*The 24rd International Electronic Conference on Synthetic Organic Chemistry (**ECSOC**)*
*Session: **Computational Chemistry***

# Influence of nonpolar medium on antioxidant capacity of bergaptol and xanthotoxol
## *- kinetic DFT study-*

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# PRESENTATION AGENDA

1

## INTRODUCTION

- Influence of reactive oxygen species (ROS) on biologically important macromolecules.
- Biological and pharmacological significance of furanocoumarins.

2

## MATERIALS AND METHODS

- A detailed description of the quantum chemical calculations on which the research is based.

3

## RESULTS AND DISCUSSIONS

- Thermodynamic parameters.
- Kinetic parameters.
- Relative antioxidant capacity (relative to Trolox (6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid)).

4

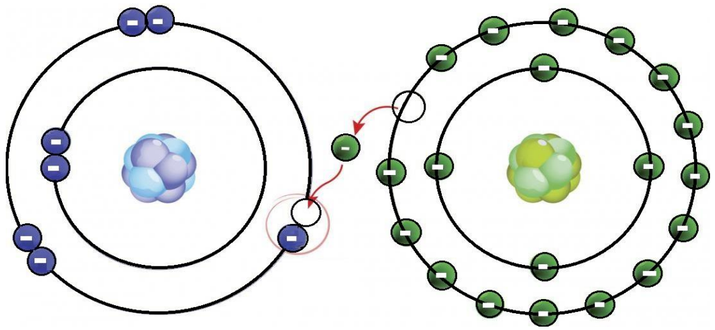
## CONCLUSION

- Comprehensive summarization of research results.


INTRODUCTION

# REACTIVE OXYGEN SPECIES (ROS)

ROS



Antioxidant

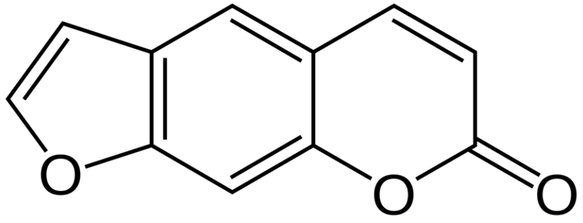
***Hydroxyl radical, HO•***

- Product of partial reduction of oxygen with a short half-life (10 $s^{-1}$).
- High electrophilicity and high thermochemical reactivity.
- It reacts quickly with organic and inorganic biocomponents in the cell.

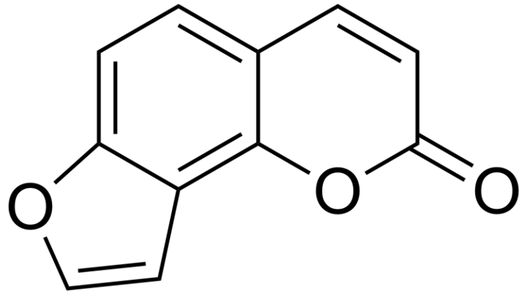
***HO•***

# FURANOCOUMARINS

**Furanocoumarins**




(*7H*-furo[3,2-g]chromen-7-one)
**(Psoralen)**




2*H*-furo[2,3-h]chromen-2-one
**(Angelicin)**

*Rutaceae*

*Moraceae*

*Fabaceae*

Important group of heterocyclic compounds

Found in the product of metabolism of plants, some microorganisms and animals

Coumarins are used in:

**Industry**

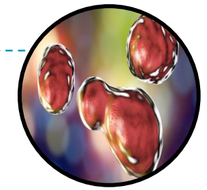
- Food industry
- Perfumes and aromatizers
- Laser dyes
- Color industry
- Industry of alcoholic beverages

**Medicine**

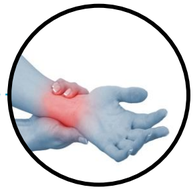
- Important biological and pharmacological activity

