INTRAMOLECULAR ADDITION OF OXYRADICALS TO BENZENE RINGS: A DFT STUDY

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This work is dedicated to Professor Pavel Kočovský on the occasion of his 60th birthday.

The reactivity of a series of oxyradicals related to the triplet state of β-phenylpropiophenone was investigated by density functional theory. Analysis of the potential energy hypersurfaces indicates that radical addition to the β-phenyl ring should occur with a smaller barrier than intramolecular hydrogen abstraction from the benzylic position, although the latter reaction is far more exothermic. Addition can occur in *ipso*- and *ortho*-position of the β-phenyl ring, with ortho addition being slightly more favourable. As both addition reactions are predicted to be mildly exothermic and exergonic, intermolecular trapping of the resulting cyclohexadienyl-type radicals should be feasible.

Keywords: *Ab initio* calculations; Density functional calculations; Radical reactions; Cyclization.

Free radical cyclization reactions count among the most useful applications of free radical chemistry in modern synthetic methodology[1–3]. Whereas intramolecular additions to C≡C bonds and olefinic C=C bonds are well explored, addition reactions to aromatic C=C bonds are few and poorly understood[4–6]. This, presumably, is due to the energetic cost of dearomatisation of the benzene ring to which addition takes place.

Oxygen-centered radicals count among the most reactive free radical species. The reactivity of the hydroxy radical towards benzene has been thoroughly investigated, both experimentally[7–10], and computationally[11,12]. While much less is known about the reactions of alkoxy radicals with benzene and other arenes, it appears that their reactivity towards arenes is greatly reduced relative to the hydroxy radical. Indeed, benzene has been used as solvent in the characterisation of cumyloxy radicals by laser flash photolysis[13]. (n,π*) Triplet excited states of ketones are related to oxygen

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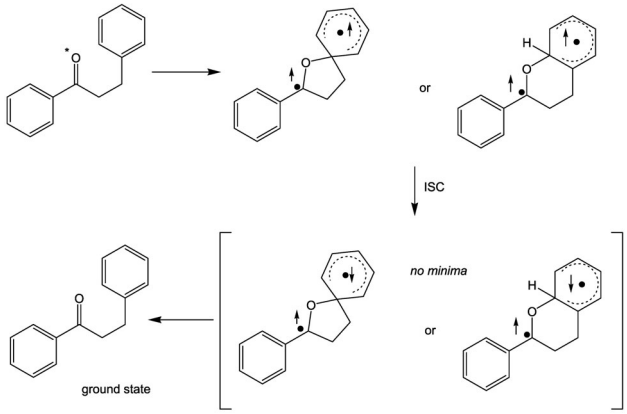
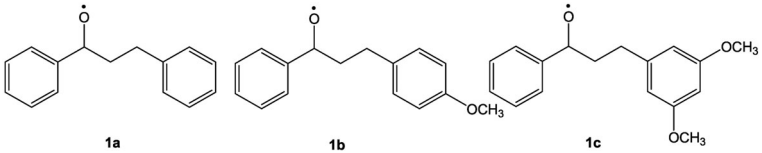
centered free radicals in that they bear significant spin density at the carbonyl oxygen atoms, making them prone to undergo hydrogen atom abstraction reactions. Recent computational work conducted in our group has shown that quenching of ketone triplet excited states by arenes, both intermolcular and intramolecular, occurs by addition of the carbonyl oxygen atom to the arene system[14,15]. In the intramolecular case, addition to the *ipso*-position is predicted to occur preferentially[14]. The regiochemistry of addition, however, can be directed by introducing suitable activating substituents (Scheme 1).



SCHEME 1
The addition–ISC–elimination pathway active in ISC of β-phenylpropiophenone

Based on this research, the current study focuses on the question, whether simple oxygen-centered radicals can be employed to achieve intramolecular addition to benzene rings. The resulting radical adducts, if quenched e.g. by stable free radicals like TEMPO, would yield attractive bicyclic or spiro-cyclic reaction products. The systems investigated are related to the triplet state of β-phenylpropiophenone, and include addition reactions to an unactivated benzene ring as well as to benzene rings activated by methoxy groups. They are shown in Scheme 2.



