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Heterolytic (2e) vs Homolytic (1e) Oxidation Reactivity. N-H vs C-H Switch in Dioxirane Oxidation of Lactams.

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Dedication ((optional))

Abstract: Dioxiranes are powerful oxidants that can act via two different mechanisms: *i*) homolytic (H abstraction and oxygen rebound) and *ii*) heterolytic (electrophilic oxidation). So far, it has been reported that the nature of substrate dictates the reaction mode, independently from the dioxirane employed. We report herein an unprecedented case in which the nature of the dioxirane rules the oxidation chemoselectivity. In particular, a switch from C-H to N-H oxidation is observed in the oxidation of lactams moving from dimethyl dioxirane (**DDO**) to methyl(trifluoromethyl)dioxirane (**TFDO**). A physical organic chemistry study, which combines the oxidation with two other dioxiranes (methyl(fluoromethyl)- (**MFDO**) and methyl(difluoromethyl)dioxirane **DFDO**) with computational studies, points to a diverse ability of either dioxirane to stabilize the homo or the heterolytic pathway.

Oxidation processes have been one of the major playgrounds for the interpretation of reactivity. This is due both to the ease for early chemists to have access to oxidants and to the widespread occurrence of oxidative processes in biological systems. These studies have offered the possibility to develop a wide variety of oxidation methods that have constantly evolved in terms of selectivity and reactivity.[1] Nowadays, the benchmark of oxidation chemistry is represented by the functionalization of C(sp^3)-H bonds.[2] This is due to: *i*) their poor reactivity and *ii*) the presence within a molecule of different C-H's or *iii*) other functional groups prone to oxidation. However, C-H bond oxidation can be selectively differentiated, based on their electronic, stereoelectronic and steric features, with very high selectivities.[3] In this context, less attention has been driven to the tuning of the electronic characteristic of the oxidant in order to bias its selectivity. In other words, the selectivity in oxidation chemistry is always under substrate control and eventually tuned by suitable steric modifications of the oxidant. Indeed, variations in the electronic features of the systems have generally small effects on the selectivities, as shown by many LFER Hammett correlation studies.

Figure 1. Dioxiranes **1a-d**.

Our interest in C-H oxidations originates from our study on the chemistry of dioxiranes (Fig. 1). Despite their extremely simple architecture, these oxidants have displayed exceptional reactivity and versatility often accompanied by examples of high chemoselectivity.[4] **TFDO** is the most reactive dioxirane and it performs a wide variety of oxidations with practically unchanged selectivity in respect to the less reactive **DDO**.[5] We have recently reported that **TFDO** and **DDO** are able to oxidize N-protected peptides and depsipeptides via a clean C-H bond hydroxylation, leaving the amide bonds untouched.[6] We have also investigated the oxidation of secondary lactams of different ring size, which undergo oxidative cleavage of the amide bond by **TFDO** oxidation in aqueous media, providing an efficient yet clean route to valuable ω-nitroacids.[7] Besides the synthetic application, very little is known on the mechanism of amide oxidation.[8] Early studies revealed that it is not a simple process: H-abstraction from C-H bonds by free radicals seems to predominate over the electrophilic oxidation of the nitrogen, due to its weak nucleophilic character.

Herein, we report an unprecedented case where a variation of the electronic features of the oxidant creates a sharp switch in the oxidation chemoselectivity. Noticeably, the presence of 1, 2 or 3 electron-withdrawing fluorine atoms in the dioxirane structure results in a switch of the reactivity from the homolytic (1 electron) C-H oxidation to the heterolytic (2 electrons) N-H oxidation. Experimental results, together with theoretical calculations, allowed us to ascribe this selectivity switch to a diverse ability of the oxidants **1a-d** to stabilize differently polarized transition states (TS's).

In order to unravel the factors influencing this reactivity, we set out to compare the oxidation of 5 to 13-membered ring lactams **2a-g** by **DDO** and **TFDO** under similar conditions (solvent, acetone; temp. 0° or 25°C), except that larger excess of the less reactive **DDO** had to be generally used in order to drive the reactions to completion. For comparison, the reactivity of the linear amide *N*-ethylacetamide **2h** was explored as well. The initial reactivity screening revealed that lactam conversions were generally high with quantitative formation of the oxidized products, namely ω-nitroacids (**3**), imides (**4**) or bicarboxylic acids monoamides (**5**) (Table 1).

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Data in Table 1 and the diagram of NH vs C$^{\omega}$H oxidation selectivity of Fig. 2 clearly show the general trend described herein: **TFDO** performs preferentially the N-H oxidation, while **DDO** reactivity is generally directed toward C$^{\omega}$-H oxidation.