# BIOLOGICAL ACTIVITY OF COUMARIN

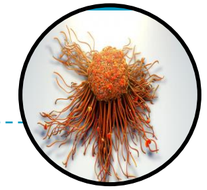
ANTIBACTERIAL ACTIVITY



ANTIFUNGAL ACTIVITY



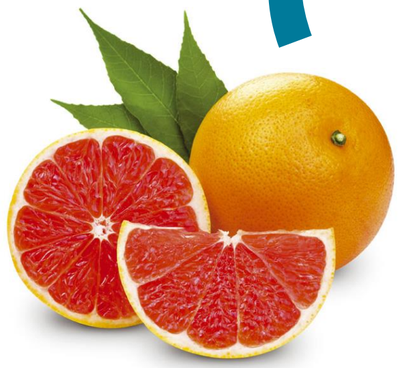
ANTIINFLAMMATORY ACTIVITY

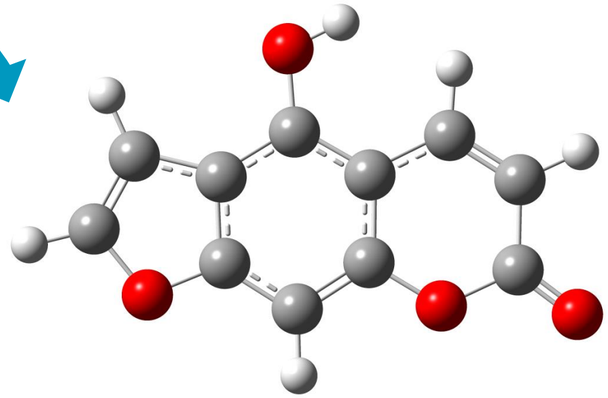


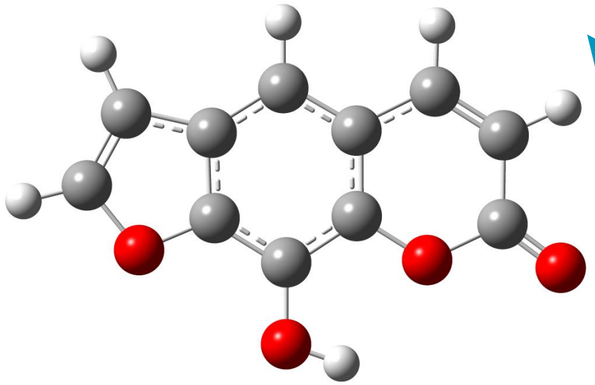
ANTICANCEROGENIC ACTIVITY

**ANTIOXIDANT ACTIVITY**

# INVESTIGATION COMPOUNDS







Bergaptol (4-hydroxyfuro[3,2-g]chromen-7-one**, BER**)

Xanthotoxol (9-hydroxyfuro[3,2-g]chromen-7-one, **XAN**)

Significant *in vitro* antioxidative activity

2,2-azobis (3-ethylbenz-thiazoline-6-sulfonic acid) (**ABTS**)

2,2-diphenyl-1-picrylhydrazil (**DPPH**)

Effective in preventing lipid peroxidation

Ž. Milanović et al.,*Journal of the Serbian Society for Computational Mechanics*, 2020, Special issue 2020, **71-84**.

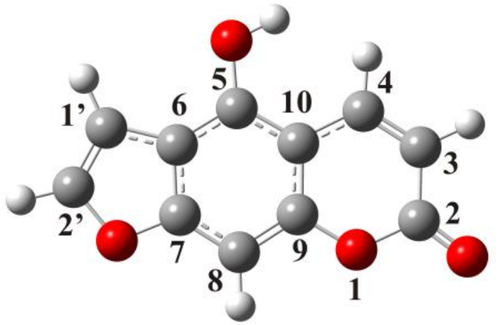

MATERIALS AND
METHODS

# METHODOLOGY

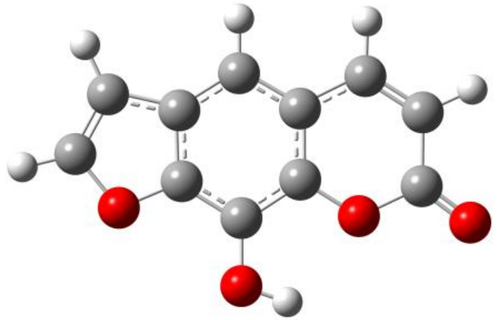
**DFT** (**D**ensity **F**unctional **T**heory) methode

- Program package *Gaussian09*
- M06-2X method
- 6-311++G(d,p) basis set
- CPCM solvation model

Quantum Mechanics-based test for Overall free Radical Scavenging Activity (**QM-ORSA**) protocol




**BER**



**XAN**

The optimized structure of investigated compounds

# METHODOLOGY

*Thermodynamic parameters*

**H**ydrogen **A**tom **T**ransfer → **HAT**: $Ar\text{-}OH + HO^{\bullet} \rightarrow Ar\text{-}O^{\bullet} + H_2O$

**S**ingle **E**lectron **T**ransfer–**P**roton **T**ransfer
- **SET**: $Ar\text{-}OH + HO^{\bullet} \rightarrow Ar\text{-}OH^{\bullet+} + HO^{-}$
- **PT**: $Ar\text{-}OH^{\bullet+} + HO^{-} \rightarrow Ar\text{-}OH^{\bullet} + H_2O$

