Chapter 6

Regioselective nitration of 4-quinolones: Convergence of theoretical and experimental findings

Regioselective nitration of 4-quinolone, the highly privileged scaffold, has been investigated through density functional theory (DFT) based approach. Nitro group can selectively be introduced in the diverse position simply by tuning the reactivity of the moiety. Discrimination is being achieved through the selective protection of free N-H group. The selection of protecting group is screened theoretically with the help of Fukui function and local softness calculations. Theoretical predictions are synchronized well with the experimental findings. Thus, this selective nitration allows the access of the structurally diverse 4-quinolones.

6.1 Introduction

Nitration is one of the most extensively studied organic reactions since its discovery in 1834.[1] Nitro compounds are significantly beneficial synthetic intermediates and have potential application in various fields especially in chemical industry as well as pharmaceuticals.[2] Nitration with mixed acids always results in the mixture of products. Many regioselective nitration techniques viz. ipso-nitration/oxidation of amine[3] or azide,[4] functional group directed nitration[5] etc., have been developed till now to overcome those shortcomings.

Quinolone scaffold is charm of medicinal chemistry as it constitutes major structural and functional components of drugs with varied applicability. A bevy of popular drugs dominating the market for more than four decades are based upon the quinolone ring system as the basic pharmacophore. Slight variation in the substituent nature or position (Figure 6.1) brings inconsiderable to magnificent potency of the quinolone based drugs. It enables effective structure activity relationship studies and hence tuning of requisite therapeutic properties. This is one of the reasons that these moieties have emerged with great success in the arena of drug chemistry. Medicinal activities of many nitroheterocycles including nitrofuranylamides, nitroimidazoles, nitroimidazopyran and 5-nitro-2, 3-dihydroimidazo-oxazole have been reported.[6] Therefore nitration in quinolones is also anticipated to enhance drug efficiency. Very limited, mostly 6-nitro derivatives of 4-quinolones have been synthesized and their medicinal values are evaluated so far.[7,8] Many nitroquinolone derivatives have been reported to possess antifilarial, antiviral, antitumor and antibacterial capabilities.[7] 4-quinolone based drug chemistry has flourished with prolific developments. Nevertheless, synthesis and study of nitroquinolones is still limited. Majority of reported nitroquinolones bear nitro substituent at 6-position of the 4-quinolone skeleton and effects of nitration at 5 and 7 positions are not extensively explored. Many 4-quinolones with 3-carboxylic acid, carboxamide, or carboxylate substitution are reported to have vital pharmacokinetic applicabilities.[9] Hence we have chosen various ethyl-4-quinolone-3-carboxylate derivatives to study the orientation effects of different C-6 and C-8

substituents on nitration and we also report tuning of regioselectivity by varying the –N protecting groups in these systems.

Many theoretical investigations on various regioselective reactions are available in literature.[10] Scales et.al.,[10b] have studied the regioselective nucleophilic substitution of unsymmetrical 3,5-dichloloropyrazine. It has been observed that the electron withdrawing groups at 2-position in pyrazine direct substitution at 5-posititon, while for the presence of electron donating groups substitution occurs at 3-position. The experimental surveillance is well correlated with theoretical rationalization using Fukui indices. Zhang et.al., have investigated the metal controlled cycloaddition of 2-alkynyl-1, 4-benzoquinones and electron rich styrenyl systems.[10a] Their DFT study shows that the regioselectivity of the cycloaddition results from the divergent activation modes of catalysts $Bi(OTf)_3$ and AuCl. Kasende et.al,[10c] studied extensively the regioselectivity of the interaction of two pyrimidone isomers with two series of ligands namely boron lewis acids and alkali lewis acids. According to the molecular electrostatic potential (MEP) map and natural bond orbital analysis, a strong regioselectivity was observed for boron acids interaction preferring the N site in both pyrimidone isomers.

