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Comparative electrochemical properties of fluorinated endoperoxides related to the G-factor series

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Abstract—Fluorinated analogues of natural product G3-factor were synthesized and evaluated for their antiplasmodium activity. Electrochemical studies allowed us to measure the reduction potential E_p of the new compounds and to compare the effect of fluorine atoms on peroxo bridge stability.

1. Introduction

G-factors (Fig. 1) are natural products extracted from the leaves of *Eucalyptus grandis* and other myrtaceae acting as phytohormones and growth regulators.[1] We described previously[2,3] the synthesis and the antimalarial properties of some analogues of G-factors and determined the reduction potential of the endoperoxide moiety. The key step in the mechanism proposed for antimalarial endoperoxide action is the contact with haeme-iron[4,5] or free iron[6] and the electron transfer (ET) resulting in the cleavage of the O–O bond. In the search for more active antiplasmodial compounds, we wish to report the preparation, biological evaluation and electrochemical properties of analogues in this series bearing fluorine atoms on the R^1 and R^2 substituents or in replacement of the *ter*-hydroxy group.

The fluorination of a drug can indeed considerably influence its activity by improving its lipophilicity and hence its bioavailability by better membrane penetration and modifying its metabolism.[7] Fluorine atoms could also be useful in biology as probes allowing metabolites to be followed by ^{19}F NMR of biological fluids. Therefore our intention was to introduce fluorine in our molecules in order to evaluate the influence of the electron withdrawing substituents on the stability of the O–O bond through determination of the E_p values and their effects on antiplasmodial activity.

2. Synthesis

Fluorine was directly introduced at the bridgehead position by treating G3 compound with diethylaminosulfur trifluoride (DAST) as described earlier.[8] The experimental conditions were improved in order to obtain fluoride **2** in 73% yield after purification by silica gel (^{19}F NMR, 282.3 MHz, $CDCl_3$, $\delta_{ppm} = -22.4$, s, by reference to CF_3COOH).

Fluorination was tested on the key compound **3** which was previously obtained as the major isomer in a five-step synthesis starting from syncarpic acid.[2]

Alcohol **3** (Scheme 1) was treated with diethylaminosulfur trifluoride (DAST) in dichloromethane, at low temperature (−78 °C) and then was refluxed for 2 h. It seems that intermediate **I** is quickly formed at −78 °C but heat is necessary to transform it into the fluoride (+/−) **4** in 58% yield (^{19}F NMR ($CDCl_3$) $\delta_{ppm} = -154$, t,

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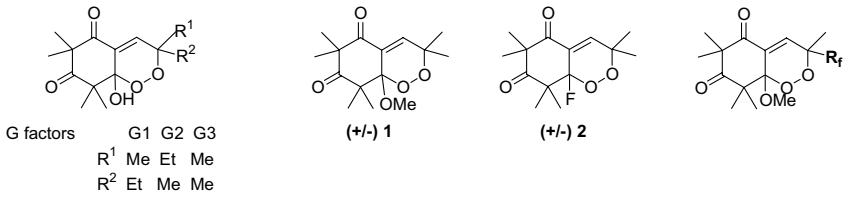
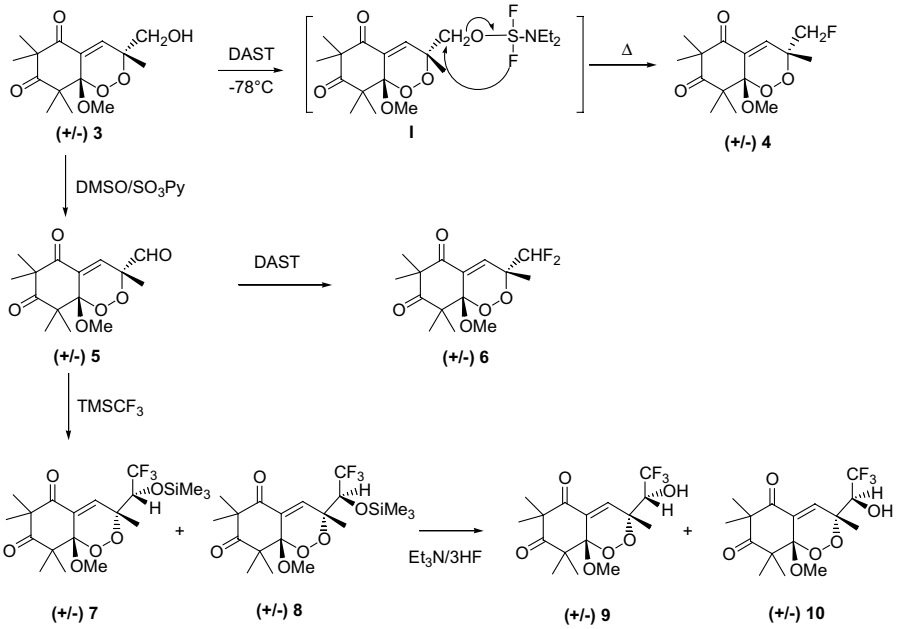


