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Monodeoxygenation of Spiro Adamantane-1,2-Dioxetanes Induced by Aminium Salt[#]

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Abstract: The reactions of 4,4-dimethylspiro[adamantane-2,3'-[1,2]-dioxetane] (**1a**) and biadamantylidene-1,2-dioxetane (**2a**) in dichloromethane, at different reaction temperatures, with tris-(2,4-dibromophenyl) aminium hexachloroantimonate A afford high yields of the rearranged ketones 2-methyladamantyl-methyl ketone (**3**) and spiro[adamantane-2,4'-homoadamantan-5'-one] (**8**), respectively. A cation radical monodeoxygenation process is suggested.

Introduction

The most common transformation of four membered ring peroxides is their thermal or photochemical chemiluminescent cleavage into two carbonyl fragments.[1a-c,2]

In our knowledge, among the few other reactions of 1,2-dioxetanes, improperly named anomalous, those of great interest for our purposes are: (a) the reaction of methylene chloride solutions of tetramethyl-1,2-dioxetane (**TMD**, $\Delta G^{\ddagger} = 25.3$ *Kcal/mol*),[2] at -78 °C, with boron trifluoride and methanol, which afforded mixtures of pinacolone (rearranged ketone), cyclic pinacolone diperoxide, and trace amounts of acetone (cleavage ketone) by Bartlett and co-workers;[3] (b) the singlet oxygenation of cyclopropylidene adamantane carried out in the presence of tetracyanoethylene (**TCNE**), which gave adamantanespirocyclobutan-2'-one and tetracyanoethylene oxide in high yields by de Boer's group;[4] (c) the facile electron-transfer reduction of trimethyl-hydroxymethyl-1,2-dioxetane (**TMHMD**, $\Delta G^{\ddagger} = 26.2$ *Kcal/mol*)[2] to the corresponding 2,3-dimethyl-1,2,3-trihydroxybutane in methylene chloride solution, upon treatment with thiols, sulphides, phenothiazines and biologically active antioxidants, reported by Adam and co-workers.[5a,b] Besides the synthetic aspects, these studies, *above all*, outlined an interesting biological conversion of potentially genotoxic substrates (1,2-dioxetanes) into inert derivatives.

[#]This paper is dedicated to the memory of Prof. Fulvio Di Furia

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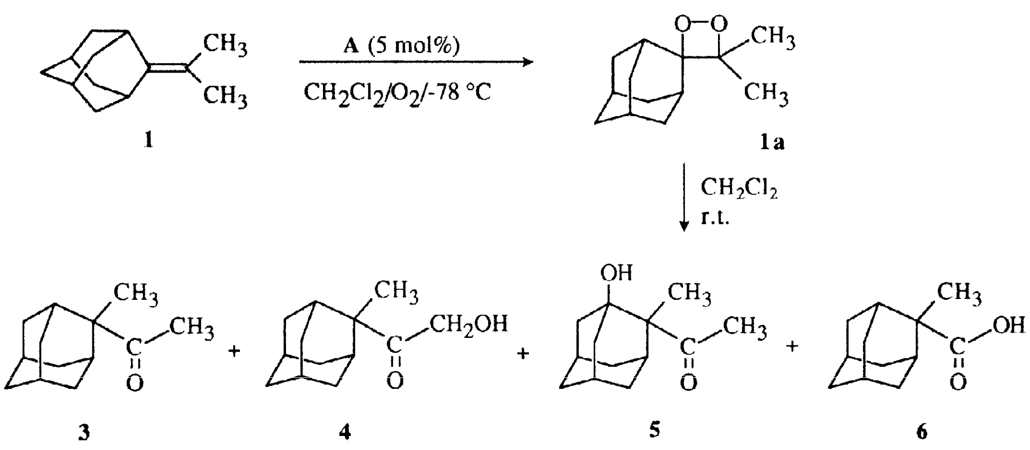
However, studies on 1,2-dioxetanes thermally and plausibly kinetically more stable than the previous, towards different chemical reagents, have not yet been published.