**S**equential **P**roton **L**oss **E**lectron **T**ransfer
- **SPL**: $Ar\text{-}OH \rightarrow Ar\text{-}O^{-} + H^{+}$
- **ET**: $Ar\text{-}O^{-} + HO^{\bullet} \rightarrow Ar\text{-}O^{\bullet} + HO^{-}$

**R**adical **A**dduct **F**ormation → **RAF**: $Ar\text{-}OH + HO^{\bullet} \rightarrow [HO\text{-}Ar\text{-}OH]^{\bullet}$

# METHODOLOGY

*Kinetic parameters*

*Conventional transition state theory (TST) (Eyring equation)*

$$k_{TST} = \frac{k_B T}{h} exp\left(\frac{-\Delta G_a^{\neq}}{RT}\right)$$

*Eckart method (ZCT_0)*

$$k_{ZCT\_0} = \sigma\gamma(T)\frac{k_B T}{h} exp\left(\frac{-\Delta G_a^{\neq}}{RT}\right)$$

h-Planck constant ($6.62 \times 10^{-34}$ $m^2$ kg/s)

$k_B$ –Boltzmann constant ($1.38 \times 10^{-23}$ $m^2$ kg $s^{-2}$ $K^{-1}$)

$\Delta G_a^{\ddagger}$ -Gibss free energy of activation

T is temperature (298.15 K)

R-gas constant (8.314 J $mol^{-1}$ $K^{-1}$)

$\sigma$-degeneracy of the reaction path

γ (T)-transmission coefficient

# METHODOLOGY

*Relative antioxidant capacity*

$$rT = \frac{k_{overall}}{k_{overall}^{Trolox}}$$

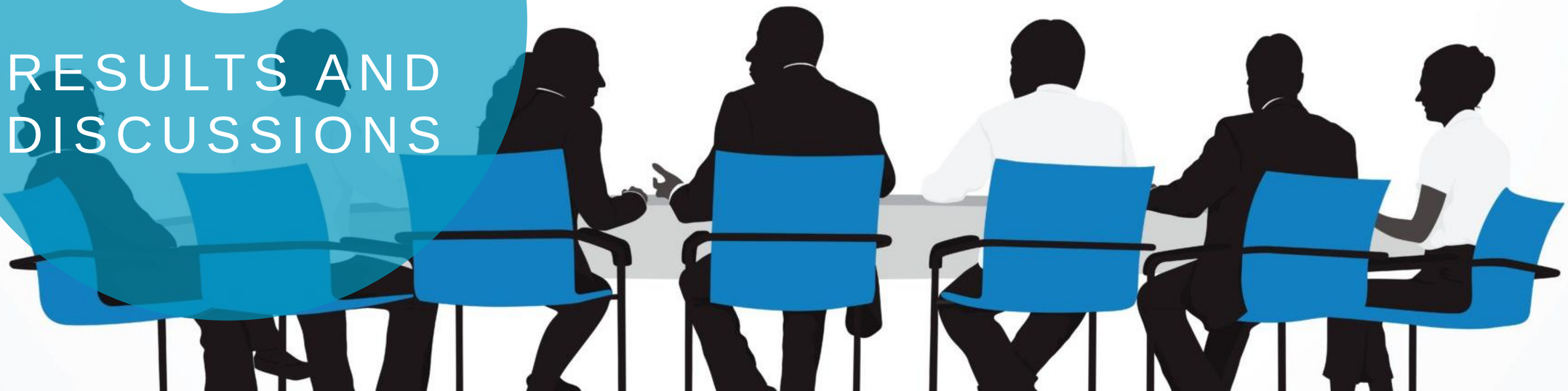
$k_{overall}$- overall rate constant of examined antioxidant