In the present contribution we have investigated the complete regioselective nitration of 4-quinolones. It has been found that the selectivity can easily be tuned by proctecting the free N-H group of 4-quinolone. Choice of protecting groups are screened with the help of DFT based reactivity descriptors Fukui function and local softness calculation. Moreover, our theoretical predictions are well synchronized with the experimental findings.

6.2 Computational methodology

All calculations were performed at the (U)B3LYP level using the Gaussian 03 W quantum chemical package[11] using the 6-31G(d,p) basis set. Reactivity of any molecule at a specific site can be determined by local reactivity indices such as Fukui function,

local softness and so on. The Fukui function (f_k^i), instigated in DFT by Parr and Yang,[12,13] is the most important local reactivity index. Regioselectivity for nucleophilic or electrophilic attack at site k can be ascertained through evaluation of Fukui function (f_k^i)[12,14] and can be estimated using population analysis as

$$f_k^+ = [\rho_k(N+1) - \rho_k(N)] \quad \text{for nucleophilic attack} \qquad (6.1)$$

$$f_k^- = [\rho_k(N) - \rho_k(N-1)] \quad \text{for eletrophilic attack} \qquad (6.2)$$

where $\rho(N)$ and $\rho(N-1)$ are the electron densities of the N+1, N and (N−1) electron systems respectively.[15,16] Local softness (s_k^i)[12,14] is another parameter in analyzing the regioselectivity, which is related to Fukui function as $s_k^i = f_k^i.S$ with $i = +$ or $-$, where S is the global softness given as $S=1/2\eta$ where η is the global hardness.[17] In this study we have calculated electrophilic Fukui function (f_k^-) and local softness (s_k^-) at different sites of a molecule.

6.3 Results and discussion

Density functional theory provides a very convenient framework for the discussion of chemical reactivity. Fukui function (f_k^i) and local softness ($s_k i$) are two reliable reactivity parameters to predict and interpret the regioselectivity of a reaction. In this work we have investigated the probable sites of nitronium ion addition of assorted ethyl-4-quinolone-3-carboxylate derivatives and their corresponding N substituted analogs. For this rationale we have calculated nucleophilic Fukui functions (f_k^-) and local softness (s_k^-) of all the compounds. The detail results of the nucleophilic Fukui function (f_k^-) and local softness (s_k^-) calculations are shown in Table 6.1and 6.2.

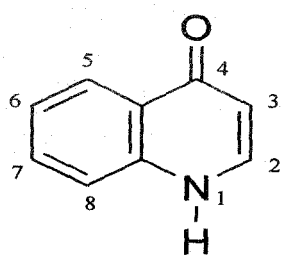
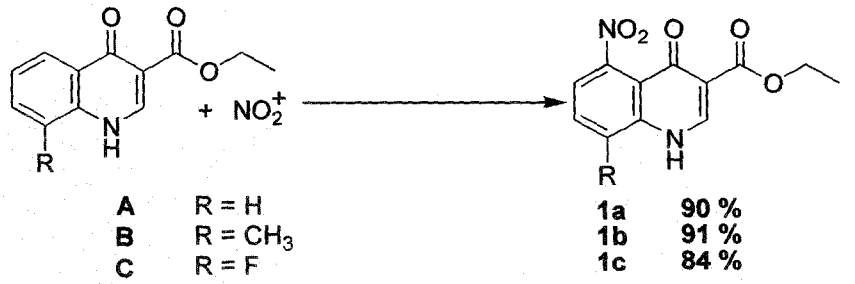


Figure 6.1 Structure of quinolone.

Our study begins with the prediction of the reactive sites for nitronium ion addition to 4-quinolone 3-carboxylate. The unsubstituted 4-quinolone 3-carboxylate **A** has been selected as a model compound for this study.

