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Topics in Catalysis

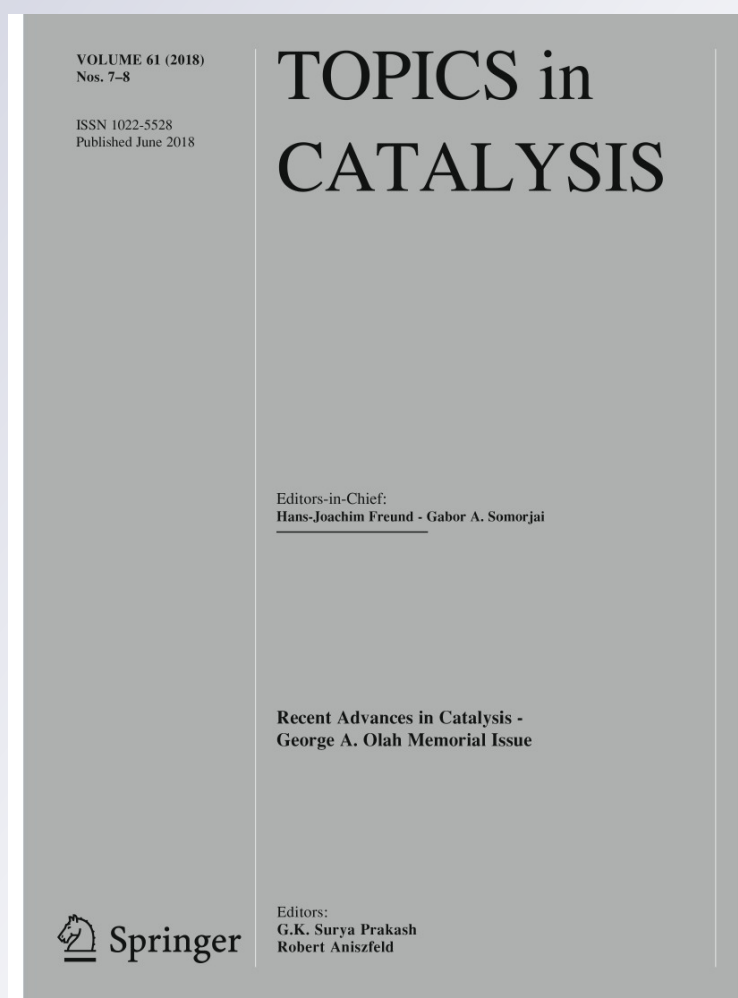
ISSN 1022-5528

Volume 61

Combined 7-8

Top Catal (2018) 61:636-642

DOI 10.1007/s11244-018-0918-1



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Iodine Activation of Alcohols: A Computational Study

Gabriela L. Borosky¹ · Stojan Stavber² · Kenneth K. Laali³

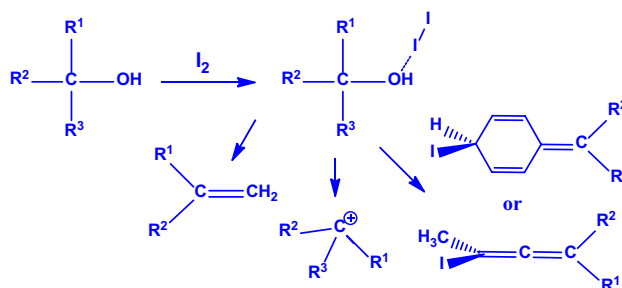
Published online: 9 April 2018

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Abstract

A DFT study aimed at unravelling the origin of catalytic activity of iodine in reaction with alcohols is presented. Computed free energies for generation of the O–I complexes from the separated reactants are around 3 kcal/mol and solvation increases endoergicity by *ca.* 1 kcal/mol. Calculations suggest that halogen bond formation between I₂ and alcohols does not lead to strong activation of the hydroxyl as a leaving group, although solvent has a notable effect in lowering endoergicity for carbocation formation. Model tertiary alcohols exhibited β-proton abstraction following breaking of the C–O bond, while model secondary and primary alcohols experienced an earlier β-proton abstraction, synchronic with the C–O bond cleavage. Consistent with computed natural bond orbital charges, benzylic and propargylic alcohols underwent iodide anion quenching at the *para* position of phenyl and C-3, respectively.