$k_{overall}^{Tx}$- and the overall rate constant of trolox

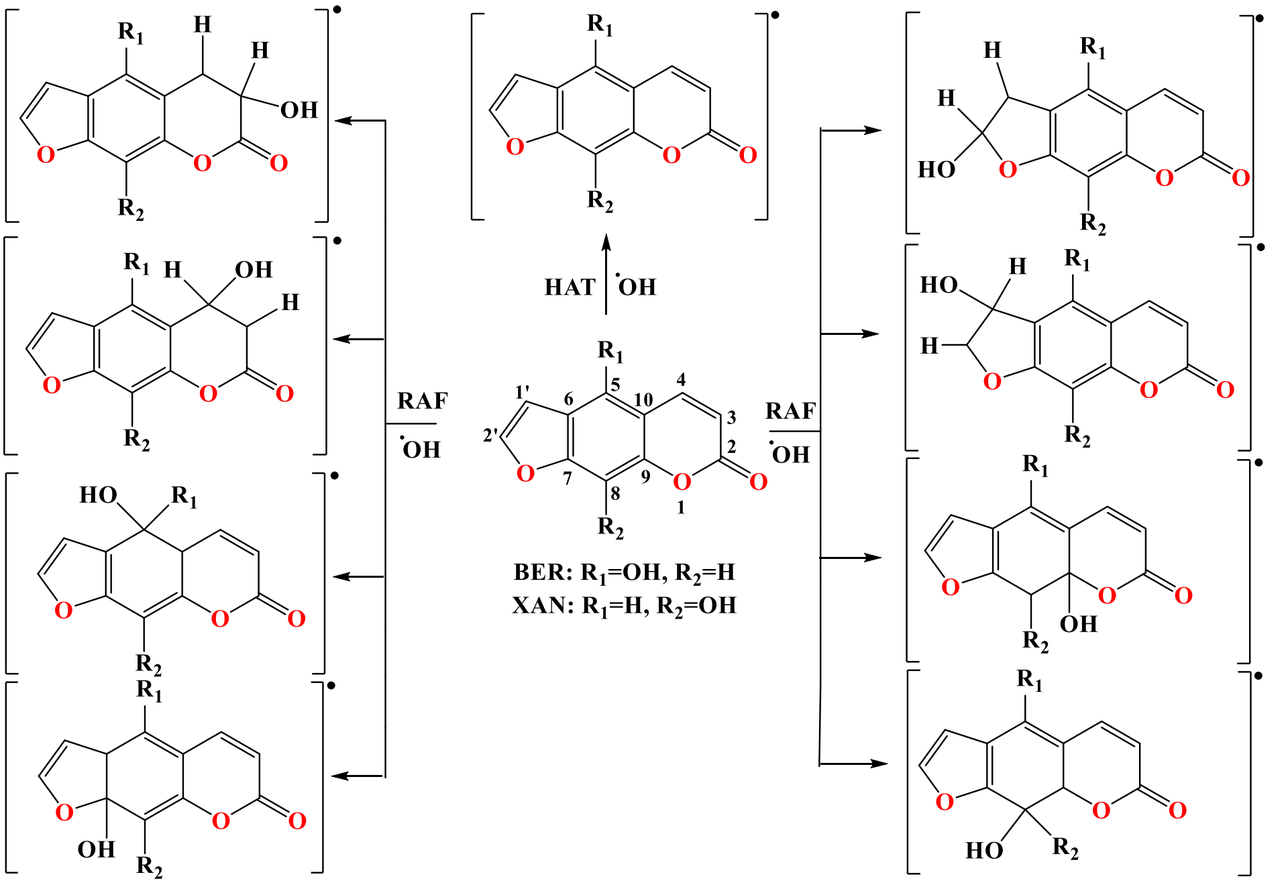
Relative amount of products (%), i.e. branching ratios ($\Gamma_i$)

$$\Gamma_i = \frac{k_i}{k_{overall}} \times 100$$

# RESULTS AND DISCUSSIONS



# THERMODYNAMIC PARAMETERS




The scheme of the thermodynamic possible mechanism of inactivation HO• radical in benzene.

