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Model Studies of β-Scission Ring-Opening Reactions of Cyclohexyloxy Radicals: Application to Thermal Rearrangements of Dispiro-1,2,4-trioxanes

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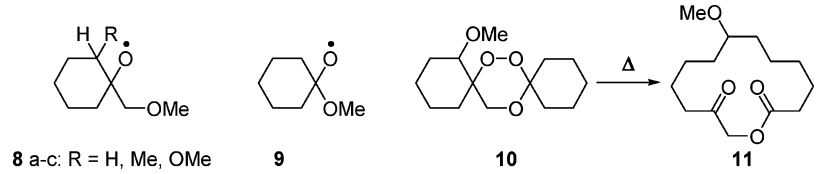
ABSTRACT



8 a-c: R = H, Me, OMe **9** **10** **11**

A DFT study of model cyclohexyloxy radicals (8a–c, 9) show that (a) the presence of an adjacent oxygen atom, and (b) α-substituents on the cyclohexyl ring, particularly methoxy, accelerate the rate of β-scission ring-opening reactions. Consistent with theoretical results, thermolysis of the methoxy-substituted dispiro-1,2,4-trioxane 10 afforded the structurally novel, 14-membered macrocyclic keto lactone 11 as the major isolable product.

Several naturally occurring and synthetic organic cyclic peroxides have been found to exhibit useful antimalarial and anticancer properties.[1,2] In particular, the 1,2,4-trioxane substructural unit has been identified as an essential pharmacophore in the antimalarial activity of artemisinin and related analogues.[3] It has been proposed that the antimalarial activity of artemisinin and other cyclic peroxides is related to iron(II)-induced cleavage of the peroxide bond followed by radical rearrangement to generate reactive carbon-centered radicals.[1a−d,4,5]

We have previously reported that, on thermolysis, dispiro-1,2,4-trioxanes **1** rearrange in a stepwise fashion to give oxalactones **4** and/or unsaturated hydroxy esters **5** by partial ring expansion. Alternatively, depending on the nature of the substituent on ring A, total ring expansion can yield macrocyclic keto lactones **7** (Scheme 1).[6] The observed products are consistent with an initial opening of the 1,2,4-trioxane ring (ring B) by O−O bond homolysis, followed by selective β-scission in ring C before that in ring A.[7] Since analogous symmetrical dispiro-1,2,4,5-tetroxanes are known to give macrocyclic products,[8] the presence of an adjacent oxygen atom may activate oxy radicals to undergo β-scission

(1) (a) Jefford, C. W. *Drug Discovery Today* **2007**, *12*, 487. (b) O'Neill, P. M.; Posner, G. H. *Acc. Chem. Res.* **2004**, *37*, 397. (c) Robert, A.; Dechy-Cabaret, O.; Cazelles, J.; Meunier, B. *Acc. Chem. Res.* **2002**, *35*, 167. (d) McCullough, K. J.; Nojima, M. *Curr. Org. Chem.* **2001**, *5*, 601. (e) Jefford, C. W. *Adv. Drug Res.* **1997**, *29*, 271.

(2) (a) Dembitsky, V. M.; Gloriozova, T. A.; Poroikov, V. V. *Mini-Rev. Med Chem.*, **2007**, *7*, 571. (b) Capon, R. J. *Eur. J. Org. Chem.* **2001**, 633. (c) Faulkner, D. J. *Nat. Prod. Rep.* **2000**, 1 and previous reviews in series. (d) Casteel, D. A. *Nat. Prod. Rep.* **1999**, *16*, 55.

(3) Klayman, D. L. *Science* **1985**, *228*, 1049.

(4) (a) Robert, A.; Benoit-Vical, F.; Meunier, B. *Coord. Chem. Rev.* **2005**, *249*, 1927. (b) O'Neill, P. M.; Posner, G. H. *J. Med. Chem.* **2004**, *47*, 2945.

(5) Tang, Y.; Dong, Y.; Wang, W.; Sriraghavan, K.; Wood, J. K.; Vennerstrom, J. L. *J. Org. Chem.* **2005**, *70*, 5103.

(6) (a) Kerr, B.; McCullough, K. J. *J. Chem. Soc., Chem. Commun.* **1985**, 590. (b) Haq, A.; Kerr, B.; McCullough, K. J. *J. Chem. Soc. Chem. Commun.* **1993**, 1076.

