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The chemical reactivities of DOPA and dopamine derivatives and their regioselectivities upon oxidative nucleophilic trapping

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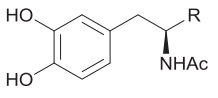
ABSTRACT

The chemical reactivities of four catecholamines, *N*-acetyl dopamine (NADA) and its dehydro derivative (NAΔDA), *N*-acetyl 3,4-dihydroxy-phenylalanine methyl ester (NADOPAME) and its dehydro derivative (NAΔDOPAME), under oxidative nucleophilic trapping and polymerisation conditions were compared and contrasted. Despite their structural similarities, varying reactivities and regioselectivities for oxidative nucleophilic trapping with ethanethiol were observed. This has possible implications on the use of these natural building blocks and their derivatives in the design and synthesis of biomimetic materials.

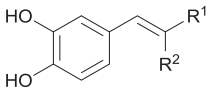
1. Introduction

Nature is remarkable in its ability to develop various materials for different functions and properties using seemingly simple building blocks. Such materials have been a source of inspiration for the design and synthesis of highly efficient and functional materials for various applications, e.g., functional coatings that are scratch resistant, materials for energy storage and so on. One of the most widely studied biomimetic materials is the material derived from dopamine (DA), a naturally occurring building block. The many applications of polydopamine are a source of continual wonder and have recently been reviewed.[1–7] In nature, *N*-acetyl dopamine (NADA) and *N*-acetyl dehydro dopamine (NAΔDA) are implicated in cuticular hardening.[8–10] Interestingly, a related catecholamine, dehydro 3,4-dihydroxy-phenylalanine is also a potential sclerotizing intermediate with its origin from L-3,4-dihydroxy-phenylalanine (L-DOPA).[11] Nature is 'economic' in this regard as these structurally related sclerotizing precursors can be derived from a common precursor tyrosine, and yet each gives rise to cuticles that have different hardness and colors.[8] This raises the interesting question as to how these catechols are different in terms of their reactivities and selectivities towards nucleophiles, which in turn may explain how these sclerotizing precursors can lead to materials of different hardness and strengths.

DOPA containing proteins have bioadhesive and sclerotizing functions in a number of invertebrates. In the former, DOPA proteins are known to be present in the attachment tendon of mussels,[2] and cements in certain Annelida species.[12,13] Their roles as sclerotizing precursors, e.g., in the egg case of parasitic trematodes, is responsible for the strength and durability of many structural materials found in nature.[12,14]



NADOPAME (1): R = COOMe
NADA (2): R = H



NAΔDOPAME (3): R^1 = COOMe, R^2 = NHAc
NAΔDA (4): R^1 = NHAc, R^2 = H

The oxidation chemistry of NADA[15–18] and NAΔDA[19–22] has been studied while that of NADOPAME[23] and NAΔDOPAME[23] is less explored. Despite these reports, the oxidation chemistry of these catecholamines cannot be easily compared in view of the varying conditions reported. Our interests stem from the desire

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to understand the chemistry of these catecholamines with the future goal of exploiting this in biomimetic material engineering. In this study, the reactivities of the four catecholamines towards oxidation, followed by nucleophilic trapping by ethanethiol are compared. The ease of polymerisation of these catecholamines under oxidative conditions was also investigated.

2. Results and discussion

2.1. Oxidative nucleophilic trapping studies of catecholamines

Our initial studies examined the oxidation of the catecholamines using three chemical oxidants, followed by in situ trapping with five equiv of ethanethiol. Oxidation of the catecholamines using sodium periodate was first attempted. Although this gave nearly full conversion to quinone (for NADOPAME and NADA as shown by NMR spectroscopy), the subsequent nucleophilic trapping by ethanethiol led to the formation of multiple products which could not be readily separated. In contrast, the use of silver oxide and DDQ as oxidants followed by trapping with ethanethiol gave cleaner reaction mixtures. Of the two oxidants, the use of silver oxide is more convenient as the oxidant can be filtered off prior to the addition of the nucleophile. This avoids complications associated with the presence of residual oxidants which may interfere in the oxidative nucleophilic trapping studies. The results are summarised in Table 1.

To rationalise the observed regioselectivities, attempts were made to identify the intermediates from oxidation. Thus, oxidation of each of the four catecholamines using silver oxide as oxidant was studied via spectrophotometric means (see ESD). For NADOPAME, NADA and NAΔDOPAME, the ortho-quinone was formed as evidenced by an absorption maximum of ca. 400 nm, as reported by others.[20,24,25] This ortho-quinone is relatively stable over 60 min. In the case of NAΔDA, the absorption maximum occurs at 485 nm which is the characteristic of a quinone methide[22] – this quinone methide imine amide is relatively unstable and decays rapidly over a 60-minute period. The formation of the quinone methide imine amide from the ortho-quinone of NAΔDA has been reported as a rapid enzymatic[22] as well as a chemical mediated isomerisation.[20] The analogous quinone methide imine amide of NAΔDOPAME was not observed. Schemes 1 and 2.