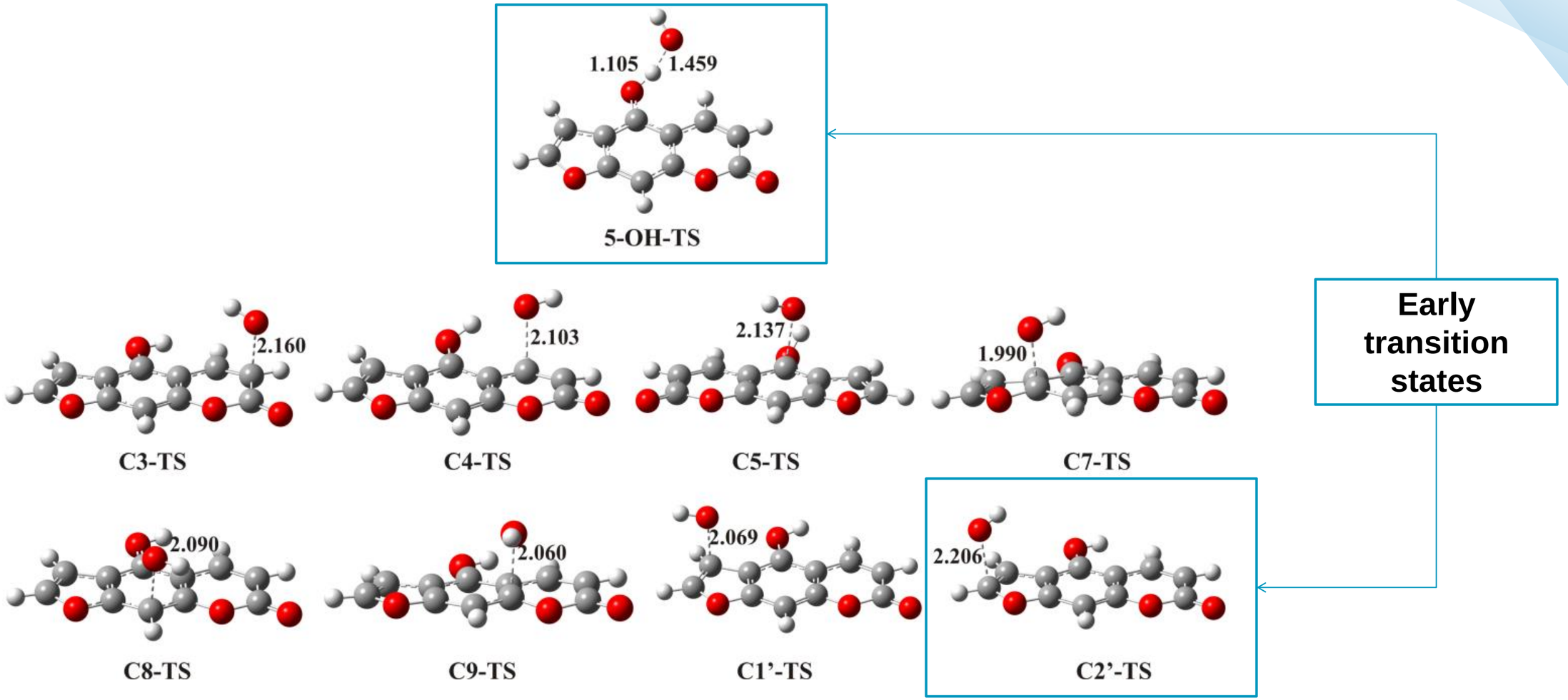
Reaction free energies, $\Delta_r G$ (kJ mol$^{-1}$) produced at the M06-2X/6-311++G(d,p) level of theory in combination with the CPCM solvation model.

| Position | HAT[a] | SET-PT[a] | | SPLET[a] | |
|---|---|---|---|---|---|
| BER | -162 | 334 | -495 | 375 | 59 |
| XAN | -137 | 340 | -478 | 427 | 32 |

| Position | BER | XAN |
|---|---|---|
| C-3 | -88 | -79 |
| C-4 | -75 | -59 |
| C-5 | -85 | -82 |
| C-6 | 20 | 34 |
| C-7 | -27 | -32 |
| C-8 | -42 | -65 |
| C-9 | -55 | -60 |
| C-10 | 4 | 17 |
| C-1' | -52 | -43 |
| C-2' | -120 | -109 |