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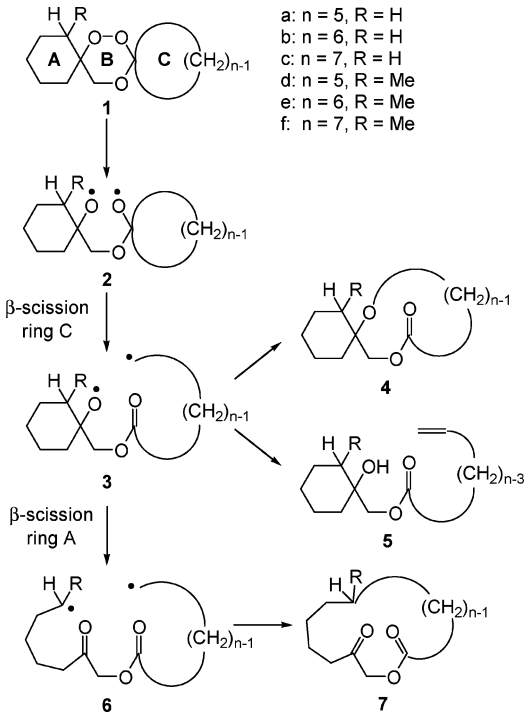
Scheme 1. Radical Rearrangement Reactions of Dispiro-1,2,4-trioxanes **1**

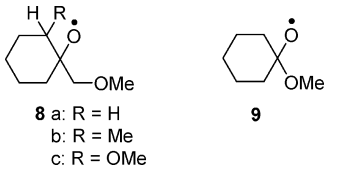


processes. In this respect, it is noteworthy that treatment of trioxane **1b** with iron(II) bromide results in the formation of a bromoester derived exclusively from β-scission in ring C as a major component of the product mixture; no species relating to β-scission in ring A were reported.[5] In addition, it is known that 3-methoxy-1,2-dioxanes also readily undergo iron(II)-mediated β-scission processes to give methyl esters.[9] In a more general synthetic sense, oxy radicals have been exploited as key intermediates in ring-expansion reactions,[10] and in ring-cleavage reactions of carbohydrates.[11]

In this paper, we report the results of a density functional theory (DFT) study[12] of β-scission ring-opening reactions of model cyclohexyloxy radicals analogous to those proposed in the thermal rearrangement of trioxanes **1**. We aim, first, to account for the fact that ring C of intermediate oxy biradical **2** opens faster than ring A and, second, to investigate how α-substituents might activate the opening of ring A and hence provide a higher proportion of macrocyclic lactones **7** from dispiro-1,2,4-trioxanes **1**.

In order to probe the relative rates of ring opening in species such as intermediate **2** calculations were carried out on the putative oxy radicals **8** and **9** (Scheme 2), model

Scheme 2. Model Species Used in the Calculations



8 a: R = H
b: R = Me
c: R = OMe

9

species for rings A and C, respectively.[13] In adopting this approach we assume the oxy radical centers in **2** will behave independently. The computed energy profiles are presented in Figure 1 and show a clear preference for opening ring C, with this process having a barrier of only 4 kcal/mol, 7 kcal/mol less than that for opening ring A. In both cases β-scission is accompanied by the expected shortening of the carbonyl C−O distances and a buildup of radical character at the incipient terminal carbon, evidenced through an increase in planarity. The breaking C−C bond is shorter in **TS 9** than in **TS 8a**, implying an earlier transition state in the former. This is consistent with the lower activation barrier for ring opening in **9** and the fact that this process is significantly exothermic compared to the endothermic ring opening in **8a**.[14] Therefore, for unsubstituted models the presence of an adjacent exocyclic oxygen strongly promotes ring opening, and this is consistent with the experimental observation of oxalactones **4** and hydroxyl esters **5** as the major products in the ring-opening reactions of **1b**.[6]

A second set of calculations was then performed to assess the effect of α-substituents, R, on the opening of ring A, where R = Me (**8b**) or OMe (**8c**). In the following we focus on isomers with R in an axial position, although analogous calculations on the equatorial-substituted species show similar trends (see Supporting Information). Computed activation barriers for ring opening in **8b** and **8c** show a clear preference for cleavage of the substituted C−C bond (see Figure 2). Moreover, the presence of Me and OMe substituents