Graphical Abstract

**Keywords** Catalysis by iodine · Halogen bonding · DFT calculations · Activation of alcohols

Respectfully dedicated to Professor George Olah in memoriam.

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s11244-018-0918-1>) contains supplementary material, which is available to authorized users.

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1 Introduction

As a readily available environmentally benign reagent, molecular iodine has become increasingly important in the repertoire of organic synthesis. As a mild electrophile and oxidant iodine has the ability to bring about a wide

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array of organic transformations including multicomponent tandem reactions, cascade cyclizations, Michael reaction, and alkene cross-coupling [1–5]. In many cases these reactions are triggered by I_2 -induced ionization of an alcohol moiety to form incipient carbocations. Other transformations such as the recently reported selenocyanation of alkenes likely proceed by addition/elimination involving transient formation of cyclic iodonium ion [6]. There are also other synthetic transformations that benefit from the oxidative nature of iodine to mediate processes such as aromatization [7], and alkene coupling to thiols [8]. Cross-dehydrogenative Csp^3-N and Csp^2-S coupling reactions represent other types of metal-free I_2 -catalyzed reactions [9–11]. Some of these transformations require the use of stoichiometric or excess iodine whereas others use catalytic amounts.

Iodine efficiently catalyzes nucleophilic substitution of benzylic alcohols including aryl-propargyl-methanols with oxygen and carbon nucleophiles in MeCN solvent [12, 13]. Under solvent-free conditions, tertiary benzylic alcohols undergo elimination, substitution, and cycloisomerization depending on the substituents [14]. Involvement of carbocations was postulated in many of these reactions. A comprehensive survey of iodine-catalyzed transformations

of compounds containing oxygen functional groups was recently given [15].

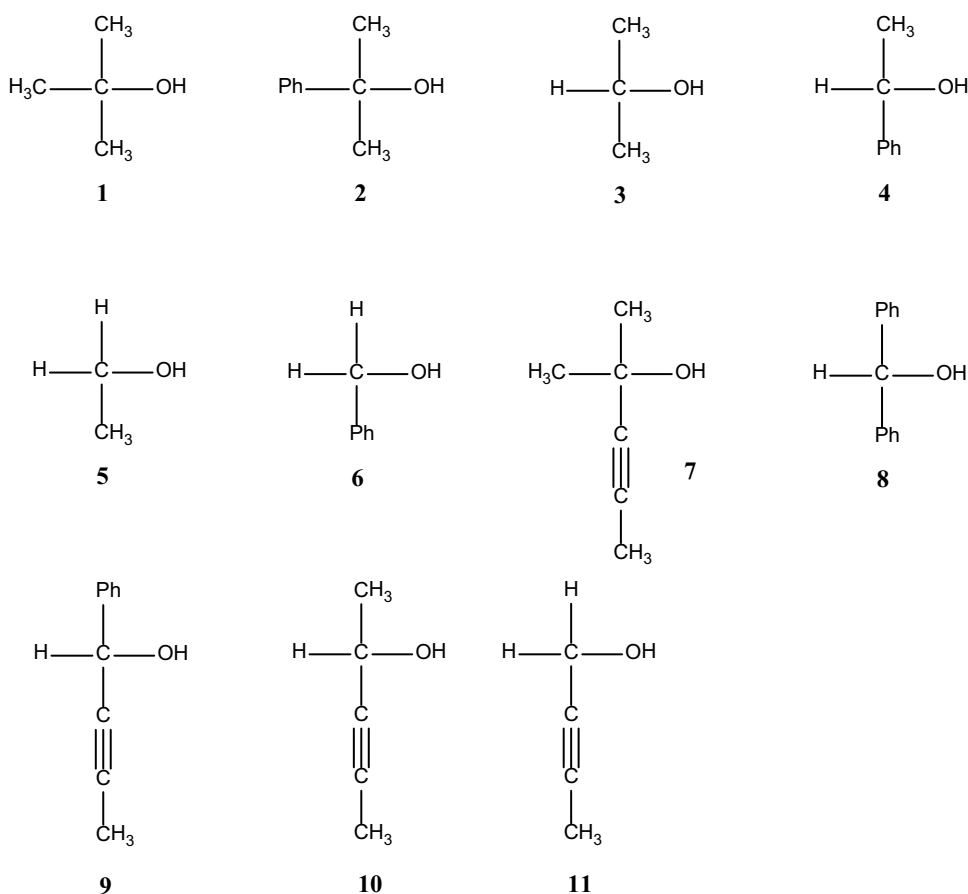
A recent DFT study examined the interactions between iodine and representative Michael acceptors and showed that the origin of catalytic activity is halogen bonding [16]. The same authors summarized the mechanistic aspects of iodine-catalyzed reactions in a review [17].