To this regard, the protocol for the synthesis of 4,4-dimethylspiro[adamantane-2,3'-[1,2]-dioxetane] ($\Delta G^{\ddagger}$= 28.5 *Kcal mol*$^{-1}$)^2 (**1a**), and bi-adamantylidene-1,2-dioxetane ($\Delta G^{\ddagger}$= 32.9 *Kcal mol* $^{-1}$)^2 (**2a**), through the well established cation-radical chain oxygenation process (CRCC),[6a,b] involves: (a) the addition of catalytic amounts (5 mol %) of *tris*-(2,4-dibromophenyl)aminium hexachloroantimonate [E^{ox} = 1.66 V. *vs* SCE][6a] **A** to oxygen saturated methylene chloride solutions of isopropylideneadamantane (**1**) [E^{red} =1.78 V. *vs* SCE][1a] and bi-adamantylidene (**2**) [E^{red} = 1.59 V. *vs* SCE][6a] at low temperature; (b) the minimum contact time between the reaction products and the aminium salt initiator. Thus, in order to avoid the formation of unidentified by-products, Nelsen and co-workers suggested that the intermediates of these very fast processes must be trapped by quenching the initiator with methanol and/or diethyl ether.[6a,b]

Results and Discussion

In continuation of our work on this topic,[7] we report herein that methylene chloride solutions of **1a**, (obtained upon treatment of **1** with catalytic amounts of **A** at -78°C), when allowed to reach room temperature without quenching of the initiator **A**, afford high yields (80-85%) of 2-methyladamantyl-methyl ketone (**3**), within 6 hours, along with minor amounts of 2-methyladamantyl-hydroxymethyl ketone (**4**), 1-hydroxy-2-methyladamantyl-methyl ketone (**5**) and 2-methyladamantyl-carboxylic acid (**6**). None of those reaction products are observed when methylene chloride solutions of **1a** are immediately quenched with diethyl ether; similar reaction mixtures are obtained carrying out the aminium-salt induced oxygenation of **1** at 0°C and/or room temperature, or upon treatment of pure methylene chloride solutions of **1a** with catalytic amounts of **A** (scheme 1).

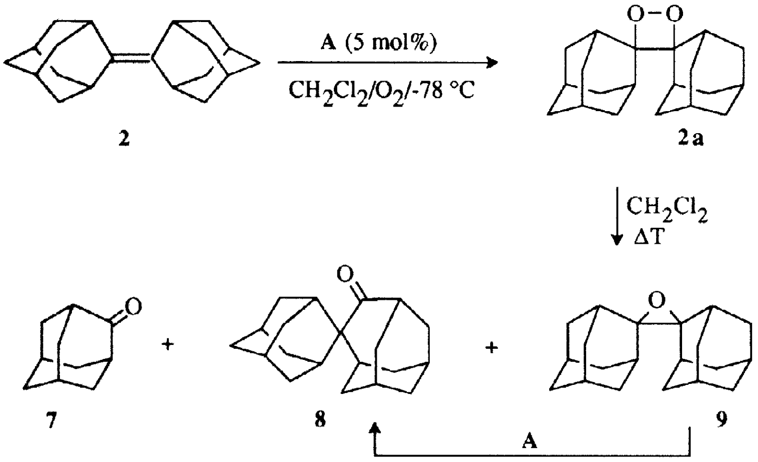
Scheme 1



On the contrary, in similar reactions performed on solutions of **2a** in methylene chloride, the thermally and kinetically stable 1,2-dioxetane ($\Delta G^{\ddagger}$= 32.9 *Kcal mol* $^{-1}$),[2] affords different mixtures of **2a**, 2-adamantanone (**7**) and spiro[adamantane-2,4'-homoadamantan-5'-one] (**8**), depending on the reaction temperatures and the relative amounts of the initiator **A** *vs* **2a**. In particular, high yields (90 %) of **8** are obtained upon addition (room temperature) of equimolar amounts of A to methylene chloride solutions of pure **2a**.

The addition of aliquots of **A** to similar solutions of **2a** reveals the intermediate formation of bi-adamantylidene oxide (**9**), whose structure is confirmed by gc/ms spectrometry and comparison with an authentic sample,[8] (scheme 2).

