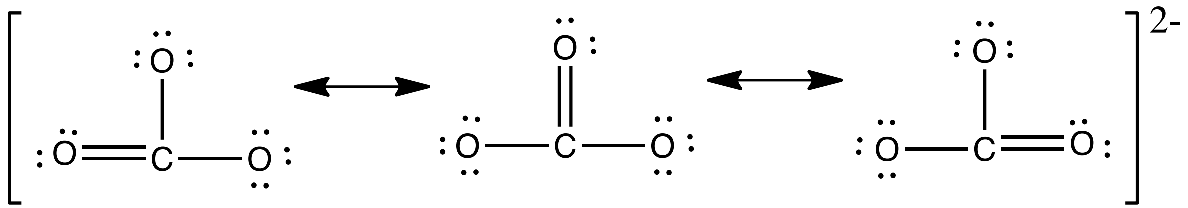
# Lewis dot structure for $CO_3^{2-}$

| | |
|---|---|
| 1. Count the number of valence electrons on each atom | 24 valence $e^-$<br>i.e. 3x O ($2s^2$, $2p^4$) C ($2s^22p^2$)<br>2 e- for the charge |
| 2. Arrange the atoms within the molecule.<br>3. Connect the centre atom with the other atoms using a single bond |  |
| 4. Complete the octet rule on the most electronegative atoms first. Then the other atom. |  |
| 5. Check central atom for octet |  |
| 6. Show any resonance forms<br><br>Don't forget to write the charge. |  |

# Bond order of C-O bonds in $CO_3^{2-}$

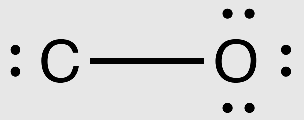
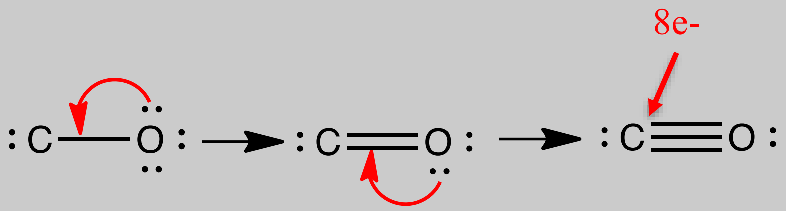
- The C-O bonds in $CO_3^{2-}$ are found to be identical.
- The actual structure is a hybrid of the three resonance structures.
- C-O bond order = $^4/_3$

$$\text{Bond Order (in } CO_3^{2-}) = \frac{\text{Number of Bonds}}{\text{Number of connections between atoms}}$$



$$\frac{4+4+4}{3+3+3} = \frac{12}{9} = \frac{4}{3}$$

# Lewis structure for CO

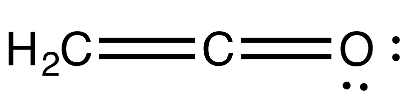
| | |
|---|---|
| 1. Count the number of valence electrons on each atom | 10 valence $e^-$s C ($2s^22p^2$) O ($2s^22p^4$) |
| 2. Arrange the atoms within the molecule.<br>3. Connect the atoms using a single bond |  |
| 4. Complete the octet rule on the most electronegative atom and then the other atom |  |
| 5. Check other atom for octet rule |  |
| 5. Show any resonance forms | No resonance structures required |

# Isoelectronic

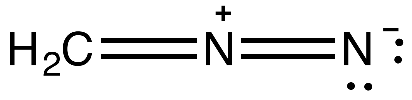
- Same number of valence electrons and the same connectivity in their structures
- They have the same number of atoms and the same number of bonds

Examples: N and $O^+$ — Same number of valence electrons

$CO$, $N_2$, and $NO^+$ — Same number of atoms, same connectivity and same number of electrons