The impetus for the present computational study was to shed light on the nature of interactions between iodine and alcohols. Primary, secondary, and tertiary alcohols bearing methyl, phenyl, and propargyl groups were selected for the present study with the aim to understand the role of the substituents on the nature of the interaction and on the resulting intermediates (Fig. 1).

2 Computational Procedures

Calculations were carried out with the Gaussian 09 suite of programs [18]. Density functional theory (DFT) was applied to carry out full optimizations with the ω B97X-D functional [19] and the 6-311+G(3df,2p) basis set. The aug-cc-pVTZ basis set with the corresponding pseudopotential (usually called aug-cc-pVTZ-PP) was employed for I [20, 21]. All

Fig. 1 Various classes of alcohols examined in the present study



optimized structures were verified to be minima (no imaginary frequencies) by harmonic vibrational frequency calculations. Solvation effects were accounted for by performing energy minimizations with the integral equation formalism polarized continuum model (IEFPCM) [22–25] in acetonitrile (dielectric constant $\epsilon = 35.69$) and dichloromethane (dielectric constant $\epsilon = 8.93$). Natural bond orbital population analysis was performed with the NBO program [26].

3 Results and Discussion

The structures of the O–I noncovalent complexes between the alcohols in Fig. 1 and I₂ were computed. The structure of a model complex is displayed in Fig. 2. According to NBO analysis, in the complex the iodine molecule presents a negative charge density of $-0.044 e$, which has been transferred from the alcohol.

For compounds presenting π systems, i.e., those with phenyl and/or propargyl substituents, the interaction between molecular iodine and the π orbitals was also analyzed, and the corresponding π -complexes were characterized. Examples of this type of complexes are shown in Fig. 3, and relative energies for both types of complexes are given in Table 1. Although in all cases the O–I complexes were the most stable, their corresponding π -complexes were very close in energy. It should be noted that hydrogen bonded complexes of the type O–H–I could not be isolated as minima, as the initial structures collapsed to the respective O–I complex or π -complex.

Free energies for generation of the O–I complexes from the separated reactants were examined (step 1 in Scheme 1). Whereas very similar values of around 3 kcal/mol were obtained for all alcohols in the gas phase, solvation increased the endoergicity by *ca.* 1 kcal/mol. These low endoergicity values indicate the feasibility of formation for this type

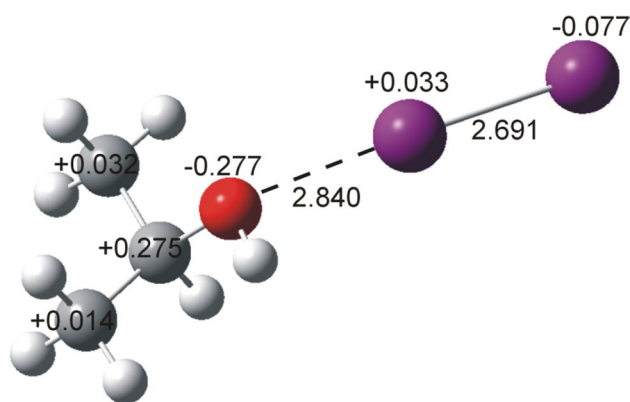


Fig. 2 Structure and NBO charge density distribution for the O–I noncovalent complex of alcohol **3** with I₂ (hydrogen charge densities added to heavy atoms; distances in Angstroms)