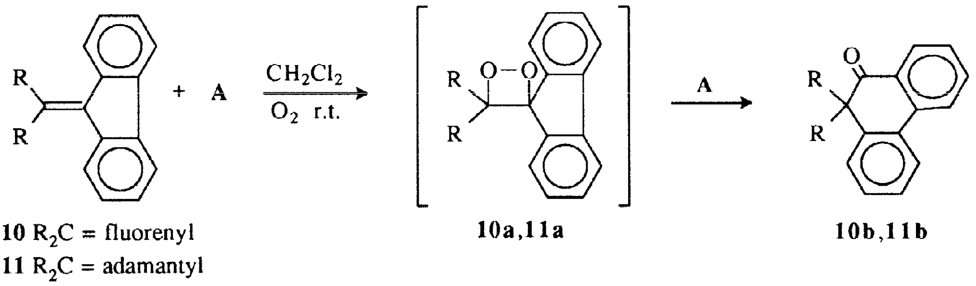
Scheme 2



In order to rationalize these results, we also verified that oxygen-saturated methylene chloride solutions of bi-fluorenylidene (**10**), and fluorenylidene adamantane (**11**) do not afford the corresponding 1,2 dioxetanes (**10a**) and (**11a**), upon treatment with catalytic amounts of A at low temperature, instead the corresponding rearranged ketones, *i.e.* spiro[9H-fluorene-9,9'-(10'H)-phenanthrene]-10'-one (**10b**) and spiro[2H-adamantyl-2,9'-(10H)-phenanthrene-10'-one] (**11b**)[9a,b] are obtained in low yields. Quantitative conversions of starting materials into **10b** and **11b** are, *indeed*, observed upon treatment of solutions of **10** and **11** with equimolar amounts of A at room temperature under air and/or oxygen atmosphere.

We believe that both reactions proceed via the corresponding 1,2-dioxetanes **10a** and **11a**, that are capable of only transient existence in the presence of the aminium salt (Scheme 3).

Scheme 3



In fact, it appears that dioxetane **10a** ($\Delta G^{\ddagger} < 26.9$ *Kcal mol* $^{-1}$).^{2,10a,b} can not be obtained, since it is too unstable to survive isolation and characterization. On the contrary, notwithstanding the dioxetane **11a** ($\Delta G^{\ddagger}=26.9$ *Kcal mol* $^{-1}$)^{2,10a,b} can be prepared by singlet oxygenation of **11**,^{10a,b} being thermally and kinetically less stable than **1a** *vs* the initiator, it might easily be deoxygenated.

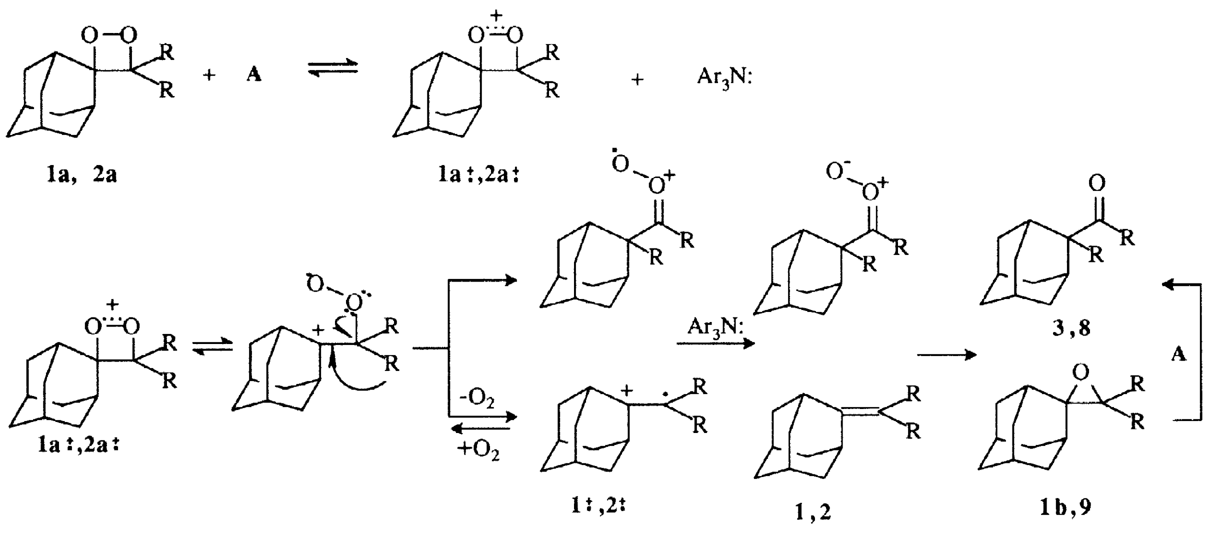
In order to verify a straight relation between the activation energy values, reported in brackets and referred to the thermal chemiluminescente cleavage of 1,2-dioxetanes without catalyst, and their kinetic stability towards the initiator, we also report that the monodeoxygenation of **1a** into **3** with catalytic amounts of **A** has been studied at 0, 5, 10, 15, 20 and 25°C. The experimental results give values for k_{obs} in the range 0.0184-0.4592 (l^2/mol^{2}sec), and an activation energy value ($\Delta G^{\ddagger} = 20.9$ *Kcal mol* $^{-1}$) lower than that observed for the thermal decomposition process of the same dioxetane without catalyst.