Figure 1. G-factors and methylated and fluorinated analogues.



Scheme 1.

$^{2}J_{F-H}$ = 47 Hz, CH_2F).[9] Bis-(2-methoxyethyl)aminosulfur trifluoride, $(CH_3OCH_2CH_2)_2NSF_3$ (Deoxo-Fluor reagent) was also tried but did not give better results than DAST. The Doëring oxidation of alcohol **3** ($Py–SO_3$, DMSO, Et_3N, CH_2Cl_2) led to aldehyde **5** in 70% yield. Without any purification this aldehyde was then treated with DAST, in dichloromethane, at low temperature (−78 °C) followed by reflux. The difluorinated compound (+/−) **6** was obtained in 76% yield from alcohol **3** after purification on silicagel (^{19}F NMR, $CDCl_3$, δ_{ppm} = −52.95, ABX syst., $^{2}J_{F-F}$ = 292 Hz, $^{2}J_{Fa-H}$ = 56 Hz, $^{2}J_{Fb-H}$ = 55Hz).[9]

We decided to submit aldehyde (+/−)-**5** to Ruppert's reagent (trifluoromethyltrimethylsilane, $TMSCF_3$),[10,11] which allowed for the introduction of a trifluoromethyl group. Tetrabutylammonium fluoride (TBAF) was chosen as fluoride source to initiate the catalytic cycle. The two diastereoisomers **7**/**8** were obtained in 80% yield (1/1) and separated on silicagel. Diastereoisomer **8** crystallized from methanol/petroleum ether. X-ray diffraction analysis of a single crystal of endoperoxide **8** (Fig. 2) allowed unambiguous confirmation of its structure and in particular of the relative configuration initially attributed on the basis of the NMR studies.[3] (^{19}F NMR ($CDCl_3$) compound **7**: δ_{ppm} = 4.2, d, $^{3}J_{F-H}$ = 6.7 Hz compound **8**: δ_{ppm} = 3.41, dd, $^{3}J_{F-H}$ = 7.6 Hz, $^{5}J_{F-H}$ = 2.7 Hz).[9]

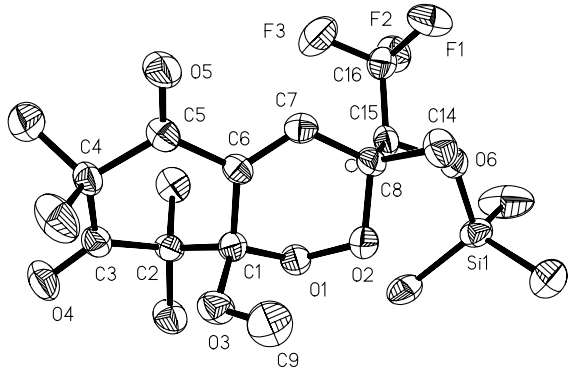


Figure 2. Crystal structure[13–15] for endoperoxide (+/−) **8**.