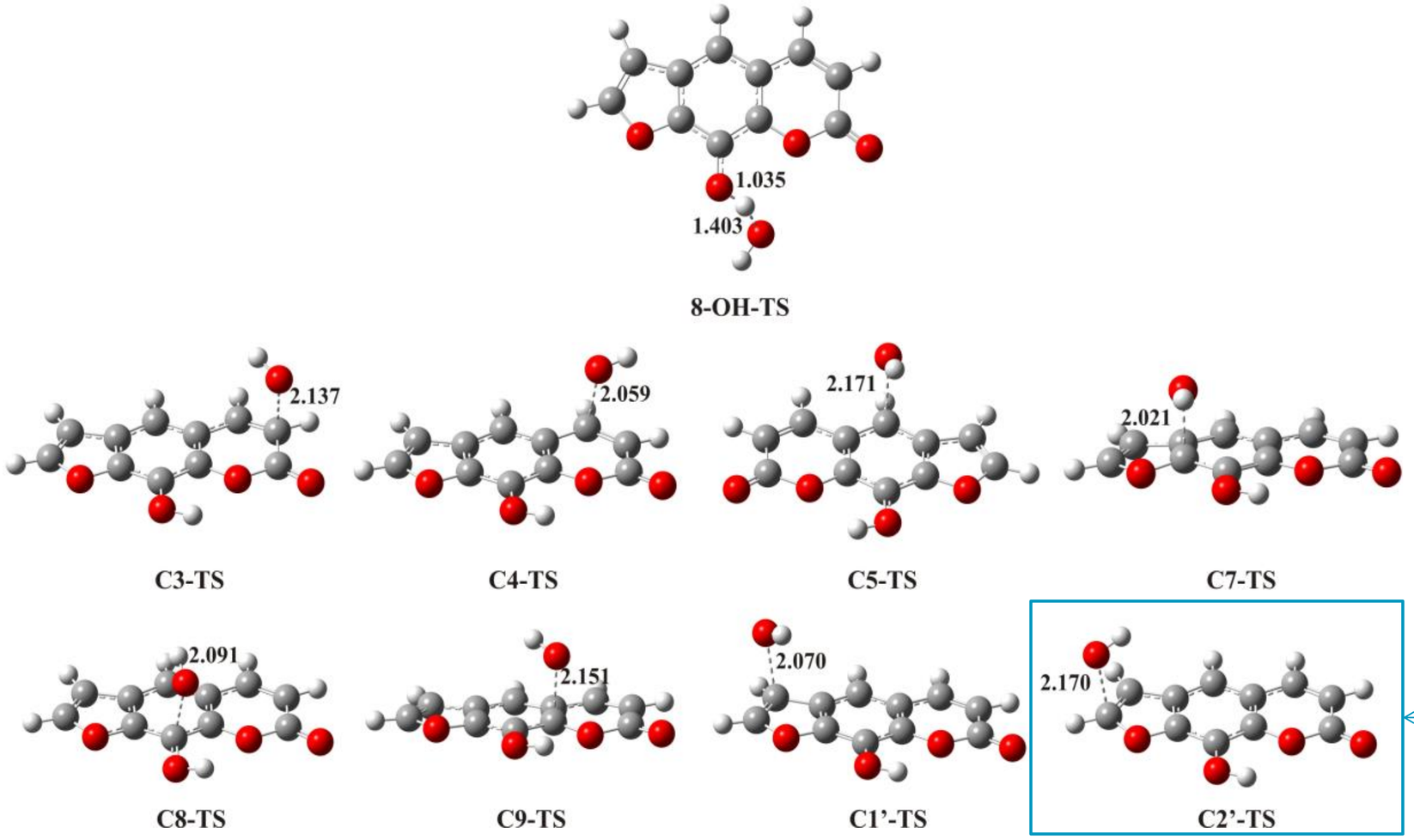
[a]Ž. Milanović et al.,*Journal of the Serbian Society for Computational Mechanics*, 2020, Special issue 2020, 71-84.

# KINETIC PARAMETERS




Optimized geometries of transition states for HAT and RAF pathways of **BER** in benzene with characteristic distance (Å) calculated at the M06-2X/6-311++G(d,p) level of theory in combination with the CPCM solvation model.