Scheme 6.1



A R = H
B R = CH_3
C R = F

1a **90 %**
1b **91 %**
1c **84 %**

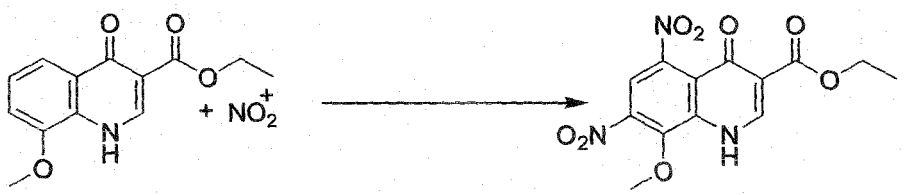
Table 6.1 Fukui function (f_k^-) and local softness (s_k^-) calculation at UB3LYP/6-31G(d,p).

Entry	Fukui functions				Local softness				Theoretically Preferred Carbon	Experimentally Preferred Carbon
	C-5	C-6	C-7	C-8	C-5	C-6	C-7	C-8		
A	0.043	0.030	0.015	-	0.244	0.170	0.085	-	C-5	C-5
B	0.038	0.027	0.019	-	0.218	0.155	0.109	-	C-5	C-5
C	0.042	0.026	0.020	-	0.240	0.149	0.114	-	C-5	C-5
D	0.037	0.025	0.027	-	0.214	0.145	0.156	-	C-5	C-5 & C-7
E	0.034	0.028	0.022	-	0.199	0.164	0.129	-	C-5	C-5
F	0.021	0.017	0.028	-	0.124	0.100	0.165	-	C-7	C-7
G	0.041	-	0.018	0.042	0.236	-	0.104	0.242	C-8	C-8
H	0.032	-	0.013	0.025	0.183	-	0.074	0.143	C-5	C-5
I	0.038	-	0.015	0.037	0.220	-	0.087	0.214	C-5	C-5

From Table 6.1, it is evident that for reactant **A** (Scheme 6.1), the preferable site for electrophilic attack is at C-5 as this carbon possesses higher reactivity indices (f_k^-=0.043, s_k^-=0.244) than the other probable sites C-6(0.030, 0.170) and C-7(0.015, 0.085). So, it has been predicted that compound **A** on nitration results 5-nitro quinolone derivative. Similar to **A**, different substituted 4-quinolones **B** and **C** possess higher values of reactivity indices at C-5 position (Table 6.1) than the other plausible sites.

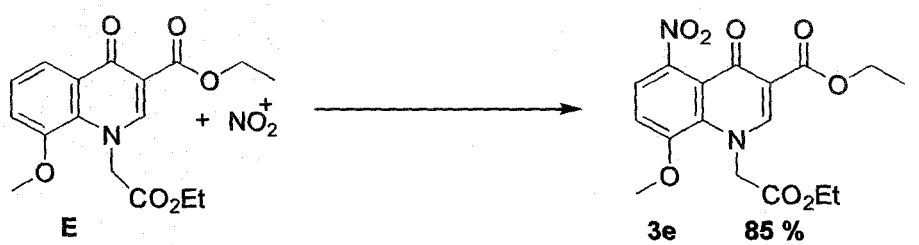
Experimentally these results have also been verified. Consequently compound **A** on nitration with mixed acid at ambient condition results in 90 % yield of the corresponding 5-nitro derivative (1a) upon isolation. In the similar situation **B** and **C** smoothly undergo selective nitration to furnish the desired 5-nitro products with excellent yields (91% and 84% respectively). These results clearly show that the presence of electron donating group ($-CH_3$) and strong electron withdrawing group (-F) literally have no significant role in defining the position of incoming electrophile (nitronium ion).

Scheme 6.2



Then we have studied the selective nitration of another model compound **D** (Scheme 6.2). According to the DFT calculation (Table 6.1), for compound **D** the order of nucleophilicity of the possible reacting sites is C-5 (0.037, 0.214)>C-7 (0.027, 0.156)>C-6 (0.025, 0.145). It reveals that for electrophilic attack the most reactive site is C-5, then comes C-7 and C-6 is the least one. It has been observed experimentally that nitration of compound **D** always results in the corresponding 5, 7-dinitro quinolone derivative (2d). To bring a control over it, nitration was carried out at lower temperature ($0^{\circ}C$) but the second nitration could not be stopped. This is probably the methoxy group which facilitates the second nitration in its ortho position.