The corresponding trifluoromethylalcohols **9** and **10** were quantitatively obtained after deprotection of the trimethylsilyl group by Et_3N/3HF complex[12] (^{19}F NMR ($CDCl_3$) compound **9**, δ_{ppm} = 3.16, qd, $^{3}J_{F-H}$ = 7 Hz, $^{5}J_{F-H}$ = 1.4 Hz, compound **10**: δ_{ppm} = 3.76, dd, $^{3}J_{F-H}$ = 7.4 Hz, $^{5}J_{F-H}$ = 2.4 Hz).

3. Electrochemical studies

According to the mode of action proposed for endoperoxides, a proper study of the role of electron transfer

(ET) in G3 systems possessing a peroxide linkage, requires knowledge of the reduction potentials of the endoperoxides. Compounds **5**–**11** were studied using a thin layer voltammetry method[16] under potentiostatic conditions as described earlier.[3] Typical current–potential curves are presented in Figure 3. E_p values are directly determined on these voltamogramms (Table 1). The increase in the E_p values observed with the number of fluorine atoms might be explained by the electron withdrawing effect of this atom, weakening the O–O bond that becomes more easily reducible. With one fluorine atom, the E_p of endoperoxide **4** is 200 mV higher than the E_p of G3Me. The same gap of 200 mV is observed between mono **4** and difluorinated compound **6**. It can be noticed for silylated derivatives **7/8** a σ-donor effect of silicon, which causes about a roughly 150 mV decrease of E_p (towards more cathodic potential) compared to hydroxylated compounds **8/9**.

In Table 1, the number of electrons which are exchanged in the rate determining step, during the reduction of endoperoxides, was also reported, the values being obtained through integration of the E_p peak. A one-electron exchange, which is observed for compounds G3, **1**, **2**, **3**, **4**, is indicative of the appearance of a radical anion at the electrode, according to the equation: $AB + e^- \rightarrow A^0 + B^-$ as previously observed for some other examples. The mechanistic aspects are more puzzling for compounds **6**–**10**. Integration of the peak falls to 0.5 electrons for trifluoromethyl compounds **7**–**10**. The 0.5-electron exchanged for these endoperoxides can tentatively be explained by a chemical reaction between the starting endoperoxide and the radical anion as soon as it appears, a chemical reaction which is faster than the electrochemical reduction and which can only partially occur for compounds **6** and **8**, lowering the E_p values, compared to G3Me **1**.

4. Biological evaluation

The compounds were tested in vitro against the Nigerian strain of *Plasmodium falciparum* (Table 2). The activity was determined according to Desjardins et al.[17] by use of [^{3}H] hypoxanthine incorporation as an assessment of parasite growth. Parasitic viability was expressed as IC_{50}. The biological activities of these new compounds are disappointing and much weaker than artemisinin one. The activity was completely blocked when the cetalic OMe in compound **1** was replaced by a fluorine atom (compound **2**).[8] It is significant that mono and difluorinated compounds **4** and **6**, which have the OMe