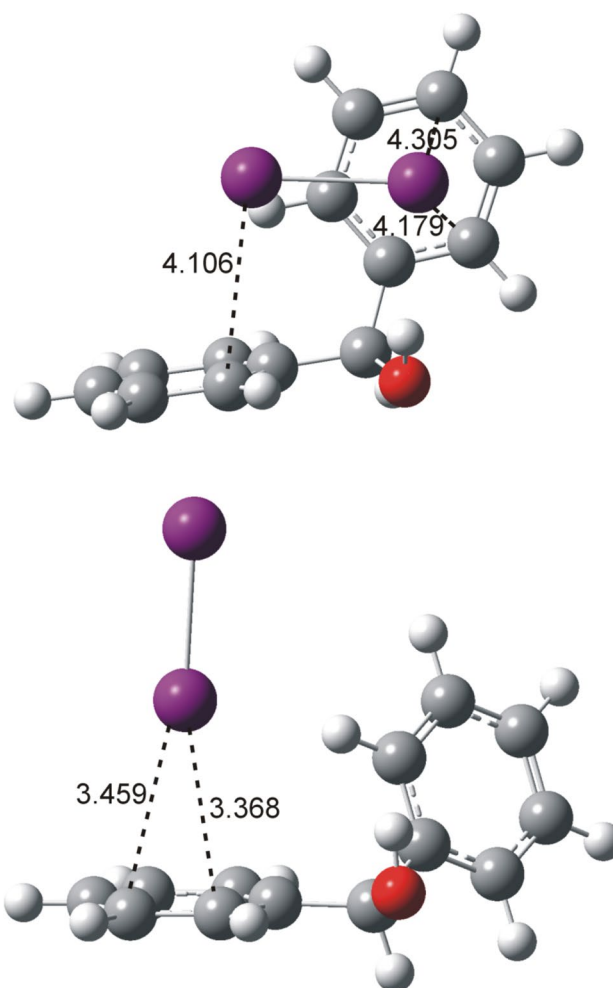


Fig. 3 Structures of noncovalent π -complexes of alcohol **8** with I₂ (distances in Angstroms)

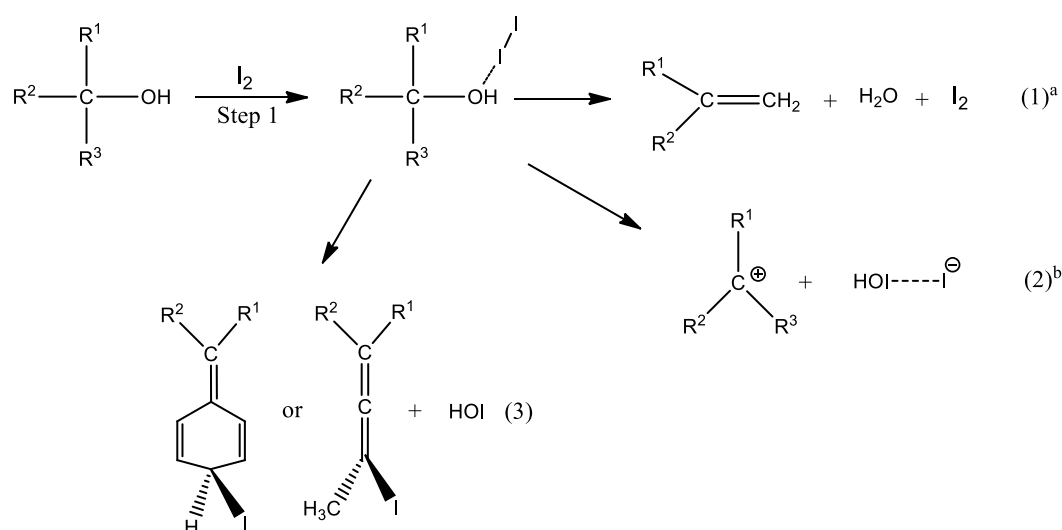
of complexes at room temperature. Analogous complexation energies were previously observed for O–I interactions between ketones and I₂ [16, 17].