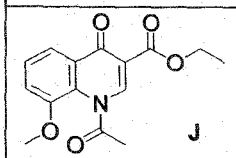
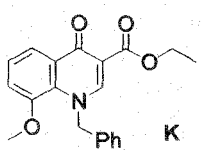
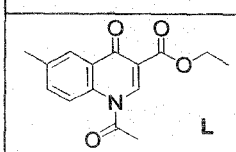
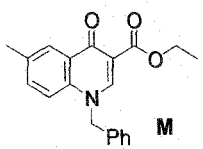
Scheme 6.3



However this observation stipulates us to develop a regioselective nitration technique. Accordingly, an additional functional group has been introduced so that it

could reduce the reactivity of the parent compound **D** and thereby restrict the second nitration. Selection of the protecting group has been done with the help of conceptual density functional theory (DFT) calculation. It is clear from theoretical rationale (Table 6.1 and 6.2) that either an alkyester or $-CH_2Ph$ group can be chosen as protecting

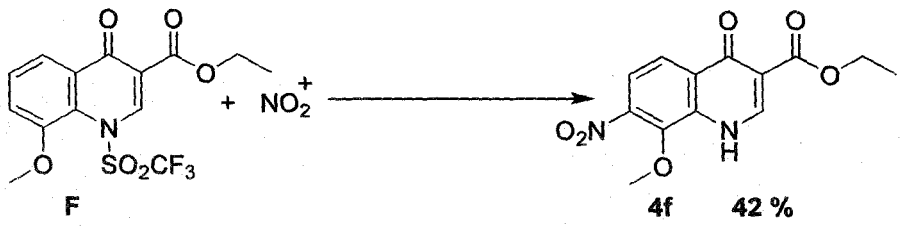
Table 6.2 Fukui function (f_k^-) and local softness (s_k^-) calculation at UB3LYP/6-31G(d,p).

Entry	Sites	Fukui function(f_k^-)	Local softness (s_k^-)	Theoretically preferred carbon
 J	C-5	0.0215	0.1311	C-7
	C-6	0.0173	0.1055	
	C-7	0.0293	0.1786	
 K	C-5	0.0330	0.1938	C-5
	C-6	0.0284	0.1668	
	C-7	0.0163	0.0957	
 L	C-5	0.0298	0.1817	C-5
	C-7	0.0187	0.1140	
	C-8	0.0272	0.1655	
 M	C-5	0.0383	0.2430	C-5
	C-7	0.0134	0.0848	
	C-8	0.0377	0.2391	

group of free N-H to restrict the second nitration. From Table 6.1, it is evident that for compound, **E** (Scheme 6.3) C-5 possesses higher Fukui function and local softness (f_k^-=0.034, s_k^-=0.199) than the other possible sites C-6 (0.028, 0.164) and C-7 (0.022, 0.129) i.e., C-5 is more prone to electrophilic attack than the other sites. For experimental verification we have selected the alkyester group for the protection of free N-H group as the resulting moiety **E** can serve as an amino acid precursor. Indeed nitration of

compound **E**, selectively results in the corresponding 5-nitroderivative (3e) in excellent yield (85%) upon isolation.