Similar studies, performed on methylene chloride solutions of **2a** show a slow conversion into **8**, which increases by adding aliquots of **A** until equimolar. At higher temperature (*ca* 50°C), the thermal decomposition process competes with the monodeoxygenation pathway.

As reported in the introduction section, only the Bartlett and de Boer's reports^{3,4} have so far centered the topic of this report. In particular, de Boer's results were rationalized on the basis of the intermediate formation of the corresponding four membered cyclic carbonyl oxide, as a precursor of both reaction products.^{4}

In the process herein, given that the three electrons π-bonded dioxetane cation radicals (**1a**$^{+\cdot}$) and (**2a**$^{+\cdot}$) are in equilibrium with the corresponding alkene cation radicals **1**$^{+\cdot}$ and **2**$^{+\cdot}$ ($\Delta G > -2$*Kcal mol* $^{-1}$ for the deoxygenation of **2a**$^{+\cdot}$),^{6a,b} through the open β-peroxycarbenium species, we suggest that these latter intermediates may also rearrange to carbonyl oxide cation radicals. Their subsequent reduction with the neutral amine would lead to the corresponding zwitterion carbonyl oxides and alkenes **1** and **2**, which would then react as envisaged by de Boer and co-workers^{4} (Scheme 4).

Scheme 4



Ar_3N: = $(2,4\text{-}Br_2C_6H_3)_3N$

Thus, since the oxidation potential of **2a** (E^{ox} = 2.29 V. *vs* SCE)[6a,b] is likely higher than that of **1a**, and the electron transfer process between the amine and **1**$^{\cdot+}$ or **2**$^{\cdot+}$ is endoergonic only in the latter case [ΔG=1.6 *Kcal mol*$^{-1}$], the observation that stoichiometric amounts of aminium salt are required for the monodeoxygenation of **2a** can also be accomodated as sketched in the previous scheme.

In support of these hypotheses stand the following observations: (a) methylene chloride solutions of pure samples of epoxides **9** and isopropylideneadamantane oxide (**1b**) quantitatively lead to **8** and **3**, upon treatment with catalytic amounts of **A** ;[8] (b) the conversion of **1a** into **3** is inhibited by addition of equimolar amounts of diazabicyclo [2.2.2] octane **DABCO** [E^{ox} = 0.67 V. *vs* SCE][11]*vs* **A**; (c) no loss of molecular oxygen, during the conversion of 1,2-dioxetanes to carbonyl compounds, is observed; (d) the Bartlett's procedure,[3] applied to methylene chloride solutions of **1a**, doesn't afford **3**, but unidentified products; (e) the hydroxy functionalized ketones **4** and **5**, whose structures appear totally consistent with the spectral data reported in the experimental section, might arise from the subsequent hydroxylation of the main reaction product, *i.e.* **3**, with the carbonyl oxide intermediate.[12] To this regard, low yields of **4** and **5** were observed upon treatment of methylene chloride solutions of **3** with equimolar amounts of trifluoromethyl-methyldioxirane.[13]

In conclusion, the reactivity of 1,2-dioxetanes with one-electron oxidizing agents appears strictly related to their thermal and kinetic stabilities and, at least for **1a**, the conversion into **3** might be accounted for a reverse chain cation radical monodeoxygenation process, involving the intermediate formation of alkene and carbonyl oxide cation radicals. Furthermore, because of the biological importance of this process detailed studies on the reactivity of several other 1,2-dioxetanes are warranted.