# KINETIC PARAMETERS



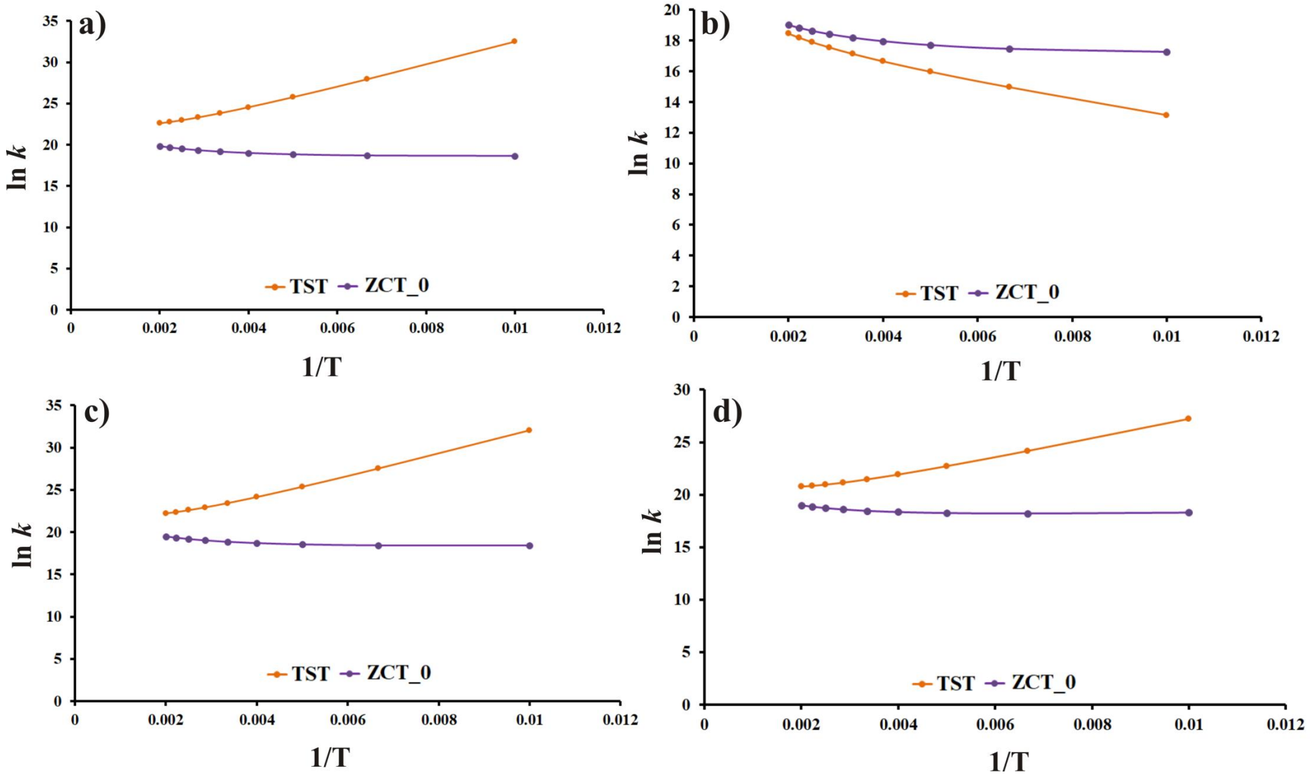

**Early transition state**

Optimized geometries of transition states for HAT and RAF pathways of **XAN** in benzene with characteristic distance (Å) calculated at the M06-2X/6-311++G(d,p) level of theory in combination with the CPCM solvation model.

# KINETIC PARAMETERS

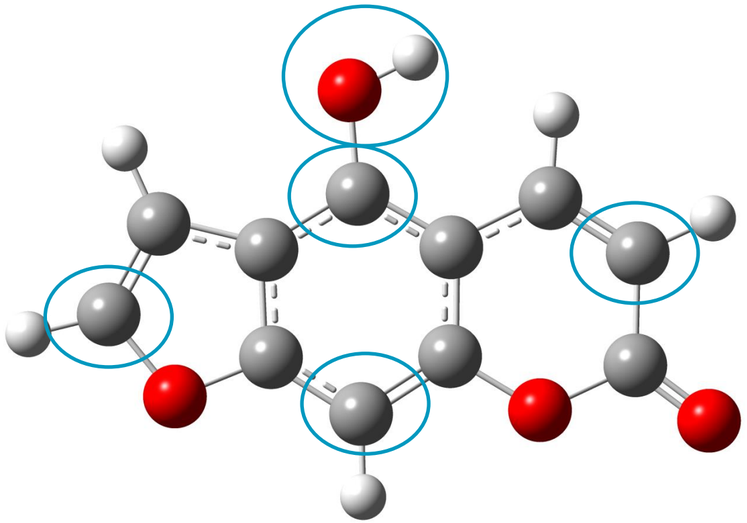
Activation energies $\Delta G_a^{\ddagger}$ (kJ mol$^{-1}$) and rate constants: $k_{TST}$ (M$^{-1}$s$^{-1}$) and $k_{ZCT\_0}$ (M$^{-1}$s$^{-1}$) produced at the M06-2X/6-311++G(d,p) level of theory in combination with the CPCM solvation model.

| Mechanism | BER | | | XAN | | |
|---|---|---|---|---|---|---|
| HAT | $\Delta G_a$ | $k_{TST}$ | $k_{ZCT\_0}$ | $\Delta G_a$ | $k_{TST}$ | $k_{ZCT\_0}$ |
| | 22 | 2.23x10$^{10}$ | 2.14x10$^{8}$ | 38 | 2.78x10$^{7}$ | 7.99x10$^{7}$ |
| RAF | $\Delta G_a$ | $k_{TST}$ | $k_{ZCT\_0}$ | $\Delta G_a$ | $k_{TST}$ | $k_{ZCT\_0}$ |
| C-3 | 30 | 7.05x10$^{8}$ | 1.44x10$^{8}$ | 33 | 2.11x10$^{8}$ | 1.06x10$^{8}$ |
| C-4 | 37 | 4.15x10$^{7}$ | 4.37x10$^{7}$ | 45 | 2.17x10$^{6}$ | 3.02x10$^{6}$ |
| C-5 | 25 | 5.52x10$^{9}$ | 1.21x10$^{8}$ | 28 | 2.01x10$^{9}$ | 1.28x10$^{8}$ |
| C-7 | 55 | 2.91x10$^{4}$ | 4.34x10$^{4}$ | 45 | 1.81x10$^{6}$ | 2.53x10$^{6}$ |
| C-8 | 34 | 1.80x10$^{8}$ | 9.41x10$^{7}$ | 35 | 1.15x10$^{8}$ | 7.46x10$^{7}$ |
| C-9 | 42 | 6.47x10$^{6}$ | 8.93x10$^{6}$ | 29 | 1.07x10$^{9}$ | 5.68x10$^{7}$ |
| C-1' | 37 | 4.20x10$^{7}$ | 5.02x10$^{7}$ | 38 | 3.46x10$^{7}$ | 4.22x10$^{7}$ |
| C-2' | 23 | 1.51x10$^{10}$ | 1.56x10$^{8}$ | 28 | 2.10x10$^{9}$ | 1.05x10$^{8}$ |