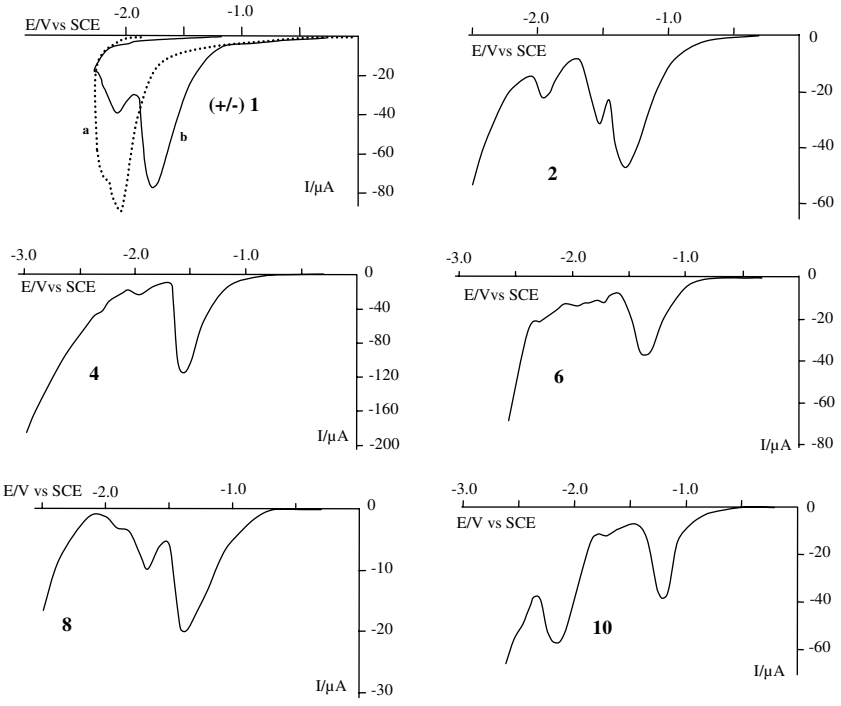


Figure 3. Current–potential curves, obtained on carbon felt enclosed in a thin layer cell with various endoperoxides at a concentration of 0.01 M in 0.3 M $NEt_4^+ClO_4^-$ in DMF solvent temp ca. 20 °C; $r = 0.5\,mV\,s^{-1}$; plotted under 1.5 atm of N_2. (+/−) **1**: (a) residual current; V_{TL}: 39 μL; (b) 0.01 M of G3Me; V_{TL}: 39 μL. **2**: V_{TL}: 32 μL. **4**: V_{TL}: 60 μL. **6**: V_{TL}: 28 μL. **8**: V_{TL}: 35 μL (residual current is subtracted). **10**: V_{TL}: 23 μL.

Table 1. E_p values and exchanged electron number

	G3	1	2	3	4	6	7	8	9	10
E_p/V[a]	−1.50	−1.76	−1.32	−1.50	−1.56	−1.35	−1.30	−1.38	− 1.15	−1.20
e^- number[b]	1	1	0.9	1	0.9	0.8	0.5	0.65	0.5	0.5

[a] E_p +/−10 mV.
[b] Values of electron number are given with an error of +/− 0.05.

Table 2. In vitro antimalarial activity of endoperoxides on Nigerian strains

	G3	**1**	**2**	**3**	**4**	**6**	**7**	**8**	**9**	**10**	Artemisinin
IC_{50} (μM)[a]	36	0.28	>100	1.4	0.69	0.74	34	15	25	3.1	0.015

[a] IC_{50} values are the drug concentrations causing 50% inhibition of parasite growth and were considered acceptable when they did not vary by more than a factor of three.

function, exhibit a biological activity in the same range as G3Me **1**.

Compared to compound **1**, the mechanism of homolytic breaking of the O–O bond seems to be different in the case of compounds **7/8** and **9/10**. If the radical anion obtained in the reduction step adds to another molecule of endoperoxide, instead of giving a C-centred radical, it can be understood that its alkylating properties will be seriously altered. This could explain the decrease in activity against *P. falciparum* compared to G3Me **1**. Nevertheless the adduct is still an endoperoxide and the composite value obtained cannot be easily discussed. Finally, mono and difluorinated products **4** and **6** could constitute interesting probes for biological studies since fluorinated atoms can be introduced, and the crucial peroxyhemiketal position maintained in the synthesis.