Experimental

Melting points were taken on Reichert Microscope and are uncorrected. ^{1}H-and ^{13}C-NMR spectra were recorded on a Varian XL-200 MHz and on Brucker AM-500 MHz instruments. IR, MS spectra were performed, respectively, on a Perkin-Elmer FT-1710 (KBr pellets), and on a Hewlett and Packard GC/Mass MSD 5970 instruments. GC analyses were carried out on HP 5890A capillary gas-cromatograph (RSL-150; 30 m; 0.25 mm i, d.). TLC were performed on silica gel sheets with fluorescent indicator (Stratocrom SIF-Carlo Erba). Dichloromethane was purified by washing with sulphuric acid solution, distillation over calcium hydride and then storage in the dark under nitrogen atmosphere and over molecular sieves. The starting materials **1, 2,10,11**, synthesized according to the known procedures,[14] showed chemical and spectral data consistent with those of pure samples. Aminium salt **A** has been synthesized by following the procedure reported in literature.[15] Trifluoromethyl-methyl dioxirane solution in the parent ketone has been prepared by Curci's group.[13]

Reactions of isopropylidene adamantane (1) and bi-adamantylidene (2) with aminium salt A: Synthesis of 2-methyl-methyladamantyl-methylketone (3) and spiro[adamantane-2,4'-homoadamantan-5'-one] (8).

Catalytic amounts of *tris*-(2,4-dibromophenyl)aminium hexachloroantimonate A (0.051 g, 0.05 mmol) are rapidly added to oxygen-saturated methylene chloride (10 ml) solutions of isopropylidene adamantane **1** (0.176 g, 1 mmol) and bi-adamantylidene **2** (0.168 g, 1 mmol), respectively, at -78 °C. The intensely green colour of the solutions fades within 30 min. The reaction mixtures, monitored by tlc (hexane:ethyl ether 9:1 as eluant), reveal the total disappearance of the starting materials with the contemporary formation of **1a** and **2a**, easily isolable as pure reaction products.[6a,b] However, when the crude reaction mixtures are allowed to reach room temperature, the two solutions show a different behaviour. In fact, the total deseappearance of **1a** and the contemporay formation of **3**, along with minor amounts of three other reaction products with different *Rf* by tlc, is observed within six hours. On the contrary, methylene chloride solutions of **2a** show a low conversion of **2a** into **8** within 24 h. In this latter case, the addition of an equimolar amount of **A** to the previous solution lead to a total conversion of **2a** into **8**. The solvent of both reactions is then removed in vacuo and the residues, adsorbed on silica gel, are purified by silica gel column chromatography with the eluant employed for tlc analyses.

After the elution of the neutral amine, several fractions containing **3** (0.150 g, 80 %) are collected. The spectral data: ^{1}H-NMR ($CDCl_3$, 500 MHz), δ: 1.11 (s, 3 H); 1.57-1.83 (m, 10 H); 1.97-2.03 (m, 2 H); 2.04-2.09 (m, 2 H); 2.10 (s, 3 H) ppm, ^{13}C-NMR ($CDCl_3$), δ: 22.6, 24.0, 27.2, 27.3, 32.5, 33.3, 35.2, 38,1, 53.6, 214.6 ppm. MS, m/z(%): 192 (M^+, 3), 149 (100), 107 (12), 93 (19), 81 (11), 79 (12), 43 (18). IR (liquid film): υ = 1097, 1351, 1452, 1702, 2861, 2911 cm^{-1}, are consistent with those of an authentic sample, synthesized by aminium salt-induced isomerization of the epoxide **1b**.[8]

The structures of **4**, **5**, **6** have been basically determined by spectral data and mass spectrometry on fractions containing pure reaction products.