Scheme 6.4

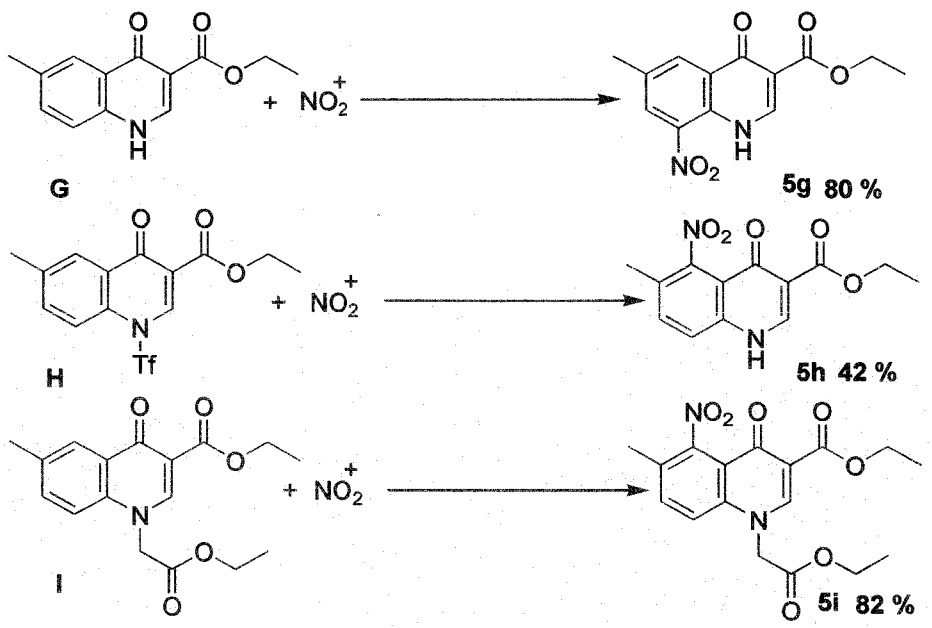


Now the remaining major challenge is the introduction of nitro group selectively at 7-position of the same moiety (compound **D**). Screening of several protecting groups with the help of conceptual DFT, we found $-SO_2CF_3$ may be chosen in this case (Table 6.1). As for $-SO_2CF_3$ N-protecting group C7 is susceptible for electrophilic attack having highest reactivity indices ($f_k^- = 0.028$, $s_k^- = 0.165$) than the other probable sites C5 (0.021, 0.124) and C6 (0.017, 0.100). Theoretical prediction is followed by experimental justification. Accordingly the parent compound **D** on treatment with triflic anhydride in the presences of tetrabutylammoniumhydrogensulfate results in desired *N*-protected 4-quinolone **F** in moderate yield. Compound **F** on nitration results in mono substituted, 7-nitro derivative selectively with excellent yield (Scheme 6.4). Thus our theoretical predictions are again is in good accordance with experimental rationalization.

The above study showed that *N*-protecting group plays a vital role for defining the position of nitration. Validity of it was further justified using another model compound **G**, where methyl group present at 6-postion (Scheme 6.5). DFT calculation suggests that the most preferred position for the nitration of compound **G** is C-8 as it possesses higher values of Fukui function and local softness ($f_k^- = 0.042$, $s_k^- = 0.242$) than the other feasible sites C-5(0.041, 0.236) and C-7(0.018, 0.104). But the position can be altered if the free N-H be protected with any of the four groups triflate, alkylester, amide and $-CH_2Ph$ (Table 6.1 and 6.2). The theoretical prediction is validated when nitration of compound **G** produces 8-nitro derivative (5g) in quantitative yield. Based on the theoretical analysis the free N-H group has been protected with triflate and alkylester and nitration has been

carried out on the protected forms (compound **H** and **I**). In fact, nitration results in the desired 5-nitro derivatives in almost quantitative yields. So based on our theoretical predictions, we have achieved selective nitration of different quinolone derivatives at 5 and 8 positions.

Scheme 6.5



6.4 Summary

In this work, we have presented a study on the regioselectivity of nitronium ion addition to 4-quinolones using DFT based reactivity descriptors. Fukui function and local softness are calculated for different model compounds (**A-M**). From theoretical analysis we have found that regioselectivity can easily be tuned by selective protection of free – NH group. Moreover our theoretical predictions are justified by experimental rationalizations. Good agreement was found when comparing the predicted regioselectivities with experimental data. Finally this selective nitration allows introducing nitro group in the diverse position of the 4-quinolone ring and this study will

definitely be useful for the target synthesis of new bioactive molecules based on the 4-quinolone system.

6.5 References and notes

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