SCHEME 2
Radicals investigated in this study. All are shown as all-antiperiplanar conformers

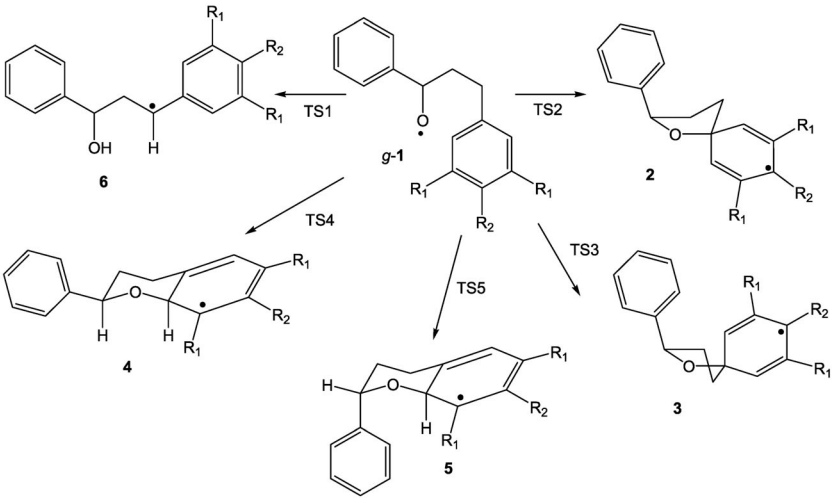
COMPUTATIONAL METHODS

All calculations were performed using Truhlar's M05-2X functional[16], which has been shown by us[15,17,18] and others[19] to give excellent thermochemical results. For geometry optimisations, a 6-31G(d) basis set[20] was utilized. Based on the geometries thus obtained, single point energy calculations were performed using a larger 6-311++G(d,p) basis set[20]. The influence of solvation (benzene, dichloromethane and acetonitrile) on the reaction energies was modelled employing Tommasi's polarized continuum model, which was employed as M05-2X/6-311++G(d,p) single point energy calculations[21,22]. All stationary points optimised were characterised as minima or transition structures by performing vibrational analyses. All calculations were done using the Gaussian09 suite of programs[23].

RESULTS AND DISCUSSION

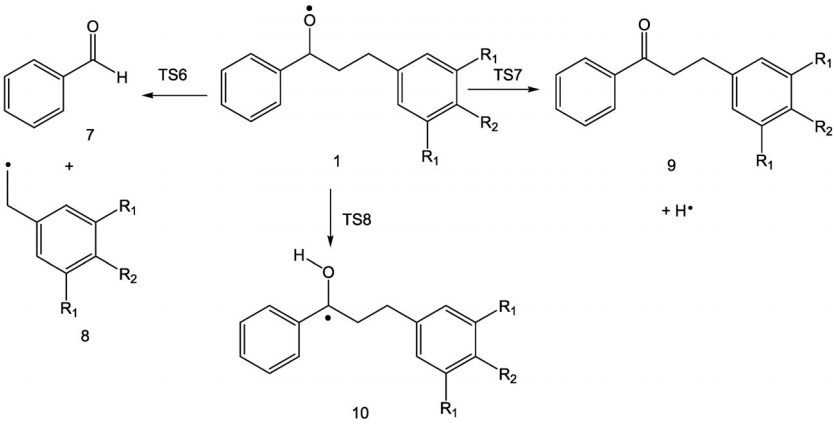
The reactions investigated are shown in Scheme 3. As reference point, the all-antiperiplanar conformers of **1** were chosen. The results obtained are given in Table I.