Some particular reactions starting from the respective O–I complexes were evaluated for each compound. The reactions

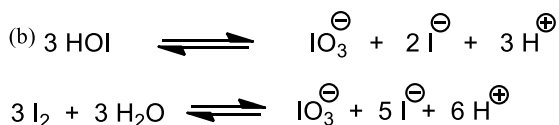
Table 1 Relative stabilities of noncovalent π -complexes between I₂ and alcohols (kcal/mol)

Alcohol	O–I ₂ complex	π -I ₂ complex
6	0.0	0.42 0.98 ^a
7	0.0	0.86
8	0.0	0.45 0.91 ^a
9	0.0	0.30
10	0.0	0.44
11	0.0	0.72

^aDifferent geometry



(a) For $\text{R}^3 = \text{CH}_3$ (products $\text{H}_2\text{O} + \text{I}_2$ are more favorable than $\text{HOI} + \text{HI}$ by 34 kcal/mol in gas phase)



Scheme 1 Reactions following I_2 complexation [elimination (1); carbocation formation (2); iodide anion trapping (3)]

considered were elimination (Reaction 1, Scheme 1), and carbocation formation (Reaction 2, Scheme 1). For alcohols with phenyl or propargyl groups, scan of the potential energy surface for C–O bond breaking exhibited iodide anion addition to the *para* position of the resulting benzylic cation, or to C-3 position of the propargylic cation; therefore, free energies for these paths were also estimated (Reaction 3). Calculated reactions are illustrated in Scheme 1, while the corresponding changes in free energy are displayed in Table 2.

According to the calculated ΔG_r values, elimination (Reaction 1) is the most plausible reaction for those alcohols with available hydrogen atoms at C_β (compounds **1**, **2**, **3**, and **5**). Gas-phase changes in free energy were nearly zero, whereas elimination reactions became exergonic by solvation (Table 2, entries 1 and 2). This observation agrees with the experimental results obtained for benzylic alcohol **2** and related compounds, which in the presence of catalytic amounts of I_2 afforded the corresponding alkenes in high yields, both under solvent-free conditions and in various solvents [14]. On the other hand, compounds **6** and **8** yielded their corresponding symmetrical ethers by nucleophilic substitution [14].

Although similar ΔG_r values were obtained for these elimination reactions, the difference concerning the type of alcohol was reflected along the respective paths. Thus,

tertiary alcohols **1** and **2** exhibited proton abstraction *after* breaking of the C–O bond, a model closely resembling an E_1 -like mechanism. Instead, secondary (**3**) and primary (**5**) alcohols experienced an earlier proton abstraction synchronous with the C–O bond cleavage; that is, the C–H bond distance was *ca.* 1.15 Å when the C–O length was *ca.* 2.5 Å, a process more similar to an E_2 -type mechanism.

The I_2 -induced carbocation formation (Reaction 2) was very endergonic for all derivatives, with calculated values above 115 kcal/mol in the gas phase, even for tertiary alcohols. Interestingly though, solvation decreased endoergicity to values between 31 and 46 kcal/mol, with the reaction being more favored in acetonitrile, the most polar of the studied solvents (Table 2, entries 1, 2, 7–9). In comparison, a gas-phase ΔG_r of less than 1 kcal/mol was obtained at the same level of theory for the cleavage of *protonated tert*-butanol to give *tert*-butyl cation and a water molecule, a typical $\text{S}_{\text{N}}1$ process. In contrast, during scan of the potential energy surface for C–O bond cleavage of the I_2 complex of *t*-BuOH (**1**), proton abstraction from a methyl group took place spontaneously; the same process also occurred with the respective I_2 complexes of compounds **2**, **3**, and **5**. These results would indicate that halogen bond formation between I_2 and alcohols does not sufficiently activate the hydroxyl as a leaving group for the $\text{S}_{\text{N}}1$ mechanism. Nevertheless, experimental evidence strongly suggests the involvement of

Table 2 Free energy changes for reactions in Scheme 1 (gas phase, kcal/mol)