(7) Thermolyses of artemisinin and other polycyclic 1,2,4-trioxanes generally result in extensive fragmentation of the trioxane ring and/or intramolecular H-abstraction processes after the initial O-O bond homolysis. See for example: (a) Luo, X.-D; Yeh, H. J. C.; Brossi, A.; Flippen-Anderson, J. L.; Gilardi, R. *Heterocycles* **1985**, *23*, 881. (b) Lin, A. J.; Theoharides, A. D.; Klayman, D. L. *Tetrahedron* **1986**, *42*, 2181. (c) Lin, A. J.; Klayman, D. L.; Hoch, J. M.; Silverton, J. V.; George, C. F. *J. Org. Chem.* **1985**, *50*, 4504. (d) Cafferata, L. F. R.; Jeandupeux, R.; Romanelli, G. P.; Mateo, C. M.; Jefford, C. W. *Afinidad* **2003**, *60*, 206. (e) Cafferata, L. F. R.; Rimada, R. S. *Molecules* **2003**, *8*, 655.

(8) Story, P. R.; Busch, P. *Adv. Org. Chem.* **1972**, *8*, 67.

(9) (a) Murakami, M.; Kawanishi, M.; Itagaki, S.; Horii, T.; Kobayashi, M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3513. (b) Kawanishi, M.; Kotoku, N.; Itagaki, S.; Horii, T.; Kobayashi, M. *Bioorg. Med. Chem.* **2004**, *12*, 5297.

(10) Sugimone, H. In *Handbook of Organic Photochemistry and Photobiology*; Horspool, W. M., Song, P.-S., Eds.; CRC Press: London, 1994; pp 1229−1253 and references therein.

(11) Recent examples include: (a) Alonso-Cruz, C. R.; Kennedy, A. R.; Rodriguez, M. S.; Suarez, E. *Tetrahedron Lett.* **2007**, *48*, 7207. (b) Alonso-Cruz, C. R.; Leon, E. I.; Ortiz-Lopez, F. J.; Rodriguez, M. S.; Suarez, E. *Tetrahedron Lett.* **2005**, *46*, 5265. (c) Alonso-Cruz, C. R.; Kennedy, A. R.; Rodriguez, M. S.; Suarez, E. *Org. Lett.* **2003**, *5*, 3729. (d) Francisco, C. G.; Gonzalez, C.; Paz, N. R.; Suarez, E. *Org. Lett.* **2003**, *5*, 4171.

(12) Frisch, M. J.; et al. *Gaussian 03*, Revision C.02; Gaussian, Inc.: Wallingford CT, 2004. Calculations used the B3LYP hybrid functional and 6-31G** basis sets. All energies include corrections for zero-point energy. See Supporting Information for full details.

(13) Recent theoretical treatments of β-scission in alkoxy radicals: (a) Thiriot, E.; Canneaux, S.; Hénon, E.; Bohr, F. *React. Kinet. Catal. Lett.* **2005**, *85*, 123. (b) Buback, M.; Kling, M.; Schmatz, S. *Z. Phys. Chem.* **2005**, *219*, 1205. (c) Leblanc, M.; Siri, D.; Marque, S. R. A.; Grimaldi, S.; Bertin, D.; Tordo, P. *Int. J. Quant. Chem.* **2006**, *106*, 676. (d) Suh, I.; Zhao, J.; Zhang, R. *Chem. Phys. Lett.* **2006**, *432*, 313.

(14) Straight-chain forms of products **P 8a** (E = +2.7 kcal/mol) and **P 9** (E = −9.0 kcal/mol) are slightly more stable than the initial intermediates shown in Figure 1 but retain the same thermodynamic preference for opening **9**.