Fragmentation of the oxygen-centered radical **1** into benzaldehyde **7** and a phenethyl radical **8**, or, less likely, into ketone **9** and a hydrogen atom are



SCHEME 3

Reaction pathways available to the *gauche*-conformers of 1,3-diphenylpropane-1-oxyl **1a** (R_1 = H, R_2 = H), 1-phenyl-3-(4-methoxyphenyl)propane-1-oxyl **1b** (R_1 = H, R_2 = OCH_3), and 1-phenyl-3-(3,5-dimethoxyphenyl)propane-1-oxyl **1c** (R_1 = OCH_3, R_2 = H)



SCHEME 4
Further reaction pathways available to radical **1**

TABLE I
Electronic energies for the stationary points shown in Schemes 3 and 4

	a (R_1 = R_2 = H)[a]	**b** (R_1 = H, R_2 = OCH_3)[a]	**c** (R_1 = OCH_3, R_2 = H)[a]
g-**1**	1.6, 1.4, 1.0, 0.8	1.3, 1.1, 0.7, 0.5	1.6, 1.6, 1.4, 1.3
2	–4.3, –4.2, –4.4., –4.5	–5.8, –5.8, –6.0, –6.6	–4.2, –4.0, –4.1, –4.1
3	–4.3, –4.4, –4.6, –4.8	–5.7, –5.8, –6.1, –6.2	–4.7, –4.3, –4.0, –3.9
4	–7.5, –7.4, –7.4, –7.5	–8.6, –8.4, –8.5, –8.6	–9.3, –9.3, –9.6, –9.8
5	–6.1, –5.9, –5.9, –5.9	–6.9, –6.8, –6.8, –6.8	–8.2, –8.0, –8.0, –8.0
6	–18.1, –18.4, –18.9, –19.1	–18.3, –18.7, –19.1, –19.4	–18.8, –19.0, –19.3, –19.5
TS1	18.8, 18.6, 18.4, 18.2	17.8, 17.5, 17.2, 17.1	17.4, 17.6, 17.7, 17.7
TS2	10.1, 9.7, 9.0, 8.7	7.2, 6.6, 5.9, 5.5	10.3, 10.2, 9.9, 9.7
TS3	11.5, 10.9, 9.9, 9.5	8.6, 7.8, 6.8, 6.3	11.8, 11.5, 10.8, 10.4
TS4	10.6, 10.1, 9.3, 8.9	9.4, 9.0, 8.3, 8.0	6.7, 6.1, 5.1, 4.5
TS5	10.2, 10.0, 9.6, 9.3	8.1, 7.7, 7.2, 7.0	6.2, 5.8, 5.3, 5.0
7+**8**	10.9, 9.9, 9.1, 8.8	10.8, 9.9, 9.1, 8.8	10.9, 10.0, 9.1, 8.8
9+H	19.2, 18.5, 17.9, 17.7	n.c.[b]	n.c.[b]
10	–21.3, –22.0, –22.9, –23.3	n.c.[b]	n.c.[b]
TS6	11.5, 10.5, 9.7, 9.4	11.3, 10.4, 9.5, 9.2	11.4, 10.5, 9.7, 9.4
TS7	27.5, 26.9, 26.3, 26.1	n.c.[b]	n.c.[b]
TS8	25.3, 25.0, 24.7, 24.5	n.c.[b]	n.c.[b]

[a] In the sequence gas phase, solvated by benzene, dichloromethane, and acetonitrile, in kcal mol^{-1}, relative to the all-antiperiplanar conformers of radical **1a**/**1b**/**1c**, as calculated at the UM05-2X/6-311++G(d,p)//UM05-2X/6-31G(d) (gas phase) or scrf=pcm UM05-2X/6-311++G(d,p)//UM05-2X/6-31G(d) (solvated) level of theory; [b] n.c., not calculated.

further reactions that have to be taken into account (Scheme 4). The related cumyloxy radical is well known to eliminate methyl radicals[13]. The results obtained on these reactions are also listed in Table I. A 1,2-hydrogen shift to yield ketyl radical **10** was also considered. Values for the entropies and free energies are listed in Table II.