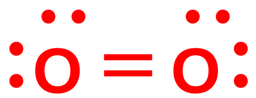
ethenone



diazomethane

# Limitations of Lewis dot structures

- For $O_2$ the structure arrived at by applying the rules is

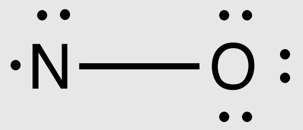
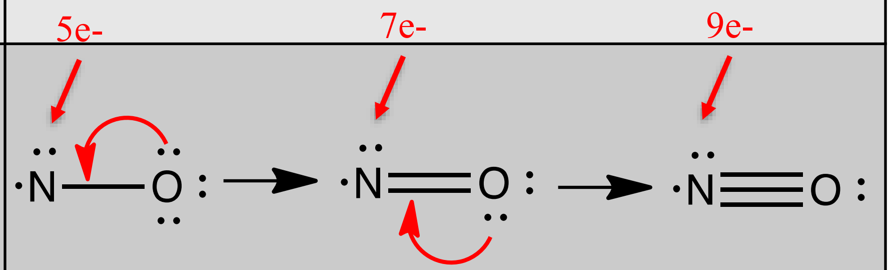
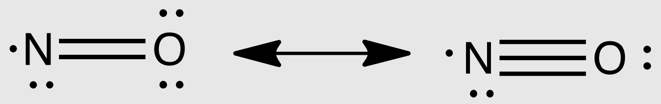


- However experiments show that $O_2$ is paramagnetic with 2 unpaired electrons and has a bond order = 2.
- A paramagnetic substance is one with unpaired electrons and weighs heavier in the presence of a magnetic field.
- Lewis Structures cannot explain the paramagnetism observed in $O_2$.
- Molecular orbital theory can.

# NO, Nitric Oxide

- Molecule of the year 1992 in Science Journal.
  - Involved in lowering blood pressure
  - Neurotransmitter
  - Antimicrobial defence
  - Relaxes muscle cells in the cardiovascular system
- In 1998 Furchgott, Ignarro, Murad won Nobel prize for work on NO.

# Lewis structure for NO

| | |
|---|---|
| 1. Count the number of valence electrons on each atom | 11 valence $e^-$s N ($2s^22p^3$) O ($2s^22p^4$) |
| 2. Arrange the atoms within the molecule.<br>3. Connect the atoms using a single bond |  |
| 4. Complete the octet rule on the most electronegative atom and then the other atom |  |
| 5. Check other atom for octet rule |  |
| 6. Show any resonance forms |  |

# NO bond length

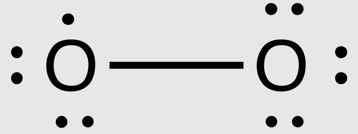
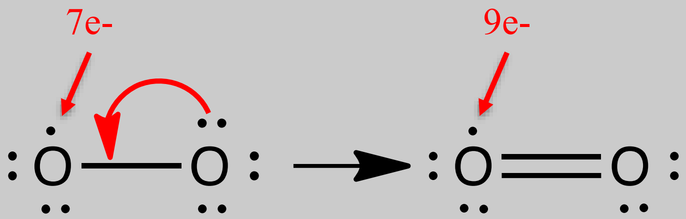
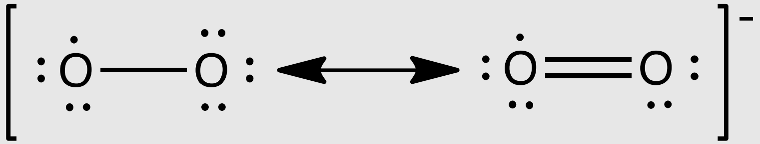
- In NO bond length = 115 pm
  - For N≡O containing compounds N≡O is 106 pm
  - For N=O containing compounds N=O is 120 pm
- NO is an example of a radical as it contains an unpaired electron.
  - Radicals are very reactive chemical species with an unpaired electron.

What is the bond order of NO?