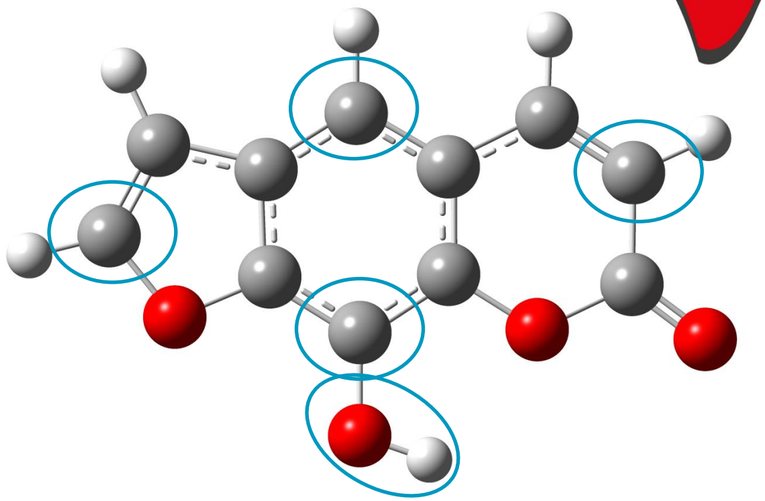



The plots of dependence $k_{TST}$ (M$^{-1}$s$^{-1}$) and $k_{ZCT\_0}$ (M$^{-1}$s$^{-1}$) on 1/T in HAT (**BER** (a) and **XAN** (b)) and RAF (C2'positions of **BER** (c) and **XAN** (d)) pathways.

# RELATIVE ANTIOXYDANT CAPACITY



**BER**



**XAN**

The $k_{overall}$ ($M^{-1}s^{-1}$), antioxidant capacity ($r^T$) and branching ratios ($\Gamma_i$, %) for all favourable mechanistic pathways ($k^{Tx}_{overall}$ is $1.31\times10^8$ $M^{-1}$ $s^{-1}$).

| Mechanism | Position | BER (%) | XAN (%) |
|---|---|---|---|
| HAT | OH | 25.72 | 13.36 |
| RAF | C-3 | 17.31 | 17.72 |
| | C-4 | 5.25 | 0.50 |
| | C-5 | 14.54 | 21.40 |
| | C-7 | 0.01 | 0.42 |
| | C-8 | 11.31 | 12.47 |
| | C-9 | 1.07 | 9.50 |
| | C-1′ | 6.03 | 7.06 |
| | C-2′ | 18.75 | 17.56 |
| $k_{overall}$ | | $8.32\times10^8$ | $5.98\times10^8$ |
| $r^T$ | | 6.35 | 4.57 |

> $1.18\times10^3$ $M^{-1}$ $s^{-1}$ *effective primary antioxidants*

Better antioxidants than Trolox (in benzene)


CONCLUSION

# CONCLUSION

## THERMODYNAMIC PARAMETERS

In benzene both compounds exhibit their antioxidant properties through HAT and RAF mechanisms.

## KINETIC PARAMETERS

Estimated values of relative antioxidant capacity indicate a better ability **BER** and **XAN** on $HO^{\bullet}$ radical scavenging than **Tx**. In addition, **BER** possess the better antioxidant ability than **XAN.**

## RELATIVE ANTIOXIDANT CAPACITY

Based on the relative amount of product, it can be concluded that for both compounds the RAF mechanism is dominant.

# THANK YOU!

*Because the people who are crazy enough to think they can change the world, are the ones who do!*
*S. Jobs*

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