The data can be analysed according to the following criteria:

Reaction thermodynamics. The calculations indicate that the intramolecular hydrogen abstraction or –shift reactions invariably are most favourable. Intramolecular addition to the *ipso*- and *ortho*-positions of the β-phenyl ring is also exothermic, but only modestly so. Addition to the *ortho*-position of the β-phenyl ring is generally slightly favoured over addition to the *ipso*-position. In the *ortho*-addition reactions, formation of radical **4** (with an equatorial phenyl substituent) is generally more favourable than formation of radical **5** with its axial Ph group. In the *ipso*-addition reactions, on the other hand, there is no clear preference for either radical conformers **2**

TABLE II
Entropies and free energies for the stationary points shown in Schemes 3 and 4

	a ($R_1 = R_2 = H$)[a]	**b** ($R_1 = H$, $R_2 = OCH_3$)[a]	**c** ($R_1 = OCH_3$, $R_2 = H$)[a]
ap-**1**	123.092 (0.0)	135.351 (0.0)	146.189 (0.0)
g-**1**	121.686 (1.4)	134.981 (1.1)	147.825 (0.7)
2	114.384 (–2.6)	127.820 (–4.0)	140.623 (–3.0)
3	116.477 (–3.6)	129.210 (–4.4)	139.669 (–2.9)
4	113.759 (–5.1)	125.957 (–5.7)	138.539 (–6.9)
5	111.683 (–3.0)	125.527 (–4.0)	137.588 (–5.6)
6	119.250 (–11.8)	132.726 (–12.2)	142.773 (–12.1)
TS1	116.031 (19.1)	128.488 (18.1)	138.903 (17.9)
TS2	113.859 (11.9)	126.615 (9.4)	139.410 (11.7)
TS3	116.202 (12.6)	129.033 (10.2)	140.289 (13.1)
TS4	113.848 (12.9)	128.425 (11.2)	140.169 (8.8)
TS5	111.671 (12.8)	124.486 (10.9)	137.356 (8.7)
7+**8**	167.045 (–3.2)	181.663 (–4.0)	190.655 (–3.1)
9+H	148.200 (7.2)	161.492 (6.9)	173.459 (6.8)
10	124.483 (–17.1)	n.c.[b]	n.c.[b]
TS6	124.284 (11.1)	136.873 (10.9)	148.520 (11.0)
TS7	123.919 (22.8)	136.467 (22.8)	148.439 (22.6)
TS8	125.149 (24.7)	n.c.[b]	n.c.[b]

[a] Entropy (in cal mol^{-1} K^{-1}), in brackets: free energy under standard conditions (in kcal mol^{-1}), as calculated at the (U)M05-2X/6-31G(d) level of theory, relative to *ap*-**1**; n.c., not calculated.

or **3**. Both fragmentation reactions investigated are predicted to be endothermic. However, if the free energies are taken, at least the fragmentation reactions to yield the phenethyl radicals **8** plus benzaldehyde **7** are predicted to be very slightly exergonic[24].

Reaction kinetics. Intramolecular hydrogen abstraction, while thermodynamically favourable, is hindered by a significant barrier of the order of 19 kcal mol^{-1}. The (electronic) barrier for the 1,2-hydrogen shift is calculated to be even higher than this, which is in-line with very recent results on the 1,2-hydrogen shift of the methoxy radical[25]. The barriers for addition of the oxy-radical to the *ortho*- and *ipso*-positions of the β-phenyl ring are calculated to be significantly smaller, with values of around 10–11 kcal mol^{-1} for **1a**. In the *ortho*-addition reactions, the thermodynamically less favourable formation of radical **5** is predicted to have a smaller barrier than formation of radical **4**. In the series of addition reactions to the *ipso*-position of the β-phenyl ring, it is formation of radical **2** that is calculated to occur somewhat faster than formation of **3**. Of the fragmentation reactions investigated, formation of ketone **9a** and a hydrogen atom is not only predicted to be endothermic, but is also hampered by a large barrier of the order of 27 kcal mol^{-1}. If the free energies of activation are considered, the picture is essentially the same, except that fragmentation into benzaldehyde **7** and a phenethyl radical **8** is predicted to be only slightly slower than intramolecular addition to the *ortho*-position at least for derivatives **a** and **b**.