# Reactive Oxygen Species

- These oxygen species are made as by-products during mitochondrial oxidation processes.
- They include:
  Superoxide ion $O_2^-$
  Peroxide ion $O_2^{2-}$
  Hydroxyl radical $\cdot OH$
  Hydroxyl ion $OH^-$

# Lewis structure for Superoxide ion $O_2^-$

| | |
|---|---|
| 1. Count the number of valence electrons on each atom | 13 valence $e^-$ 2 x O ($2s^22p^4$) O and $1e^-$ from charge. |
| 2. Arrange the atoms within the molecule.<br>3. Connect the atoms using a single bond |  |
| 4. Complete the octet rule on the most electronegative atom and then the other atom |  |
| 5. Check other atom for octet rule |   |
| 6. Show any resonance forms |  |

# Superoxide ion and Superoxide Dismutase

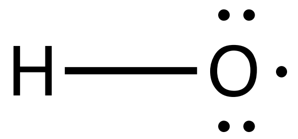
- Superoxide ion is a physiologically damaging ‘reactive oxygen species’ which is removed by a disproportionation (dismutation) reaction
- This is a special type of redox reaction in which an element in one oxidation state is simultaneously oxidized and reduced.
- This reaction is catalysed by the enzyme, superoxide dismutase.

$$2(O_2^-) \xrightarrow[\text{superoxide dismutase}]{} O_2 + O_2^{2-}$$

| | superoxide | oxygen | peroxide |
|---|---|---|---|
| **Oxidation No. [O] :** | $-{}^{1}/_{2}$ | 0 | -1 |

# Hydroxyl radical (HO·)

- This is the most reactive of the ROS



Hydroxyl radical is produced by the following reactions:

$$O_2^{-} + H_2O_2 \longrightarrow O_2 + \cdot OH + OH^{-}$$

Superoxide Hydrogen peroxide Oxygen Hydroxyl radical Hydroxide ion

$$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + \cdot OH + OH^{-}$$

# Reactive oxygen species in biological systems

- Reactive oxygen species can:
  - Oxidize cholesterol
  - Oxidize unsaturated fatty acids
  - Causing membrane lipid peroxidation
- Reactive oxygen species can also react with a large variety of easily oxidisable cellular components, including
  - NADH, NADPH, ascorbic acid, histidine, tryptophan, tyrosine, cysteine, glutathione, proteins and nucleic acids.

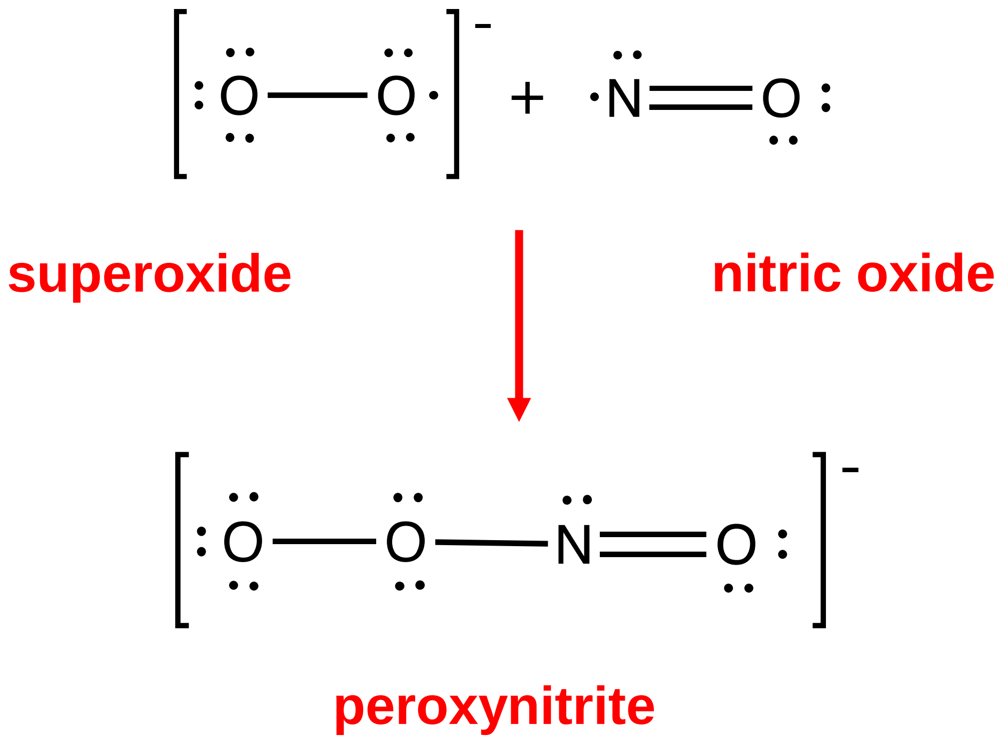
$$RH + \cdot OH \longrightarrow R\cdot + H_2O$$