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9. Compound **4** ^{1}H NMR (250 MHz, $CDCl_3$, δ ppm): 1.00 (s, 3H), 1.30 (s, 6H), 1.34 (s, 3H), 1.47 (d, 3H, $^4J_{H-F}$ = 1.8 Hz), 3.47 (s, 3H), 4.38 (dd, 1H, $^2J_{H-H}$ = 10 Hz, $^2J_{H-F}$ = 47 Hz, CH_2F), 4.58 (dd, 1H, $^2J_{H-H}$ = 10 Hz, $^2J_{H-F}$ = 47 Hz, CH_2F), 7.33 (s, 1H, =C*H*). ^{13}C NMR (75.5 MHz, $CDCl_3$, δ ppm): 15.6, 18.0, 21.7, 24.8, 26.0, 53.1, 54.8, 54.9, 78.7 ($^2J_{C-F}$ = 32 Hz), 83.0 ($^1J_{C-F}$ = 162 Hz) 100.1, 132.0, 139.9, 197.8, 209.6. Compound **6** ^{1}H NMR ($CDCl_3$, δ ppm): 1.01 (s, 3H), 1.29 (s, 3H), 1.31 (s, 6H) 1.43 (t, 3H, $^4J_{H-F}$ = 1.6 Hz), 3.46 (s, 3H), 5.88 (dd, 1H, $^2J_{H-Fa}$ = 56 Hz, $^2J_{H-Fb}$ = 55 Hz), 7.31 (d, 1H, $^2J_{H-F}$ = 1.8 Hz). ^{13}C NMR ($CDCl_3$, δ ppm): 15.0, 15.6, 21.6, 2.4.8, 26.0, 53.1, 54.9, 55.0, 79.9, 100.3, 113.2 ($^1J_{C-Fa}$ = 245 Hz, $^1J_{C-Fb}$ = 251 Hz), 132.3, 137.6, 197.9, 209.5. Compound **8** ^{1}H NMR ($CDCl_3$, δ ppm): 0.24 (s, 9H), 1.05 (s, 3H), 1.31 (s, 6H), 1.34 (s, 3H), 1.38 (s, 3H), 3.45 (s, 3H), 4.33 (q, 1H, $^3J_{H-F}$ = 7.63 Hz), 7.31 (q, 1H, $^5J_{H-F}$ = 2.73 Hz). ^{13}C NMR ($CDCl_3$, δ ppm): 0.0, 16.0, 16.5, 22.3, 25.3, 26.2, 53.2 55.05, 55.13, 72.0 ($^2J_{C-F}$ = 30.2 Hz), 81.7, 100.7, 124.2 ($^1J_{C-F}$ = 283.13 Hz), 130.4, 140.9 ($^4J_{C-F}$ = 2.27 Hz), 198.6, 210.2.
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13. Crystal data for **8**: $C_{19}H_{29}F_3O_6Si$, M = 438.51, monoclinic, $P2_1/n$, a = 11.978(1) Å, b = 11.581(1) Å, c = 16.729(2) Å, β = 106.085(2)°, V = 2229.8(4) Å^3, Z = 4, T = 193(2) K. 9533 reflections (3141 independent, R_{int} = 0.0707) were collected at low temperatures using an oil-coated shock-cooled crystal on a Bruker-AXS CCD 1000 diffractometer with Mo Kα radiation (λ = 0.71073 Å). The structure was solved by direct methods (SHELXS-97)[14] and all nonhydrogen atoms were refined anisotropically using the least-squares method on F^2.[15] Largest electron density residue: 0.222 e Å^{-3}, R_1 (for $I > 2\sigma(I)$) = 0.0494 and wR_2 = 0.1166 (all data) with $R_1 = \Sigma||F_o|-|F_c||/\Sigma|F_o|$ and $wR_2 = (\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2)^{0.5}$.
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16. Carbon felt (COMAIP France; reference CFT 3000 10), set between two glass slides delimiting a compartment with a volume of a few tens of microlitre, was used as working electrode. The choice of carbon was justified by the high cathodic overvoltage in DMF solvent (~2 V). Due to the small volume of the thin-layer cell, all the electroactive molecules present in solution can be transformed during one scan. There is no mixing between the solution of the thin layer cell and the solution of the auxiliary electrode compartment, so it is possible to examine the behaviour of products appearing at the electrode during the potential scan. From the amount of charge, determination of the number of electrons exchanged during the electrode reaction is straightforward. All the electrode potentials were measured with respect to a saturated calomel electrode (SCE i.e., Hg/Hg_2Cl_2/Cl-saturated), immersed in a Luggin capillary located near (3–4 mm) the working electrode and containing DMF and the electrolyte in large excess. The auxiliary electrode was made of platinum. The electrochemical apparatus used was a Radiometer Voltalab PGZ 100 computerised potentiostat. The electrochemical cell was kept under an inert atmosphere (nitrogen at 1.5 atm) and all experiments were performed in the absence of oxygen.
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