Entry	Alcohol (compound, type)	ΔG_{Step1}	$\Delta G_{\text{Reaction2}}$	$\Delta G_{\text{Reaction1}}$ ($\Delta G_{\text{Reaction3}}$)
1	<i>t</i> -butanol (1 , 3°)	2.66 [3.56] {3.45}	136.76 [37.86] {46.36}	0.66 ^a [− 2.45] {− 2.09}
2	2-Phenyl-2-propanol (2 , 3°)	2.60 [3.94] {3.63}	121.70 [31.45] {39.52}	− 0.97 ^a [− 5.10] {− 4.53}
3	2-Propanol (3 , 2°)	3.30	150.88	0.32 ^b
4	Phenyl-ethanol (4 , 2°)	1.14	128.78	(51.64) ^c
5	Ethanol (5 , 1°)	3.48	169.13	− 0.28 ^b
6	Phenyl-methanol (6 , 1°)	3.05	138.15	(50.25) ^c
7	2-Methyl-3-pentyn-2-ol (7 , 3°)	2.31 [3.55] {3.47}	125.40 [33.90] {41.71}	(22.70) ^d [21.37] {21.41}
8	Diphenyl-methanol (8 , 2°)	3.10	117.64 [33.00] {40.55}	(48.59) ^c [46.23] {46.42}
9	1-Phenyl-2-butyn-1-ol (9 , 2°)	2.33	117.40 [31.19] {38.66}	(18.80) ^d
10	3-Pentyn-2-ol (10 , 2°)	2.82	136.02	(23.10) ^d
11	2-Butyn-1-ol (11 , 1°)	2.44	150.72	(23.04) ^d

Results in acetonitrile in square brackets, and in dichloromethane in curly brackets

^aAfter breaking of the C–O bond, a proton from a methyl group is abstracted

^bDuring breaking of the C–O bond, a proton from a methyl group is abstracted

^cAfter breaking of the C–O bond, I[−] adds to the *p*-position of the benzylic cation

^dDuring breaking of the C–O bond, I[−] adds to position C-3 of the propargylic cation

electron-deficient intermediates with partial charge development in the rate-determining step [5, 27].

A halogen bond mechanism as well as hidden Brønsted acid catalysis are frequently proposed to explain the catalytic effect of iodine. Hydrolytic disproportionation of HIO or I₂ itself [29] (see Scheme 1, footnote b) forming HIO₃ in solvent or via adventitious moisture under solvent-free conditions may also be suggested. The present calculations show that formation of water and iodine (Scheme 1) is favored over the formation of HOI and HI by 34 kcal/mol in gas phase. Similar conclusions were reached in ref 16 examining I₂-interactions with α,β -unsaturated carbonyl models. Recent experimental investigations rule out partial decomposition of I₂ to HI and strongly indicate molecular iodine as the active catalyst in these reactions [27, 30].

It is interesting to note that, even though phenylethanol **4** presents hydrogen atoms at C _{β} , spontaneous proton abstraction was not observed. Instead, the potential energy surface for C–O bond breaking showed addition of iodide anion (Table 2, entry 4). In a very recent study on iodine-catalyzed transformations of alcohols, under solvent-free (SFRC) and highly concentrated reaction conditions (HCRC), quantitative formation of the symmetrical ether was observed from compound **4** at 25 °C [27].

It had been shown previously that phenylethanol (**4**), diphenylmethanol (**8**) and 1,3-diphenyl-propyn-1-ol (**9**) underwent dehydrative coupling with alkenes using molecular iodine as a Lewis acid catalyst under solvent-free conditions at 70 °C [5]. Molecular iodine was also shown to efficiently catalyze the nucleophilic substitution of the hydroxyl group of benzylic alcohols by a suggested S_N1-type

mechanism [12]. Phenyl-propargylic methanol (**9**) and aryl propargyl-methanols similarly underwent nucleophilic substitution reactions in the presence of a catalytic amount of I₂, but an S_N2 process was suggested for these systems [13].