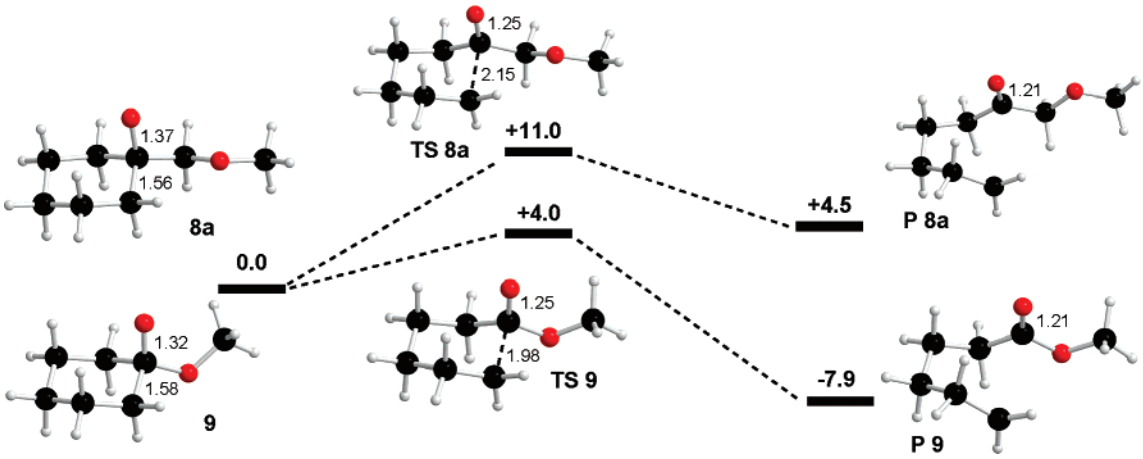


Figure 1. Computed ring-opening energy profiles in model species **8a** and **9** (kcal/mol; selected distances in Å).

significantly decrease the ring-opening barrier. For **8c** an important additional feature of the transition state, **TS 8c**, is

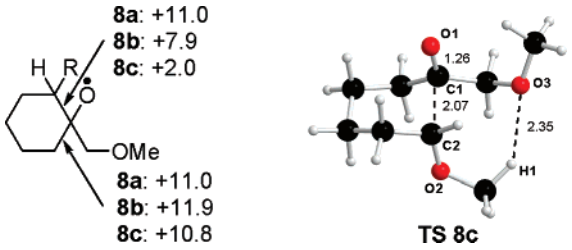


Figure 2. Computed activation barriers (kcal/mol) for ring opening in **8a** (R = H) and axially substituted **8b** (R = Me) and **8c** (R = OMe). **TS 8c** is also shown (selected distances in Å).

a short contact between the ether oxygen and one methoxy hydrogen (O3···H1 = 2.35 Å). This interaction is shown to facilitate ring opening, as an alternative transition state where the ether group is rotated to obviate this effect was found to be 2.5 kcal/mol higher in energy.[15]

It is well-known that α-substituents, in particular those bearing lone pairs, stabilize C-centered radicals, the so-called "α-effect".[16,17] In the present case this factor is already apparent in the *β*-scission transition states, and it is enough to make ring opening for **8c** via **TS 8c** a more accessible process than opening ring C in **9** via **TS 9**. To quantify this substituent effect on opening ring A we have performed a natural atomic orbital analysis[18] to obtain the spin density distributions for the stationary points associated with **8a**, **8b**, and **8c** (see Table 1). The results show the anticipated transfer

Table 1. Computed Natural Spin Densities at Selected Positions for Ring-Opening of **8a** and the Axial Isomers of **8b** and **8c** (see Figure 2 for Numbering)

	position	reactant	ts	product
8a (R = H)	O1	0.89	0.35	0.00
	C1	−0.03	−0.07	0.00
	C2	0.03	0.69	0.99
	R[a]	0.00	−0.02	−0.05
8b (R = Me)	O1	0.85	0.40	0.01
	C1	−0.03	−0.06	0.00
	C2	0.09	0.58	0.93
	R	0.02	0.03	0.03
8c (R = OMe)	O1	0.80	0.38	0.13
	C1	−0.03	−0.02	0.00
	C2	0.11	0.45	0.77
	R	0.06	0.13	0.14

[a] For R = Me and OMe the total spin on the substituent is indicated, although the major contribution comes from the α-atom.

of spin density from O1 in the reactants onto C2 in the transition states and products. For **TS 8a** the redistributed spin density is localized on C2; however, in **TS 8c** a significant contribution (0.13) is localized on the methoxy substituent. This delocalization serves to stabilize **TS 8c** and thus significantly lowers the barrier to ring opening. For **8b** the situation is intermediate between those of **8a** and **8c**.