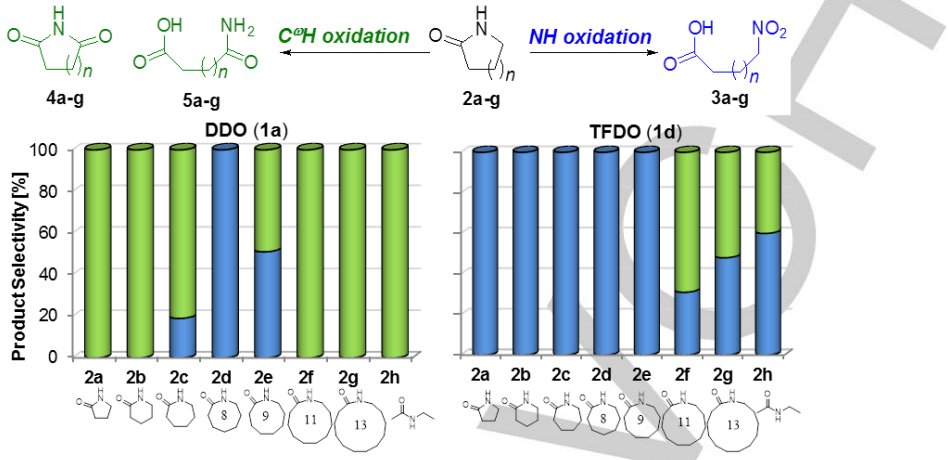
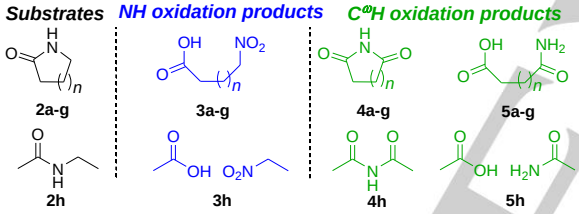


Figure 2. NH (■) *vs*. CH (■) oxidation product selectivity (%) based on isolated yields reported in Table 1

Table 1. Oxidation of lactams **2a-g** and *N*-ethylacetamide **2h** with isolated **DDO** (**1a**) and **TFDO** (**1d**) in acetone.[a]



Sub-strate	Oxi-dant	Ox/ Sub[b]	Conv [%][c]	Isolated Yields [%] NH Ox. Products	Isolated Yields [%] C$^{\omega}$H Ox. Products	
n = 1, **2a**	**1a**	5	99	-	**4a**, 99	-
	1d	3.5	99	**3a**, 99	-	-
n = 2, **2b**	**1a**	5	99	-	**4b**, 99	-
	1d	3.5	99	**3b**, 90	-	-
n = 3, **2c**	**1a**	20	73[d]	**3c**, 13	-	**5c**, 57
	1d	3.5	99	**3c**, 99	-	-
n = 4, **2d**	**1a**	20	40[d]	**3d**, 40	-	-
	1d	3.5	99	**3d**, 99	-	-
n = 5, **2e**	**1a**	20	71[d]	**3e**, 35	-	**5e**, 33
	1d	3.5	99	**3e**, 96	-	-
n = 7, **2f**	**1a**	5	99	-	-	**5f**, 98
	1d	3.5	99	**3f**, 25[e]	**4f**, 55[e]	-
n = 9, **2g**	**1a**	5	99	-	-	-
	1d	3.5	99	**3g**, 26[e]	**4g**, 28[e]	**5g**, 98
2h	**1a**	5	99	-	**4h**, 60[f]	**5h**, 40[f]
	1d	3.5	99	**3h**, 60[f]	**4h**, 40[f]	-

[a] Reactions were run at 25°C with **1a** and at 0°C with **1d**; unless otherwise noted, reaction time was 48 h or 3 h for oxidation with **1a** or **1d**, respectively. [b] Oxidant to Substrate molar ratio. [c] Estimated on the basis of the amount of unreacted substrate recovered. [d] At 60 h. [e] Accompanied by unidentified products of over-oxidation (Ref. 7b). [f] Estimated from calibrated GC-MS analyses.

This switch in selectivity, which is unprecedented in dioxirane chemistry, is well represented by the oxidation of 2-pyrrolidinone (**2a**), in which case attack of **DDO** (**1a**) selectively occurs at the C$^{\omega}$-H, affording quantitatively succinimide **4a**. The divergence from this selectivity is outstanding with the trifluoro dioxirane **TFDO** (**1d**), which provides the nitroacid **3a** as a single product in quantitative yield. This trend of reactivity is common to most of the substrates of the series and shows exceptions only for larger rings. Only in the case of the 8-membered lactam **2d** both oxidants selectively gave the same nitroacid **3d**, although **DDO** with only 40% conversion even working in the presence of large excess of the oxidant (up to 20 equiv). On the other hand, lower chemoselectivities are obtained in the **TFDO** oxidation of caprinolactam **2f** and laurolactam **2g**, where ω-nitro acids are produced as minor products, together with increasing amounts of the corresponding imides **4f-g**. Similarly, reaction of **2h** by **DDO** affords, with high chemoselectivity for C$^{\omega}$H oxidation, a mixture of *N*-acetylacetamide (**4h**, 60%) and acetic acid/acetamide (**5h**, 40%), while the reaction with **TFDO** gives principally the NH oxidation products, nitroethane/acetic acid (**3h**, 60%), along with *N*-acetylacetamide (**4h**, 40%) as the C$^{\omega}$H oxidation product. As partially expected, this is the same behaviour observed with larger lactams **2f**,**g**.