Substituent effects. It is little surprising that functionalisation of the β-phenyl ring with methoxy groups is generally predicted to facilitate the abstraction and addition reactions. The substituent effects mirror the trends expected for electrophilic attack on a benzene ring. Thus, 4-methoxy substitution as in **1b** is predicted to reduce the barrier for *ipso*-addition by 2.9 kcal mol^{-1}, wheras the activating effect for *ortho*-addition is less pronounced. Independent of substitution, radical **4** is always predicted to be the most stable radical resulting from intramolecular addition of **1**. The reaction kinetics, on the other hand, can be shifted towards formation of **2**, if a single methoxy subsituent is introduced as in system **b**. In the case of the 3,5-dimethoxy-substituted radical **1c**, both kinetic and thermodynamic effects clearly favour formation of radicals **4c** and **5c**.

Solvent effects. In general, solvation by polar-aprotic solvents is predicted to facilitate all reactions investigated. Whereas the transition state for hydrogen abstraction (TS1) is only slightly stabilized relative to the energy of radical **1**, the four transition states for *ipso*- and *ortho*-addition are stabilized by up to 2.2 kcal mol^{-1}, again relative to radical **1**.

Figure 1 shows the optimized geometries (UM05-2X/6-31G(d)) for the reactions of **1a**. Geometric parameters for all reactions are listed in Table III.

The most interesting O–C distances calculated are those of the transition structures, R6–R9. The values are similar to the TS structures for β-phenyl quenching of triplet β-phenylpropiophenone, where the R(O–C) in the TS

TABLE III
Selected O–C distances (R1–R9 in Fig. 1) for stationary points in the intramolecular addition reactions of **1a–1c**. All values in Å, as calculated at the UM05-2X/6-31G(d) level of theory

System	R1	R2	R3	R4	R5	R6	R7	R8	R9
1a	2.93	1.46	1.45	1.44	1.45	1.97	1.97	1.95	1.95
1b	2.89	1.47	1.46	1.44	1.45	1.99	1.99	1.97	1.96
1c	3.06	1.46	1.45	1.44	1.45	1.97	1.98	1.99	1.97