The present computations revealed I[−] addition to the *para* position of the benzylic cation after breaking of the C–O bond in the case of compounds **4**, **6**, and **8** (Table 2, entries 4, 6, and 8). For propargylic alcohols **7** and **9–11**, iodide anion added to the C-3 position of propargyl cation during breaking of the C–O bond (Table 2, entries 7, 9–11). Charge delocalization maps based on computed NBO charges (Fig. 4) show extensive positive charge residing in the phenyl rings in **8**⁺, and at C _{β} in **7**⁺ indicative of significant allenyl cation character, and at both C _{β} and the phenyl ring in the case of **9**⁺. These NBO-derived charge maps provide a rationale for

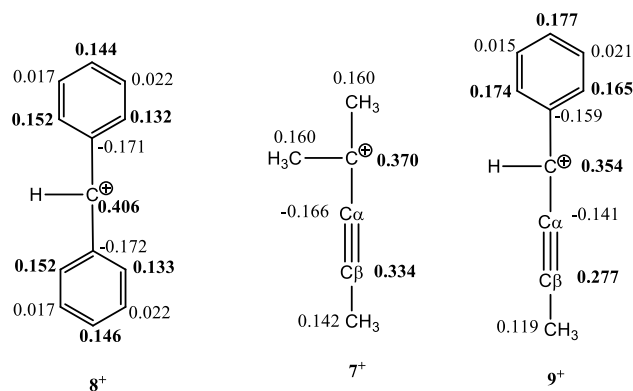


Fig. 4 Computed NBO charges for model benzylic and propargylic cations

Table 3 Comparison between experimentally inferred mechanisms and calculations in this work

Alcohol	Experimental results (lit. reference)	Computational results
2	E [14]	E1-like
4	S _N 1 [5], S _N 1-like [27]	S _N 1-like
6	S _N [14]	S _N 1-like
8	S _N 1-like [14], S _N [14], S _N 1 [5]	S _N 1-like
9	S _N 2 [13], ^a S _N 1 [5] ^a Ph	S _N 2

^a1,3-diphenyl-propyn-1-ol was employed instead of 1-phenyl-2-butyne-1-ol (**9**)

remote iodide anion quenching in reactions that resemble the S_N1' and S_N2' processes in the gas phase. The endergonicity of the reactions of addition of iodide was slightly decreased by solvation (Table 2, entries 7 and 8).

Table 3 shows a comparison between mechanistic inferences from the present calculations and those deduced from the available experimental reports for the I₂-catalyzed reactions of alcohols. Computed results nicely agree with a recently reported study of iodine-catalyzed transformations of aryl-substituted alcohols under SFRC and under HCRC, showing that, in absence of a good nucleophile, primary and secondary alcohols underwent dimerization, while substitution prevailed in the presence of efficient nucleophiles [27]; in contrast, dehydration to alkenes predominated in the case of tertiary alcohols [27].

4 Summary and Conclusions

DFT calculations were applied in the present study to examine noncovalent interactions between molecular iodine and primary, secondary, and tertiary alcohols, along with the alternative reaction pathways for the different reactants. Formation of the O–I complexes proved favorable and close in energy to the corresponding π -complexes, when available. The calculated endoergicities for carbocation formation via C–O bond breaking would indicate that halogen bond formation between I₂ and alcohols could not sufficiently activate the hydroxyl as a leaving group for an S_N1 process, even in polar solvents. Instead, elimination becomes the most plausible reaction for alcohols bearing hydrogen atoms at C $_{\beta}$. Model tertiary alcohols experienced proton abstraction following cleavage of the C–O bond (E₁-like mechanism), while model secondary and primary alcohols presented an earlier proton abstraction, synchronic with the C–O bond rupture (E₂-type mechanism). On the other hand, for benzylic and propargylic alcohols I[−] addition was observed, pointing to nucleophilic substitution of the hydroxyl group as the favored path.

Acknowledgements We thank the University of Florida for access to computational facilities at UF High-Performance Computing Center. Access to computational resources at Mendieta cluster from CCAD-UNC, which is part of SNCAD-MinCyT, Argentina, is also acknowledged. GLB acknowledges funding from CONICET and Secyt-UNC. S. S. acknowledges the Slovenian Research Agency (Programme P1-0134) for financial support and helpful discussions with Dr. Anton Kokalj (Jožef Stefan Institute).

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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