Products obtained from oxidation of lactams are compatible with the two different mechanistic pathways currently accepted for oxidations by dioxiranes. In particular, heteroatom oxidation (common to nitrogen-, sulfur- and phosphorous-containing compounds), where a two-electron (2e) oxo-transfer is involved, is substantially a S_N2-type reaction which, similarly to the

stepwise dioxirane oxidation of primary amines,[9] should underlie the formation of ω-nitroacids **3**. On the other side, H abstraction (1e), followed by an "oxygen rebound" step,[4d,10] underlies the O-insertion into the C(sp^3)-H bond, which can also be envisaged in the $C^{\omega}H$ oxidation of **2** to imides **4** or bicarboxylic acids monoamides **5** (Scheme S1, Supporting Information). Therefore, based on data in Table 1, it seems, that **DDO** is mainly or exclusively favouring the 1e C-H oxidation pathway, while **TFDO** has a strong tendency toward the 2e N-H oxidation pathway.

With the aim to gain insights into this remarkable chemoselectivity switch, we investigated the 2-pyrrolidinone (**2a**) oxidation with two other dioxiranes, namely methyl(fluoro-methyl)-**MFDO** (**1b**) and methyl(difluoro-methyl)dioxirane **DFDO** (**1c**) (Fig. 1). Oxidations by these two oxidants have been tested with the twofold purpose to evaluate the change in selectivity/reactivity with the increasing fluorine atoms and to correlate the observed data with theoretical calculations. Since isolation of **MFDO** and **DFDO** proved unsuccessful,[11] oxidations of lactam **2a** were carried out with the *in-situ* generated dioxirane method, according to the well-established ketone/caroate protocol. For comparison, oxidations with *in-situ* generated **DDO** and **TFDO** were also examined (Table 2). Experimental data point out that an increase in the fluorine content of the oxidant corresponds to a monotonic increase in the N-H oxidation product **3a**. While it is known that addition of fluorine atoms within the dioxirane framework results in a higher reactivity as a consequence of their electron-withdrawing character, these results suggest that addition of fluorine atom to the dioxirane skeleton stabilizes a "more polar" TS or, in other words, a TS where a higher amount of charge is transferred from the substrate to the oxidant. However, it should be noted that data in Table 2 show that oxidation of **2a** with the *in-situ* generated **TFDO** results in lower selectivities, compared with the same reaction conducted with the isolated dioxirane (Fig. 2). However, the fact that traces (ca. 5%) of imide **4a** are formed in the background reaction (in the absence of ketones; Entry 1, Table 2) confirms, according to previous studies,[12] that the *in-situ* oxidation environment can promote undefined radical oxidation pathways. In the presence of dioxiranes (Entries 2-5, Table 2), these trigger the concomitant radical reactivity of dioxiranes,[13] which may account for the lowered selectivity observed.

Table 2. Product selectivity in the oxidation of γ-butirrolactam (**2a**) by *in-situ* generated dioxiranes **1a-1d** after 48 h reaction.

Entry	Oxidant	Product Selectivity [%][b]	
		3a	**4a**
1	Caroate[a]	0	100
2	*in-situ* **1a**	0	100
3	*in-situ* **1b**	31	69
4	*in-situ* **1c**	45	55
5	*in-situ* **1d**	64	36

[a] Background reaction (in the absence of ketones). [b] Relative percentage based on integration of characteristic ^{1}H NMR signals; reaction conversions were from 5% (background reaction) to 90% for reaction with **1d**.

Unrestricted MP2 calculations have been performed to determine the transition structures for dioxirane oxidation at C^{ω}-H or N-H of amide **2a**. As far as the C^{ω}-H oxidation is concerned, it can be evidenced that dioxirane attack to the C^{ω}-H occurs with a similar geometry to the one already observed by Houk in the case of cyclohexanes.[10b] It is also worth of notice that the abstracted H atom is in axial conformation and perpendicular to the amide plane (Fig. 4, left side).[14] In all the cases examined, IRC calculations confirm that after H abstraction, the reaction proceeds with an "oxygen rebound" mechanism, yielding the corresponding alcohol. On the other hand, N-H oxidation strongly resembles the single-step S_N2-type dioxirane-mediated oxygen transfer to sulfides,[15] in which the reactive lone pair of the substrate controls the direction of the dioxirane attack.