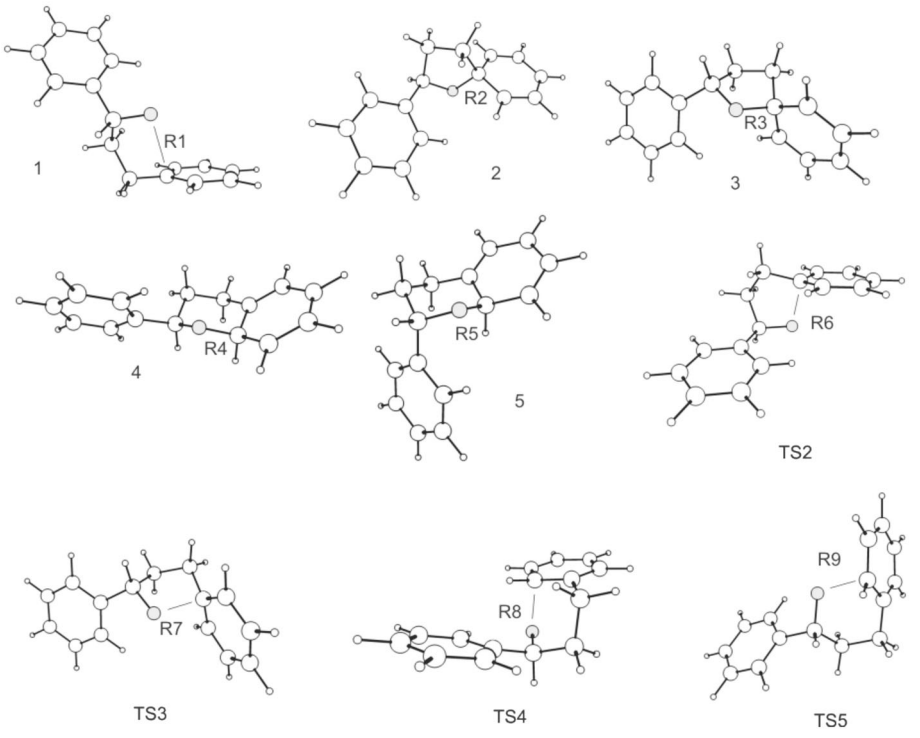
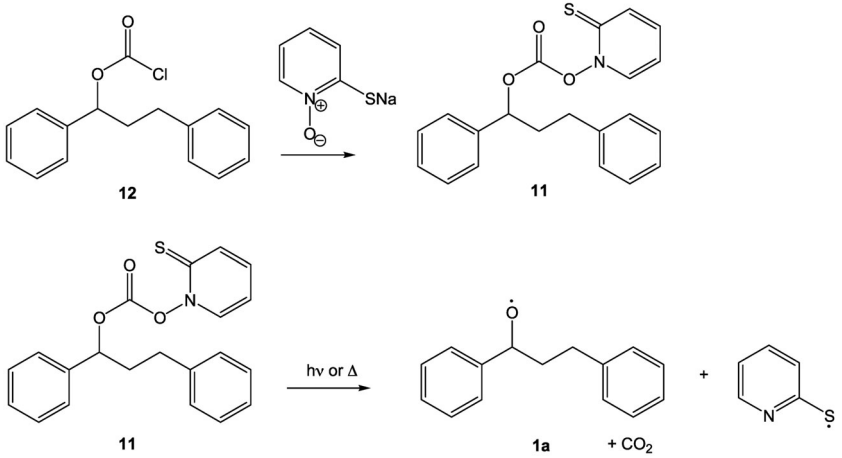


FIG. 1
Geometries of stationary points relevant to addition reactions of **1**

for *ipso*-addition is calculated (UB3LYP/6-31G(d)) to be 1.93 Å [14]. As expected, the more facile reactions (*ipso*-addition for **1b**, *ortho*-addition for **1c**) have slightly earlier, looser transition structures with a longer O–C distance. Over all, the reactions investigated here bear great similarity with the mechanism for β-phenyl quenching of β-phenylpropiophenone outlined earlier[14].

The results presented in this work suggest that intramolecular addition reactions of oxygen-centered radicals to benzene rings can occur, and that it should be possible to use them preparatively. Compared with addition reactions to ordinary C=C bonds, the reactions presented certainly do have the disadvantage of being only moderately exothermic. Nevertheless, in the presence of suitable trapping agents such as tetramethylpiperidine *N*-oxyl (TEMPO), that selectively trap carbon-centered radicals – either by C–O bond formation or by hydrogen abstraction – but do not react with oxygen-centered radicals, a successful generation and interception of radicals such as **2**–**5** should be feasible. The present work suggests that the benzene ring undergoing the addition reaction ideally should have activating substituents, and that polar solvent should be used. The trapping reaction used to capture **2**–**5** should be very efficient, as the competing fragmentation of the oxygen-centered radicals **1** into benzaldehyde **7** and a phenethyl radical **8** otherwise becomes an issue. This unwanted side reaction, however, could likely be minimized by conducting the reaction photochemically at low temperature. Possible precursor molecules to the oxyradicals discussed in



SCHEME 5
Suggested synthetic route to oxyradicals **1**

this work could be carbonates of the Barton type such as **11**, synthesised by reaction of the corresponding chloroformate **12** with the sodium salt of 2-mercaptopyridine *N*-oxide (Scheme 5).

SUPPORTING INFORMATION AVAILABLE

Cartesian coordinates and energies of all stationary points optimised.

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24. It is noted that the computational method used for obtaining the free energies uses a smaller basis set than the method used to calculate the electronic energies (6-31G(d) as opposed to 6-311++G(d,p)) and is therefore anticipated to be less accurate.
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