Cellular component

Highly reactive radical from cellular component

# NO (Nitric Oxide)

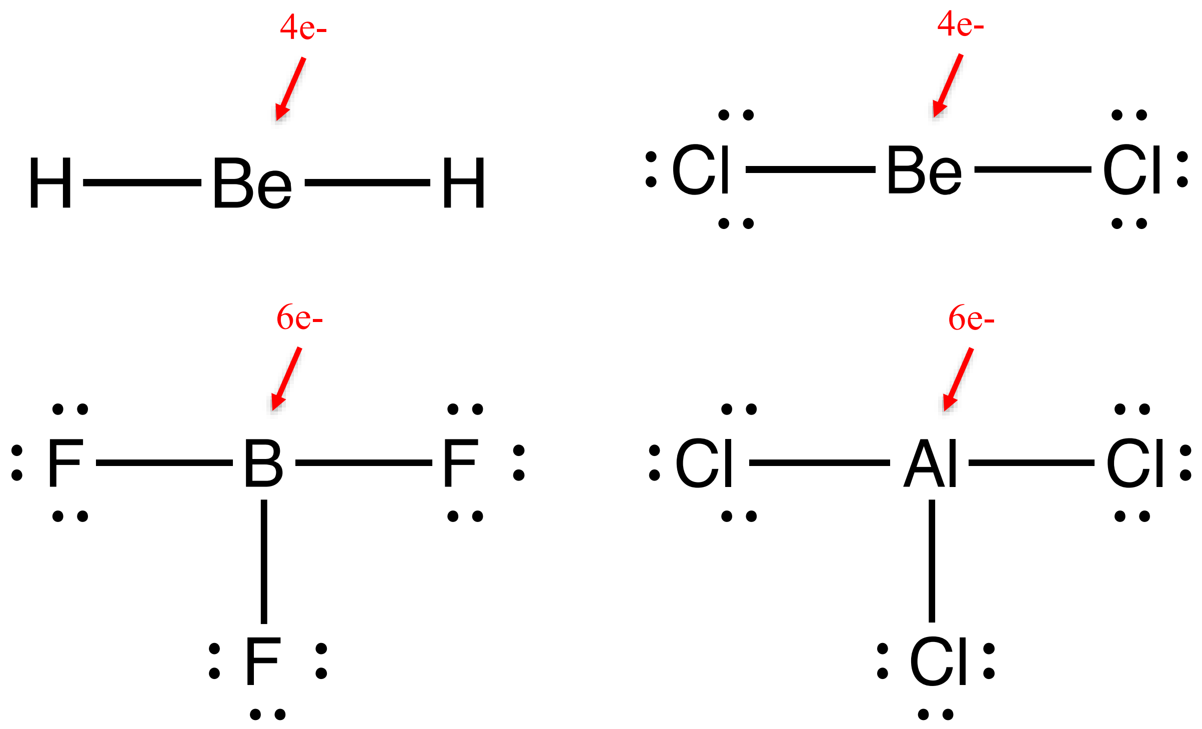
- NO can be neurotoxic.
- Excess NO formed → formation of peroxynitrite.
- Peroxynitrite is an oxidant and nitrating agent. Because of its oxidizing properties, peroxynitrite can damage a wide array of molecules in cells, including DNA and proteins
- Superoxide dismutase reduces effects of excess NO




Other reactive oxygen species are various peroxides (ROOR') and hydroperoxides (ROOH).

# Exceptions to the octet rule

- Group 2A and 3A elements tend to form stable compounds with fewer than 8e$^-$ around the central atom.




**Read Section 9.9 in General Chemistry The Essential Concepts to see what it say about Exceptions to the Octet Rule**