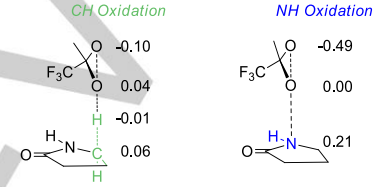


Figure 4. Variation in calculated NBO charges (au) from reactants to TS for the C-H(■)/N-H(■) oxidation of **2a** (Ref. 16).

Table 3. Calculated Activation Free Energies ($\Delta G^{\neq}$) for C^{ω}H/NH oxidation of lactam **2a** by dioxiranes **1a-d**.

TS	$\Delta G^{\neq}$ [Kcal/mol][a]			
	1a	**1b**	**1c**	**1d**
N-H Ox.	29.3	26.1	21.5	19.2
C^{ω}-H Ox.	22.1	20.5	20.5	18.3

[a] MP2 calculations were performed with Gaussian 09 (Ref. 17). Minima and transition structures were optimized using the unrestricted MP2 method with the 6-311++G(d,p) basis set with solvation (CPCM acetone).

Calculated activation energies $\Delta G^{\neq}$ (Table 3) for the reaction of the four dioxiranes **1a-d** with **2a** correlate well with the experimental results.[18] More in detail, calculated $\Delta G^{\neq}$ values open to three considerations: *i*) "addition" of fluorine atoms increase the electrophilic character of the oxidant, thus lowering the TS energy for all the processes, *ii*) this effect is more pronounced in the case of N-H oxidation rather that in the case of C-H, *iii*) while C-H oxidations are favored by **DDO**, in the case of **TFDO** the two activation energies ($\Delta G^{\neq}$) are similar. In the latter, the CF_3 group is able to delocalize more effectively along the oxidation pathway the negative charge developing at the "leaving" oxygen atom.[19] This polarization is evident in the NBO calculated amount of charge transferred in the TS (Fig. 4).

The calculated energies pair with the two observed reaction pathways, which substantially occur through a 1e and a 2e

mechanism, respectively. The CF_3 group in the **TFDO**, owing to its strong electron-withdrawing nature, is able to better stabilize the charge transfer required for the heterolytic pathway. The N-H oxidation occurs via a "more polarized" TS, and this difference accounts for the observed switch of chemoselectivity of the two oxidants. On the basis of the gathered data for lactam **2a**, it is possible to ascribe the trends observed in the different lactams series to the higher energy required by the C-H bond to get perpendicular to the amide plane in order to react and by the different amide geometries depending upon ring size.[14,20]

In conclusion, results from experiments and theoretical calculations support the view that the polar TS arising from interaction of the nitrogen atom with dioxiranes can be more easily accessible by **TFDO**. The CF_3 group is able to stabilize the "2e flow" better than the corresponding methyl substituted **DDO**. On the contrary, an "oxygen rebound" mechanism, featuring the dioxirane oxidation of C-H, goes through lower-energy TS's for **DDO**, most likely because of the higher propensity of the latter to undergo O-O homolysis. The study has also offered the possibility to use two new oxidants **1b,c** as a novel physical organic chemistry "tool" for the determination of the homo- *vs* heterolytic character of oxidations. These results draw also the attention to the fact that the complex chemistry of oxidations is highly determined by the intrinsic characteristics of the oxidant moiety which is not transferred, the formal "leaving group", rather than the features present at the reactant state.[21]

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Keywords: Oxidation • Dioxiranes • Lactams • Oxidation chemoselectivity • MP2 calculations

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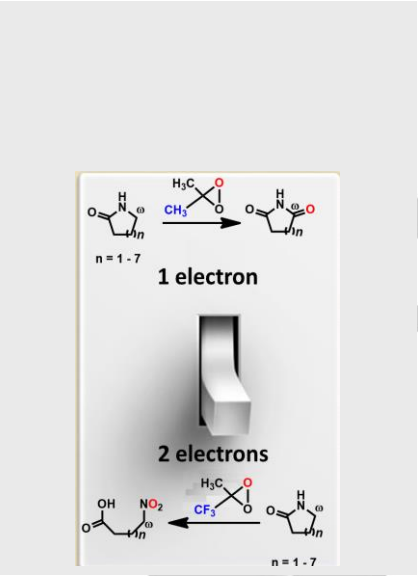

C. Annese, L. D'Accolti, C. Fusco, G. Licini, C. Zonta***

Page No. – Page No.

Heterolytic (2e) vs Homolytic (1e) Oxidation Reactivity. N-H vs C-H Switch in Dioxirane Oxidation of Lactams.

Layout 2:

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Page No. – Page No.

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Text for Table of Contents