Most importantly, the calculations allow us to predict that a methoxy substituent will make opening ring A competitive with that of ring C. This should enhance the possibility of both processes occurring to form fully expanded macrocycles such as **7** in preference to partially opened **4** and **5**. With this in mind we synthesized the methoxy-substituted dispiro-

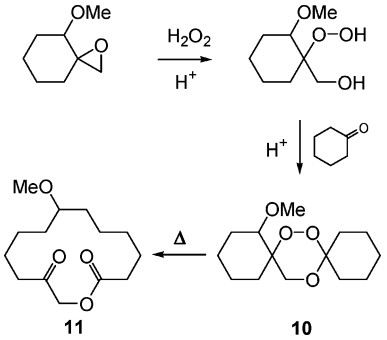
(15) Preliminary calculations on the analogous OMe-substituted dispiro-1,2,4-trioxanes show this interaction is retained in the full systems; thus, this stabilization is not an artefact of our truncated models.

(16) Nelson, S. F. In *Free Radicals*; Kochi, J. K., Ed.; Wiley: New York, 1973; Vol. 2.

(17) For recent examples where the α-effect is highlighted see: (a) Rauk, A.; Boyd, R. J.; Boyd, S. L.; Henry, D. J.; Radom, L. *Can. J. Chem.* **2003**, *81*, 431. (b) Henry, D. J.; Parkinson, C. J.; Mayer, P. M.; Radom, L. *J. Chem. Phys. A* **2001**, *105*, 6750. (c) Zipse, H. *Top. Curr. Chem.* **2006**, *263*, 163.

(18) Glendening, E. D.; Reed, A. E.; Carpenter, J. E.; Weinhold, F. *QCPE Bull.* **1990**, *10*, 58.

Scheme 3. Formation and Thermolysis of **10** to Give **11**



1,2,4-trioxane **10** as outlined in Scheme 3. Thermolysis of a solution of **10** in decane (1% w/v) at 180 °C afforded a relatively clean thermolysate, the major component of which was isolated in 67% yield as a low-melting solid.[19] This was subsequently identified by spectroscopic and X-ray crystallographic analysis as the structurally novel 14-membered macrocyclic lactone **11** (Figure 3).

From the thermolysis results it is therefore clear that the α-methoxy group accelerates the opening of ring A in the dioxy diradical derived from **10**, as predicted from the calculations on the model systems **8c** and **9**. The preponderance of keto lactone **11** suggests that the rates of opening rings A and C must be comparable, with the resulting carbon-centered radicals being in relative close proximity to enable efficient in-cage coupling. Further studies of substituent effects on *β*-scission processes of oxy radicals are in progress to design systems that will readily undergo radical cyclization reactions.

(19) Trace quantities of the ring B fragmentation products cyclohexanone and methoxycyclohexanone were also identified by gas chromatography.

(20) Sheldrick, G. M. *SHELXTL PC* (vers. 5.1); Brucker AXS: Madison, WI, 1997.

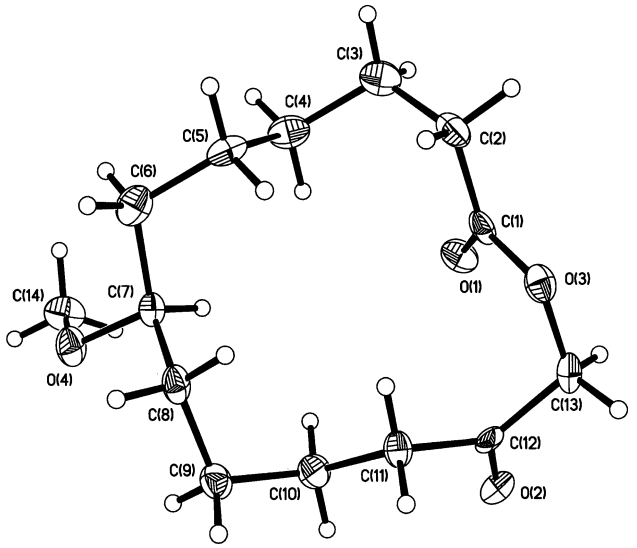


Figure 3. X-ray crystal structure of 14-membered methoxy substituted lactone **11** (ORTEP, 50% probability ellipsoids for non-hydrogen atoms).[20]

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Supporting Information Available: Experimental procedures for the synthesis of **10** and related compounds, copies of ^{1}H and ^{13}C NMR spectra, tables of atomic coordinates and derived crystallographic data. Tables of computed Cartesian coordinates and energies for all species, full reference 12. This material is available free of charge via the Internet at http://pubs.acs.org.

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