4 (0.011g, 5 %) ^{1}H-NMR ($CDCl_3$, 500 MHz), δ: 1.21 (s, 3 H); 1.55-1.73 (m, 9 H); 1.77-1.85 (m, 2 H); 1.95-2.02 (m, 2 H); 2.05-2.10 (m, 2 H); 4.38 (s, 2 H) ppm; ^{13}C-NMR ($CDCl_3$), δ: 23.2, 27.0, 27.1, 32.2, 33.2, 35.2, 27.9, 45.3, 53.7, 206.3 ppm (DEPT and APT experiments show that the signals at 53.7 and 45.3 ppm are Cq and CsecH_2-OH respectively); MS, m/z (%): 177 (2), 149 (100), 107 (10), 93 (14), 81 (9), 79 (11); IR (liquid film): υ= 1451, 1637, 1714, 2862, 2911, 3441 (br O-H) cm^{-1}.

5 (0.012 g, 5 %) ^{1}H-NMR ($CDCl_3$, 500 MHz), δ: 1.10 (s, 3 H); 1.57-1.83 (m, 8 H); 1.92-2.08 (m, 5 H); 2.11 (s, 3 H); 4.27 (br s, 1 H) ppm. ^{13}C-NMR ($CDCl_3$), δ: 18.0, 24.8, 29.5, 30.6, 31.5, 35.2, 36.7, 37.1, 39.3, 42.8, 57.6, 71.1, 218.5 ppm. (DEPT and APT experiments show that the signals at 57.6 and 71.1 ppm are quaternary carbons). MS, m/z (%): 208 (M^+,1), 190 (4), 165 (100), 147 (12), 107 (16), 93 (8), 81 (8), 79 (11), 43 (33). IR (liquid film): υ= 1121, 1147, 1361, 1682, 2857, 2919, 3473 cm^{-1}.

6 (0.010 g, 5 %) ^{1}H-NMR ($CDCl_3$, 500 MHz), δ: 1.33 (s, 3 H); 1.58-1.64 (m, 2 H); 1.65-1.73 (m, 4 H); 1.77-1.83 (m, 2 H); 1.87-1.94 (m, 2 H); 1.95-2.02 (m, 2 H); 2.03-2.07 (m, 2 H) ppm. ^{13}C-NMR ($CDCl_3$), δ: 24.0, 27.0, 27.2, 32.2, 33.4, 35.6, 38.2, 48.6, 184.2 ppm. MS, m/z (%): 194 (M^+, 6) 149 (100), 107 (8), 93 (13), 81 (8), 79 (12). IR (KBr): υ= 1104, 1278, 1294, 1693, 3200-2450 (br CO_2H) cm^{-1}.

The reaction product **8** (0.150 g, 81 %) has been isolated as usual, and it has been fully characterized by physical and chemical properties, fitting those of an authentic sample.[4,16] The intermediate formation of **9** has been confirmed by comparison of the mass fragmentation pattern, R_f by tlc and retention time by gc of an authentic sample with those of the elusive intermediate **9**. Furthermore, the easy aminium salt- induced isomerization of **8** into **9** had been stated by us and other authors.[8,17]

Reactions of bi-fluorenylidene (10) and fluorenylidene adamantane (11) with aminium salt A: Synthesis of spiro[9H-fluorene-9,9'-(10'H)-phenanthrene]-10'-one (10b) and spiro[2H-adamantyl-2,9'-(10H)-phenanthrene-10'-one] (11b)

The same procedure, applied to oxygen-saturated methylene chloride solutions of **10** and **11** at -78°C, directly lead to trace amounts of the corresponding spirocycloalkanones **10b** and **11b**. However, upon addition to the same methylene chloride solutions of equimolar amounts of A at room temperature, the total conversion of starting materials into the corresponding spirocycloalkanones is observed. The reaction products have been isolated as usual and fully characterized by physical and spectral data, consistent with those of authentic samples.[5a,b]

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