In the oxidative nucleophilic trapping studies with NADOPAME, NADA and NAΔDOPAME using silver oxide as the oxidant and ethanethiol as the nucleophile, a small amount of the starting catechol and the di-substituted adducts were isolated (Schemes 1 and 2). According to Huang et al., the oxidation potentials of NADA, its mono-substituted adduct, and its di-substituted adduct decrease in order of increasing substitution.[16] Hence, the observation above is believed to arise from the re-oxidation of the mono-substituted adduct by the intermediate catecholamine quinones, followed by a second nucleophilic substitution onto the quinone of the mono substituted adduct. To prove this, 1 equiv of 5-SEt NADA adduct (**6**) was added to freshly prepared NADA quinone in deuterated acetone. An immediate colour change was observed and the ^{1}H NMR spectrum of the reaction mixture after 3 min showed the presence of NADA (**2**) and 5-SEt NADA quinone. This is consistent with the notion of the redox reaction as shown in Scheme 3 and potentially explains the similar observations for the other three derivatives.

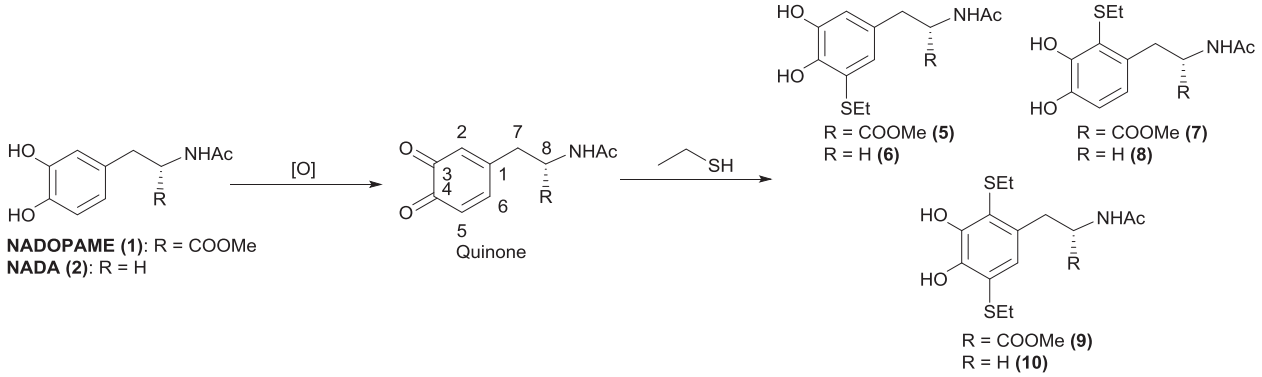
2.2. Semi-empirical calculations for predictions of regioselectivity

The semi-empirical method PM6[26] was used to calculate the LUMO coefficients of the atoms of both the ortho-quinone and the quinone methide or quinone methide imine amide for each of the catecholamines as summarised in Table 2 using Gaussian09.[27] In the case of NADOPAME quinone and NADA quinone, the size of the LUMO orbital coefficients are in the order of decreasing size, i.e., C-

Table 1
Reaction conditions, ratio and yields for DOPA and DA derivatives under different oxidation conditions followed by addition of 5 equiv of ethanethiol

Catechol derivatives	Reaction conditions[a]	Ratio of compounds and isolated yield (recovered SM)
NADOPAME (**1**)	5 *eq.* Ag_2O, acetone, RT, 30 m	**5:7**=2:1, 80%, **9**=7% (**1**=10%)
	1.2 *eq.* DDQ, THF, −40 °C, 1 h	**5:7**=2:1, 81% (**1**=7%)
NADA (**2**)	5 *eq.* Ag_2O, acetone, RT, 30 m	**6:8**=7:1, 70%, **10**=3% (**2**=3%)
	1.2 *eq.* DDQ, THF, −40 °C, 1 h	**6:8**=6:1, 72%, **10**=1% (**2**=4%)
NAΔDOPAME (**3**)	5 *eq.* Ag_2O, acetone, RT, 30 m	**11:12**=1:5, 18%, **13**=2% (**3**=8%)
	1.2 *eq.* DDQ, THF, −40 °C, 1 h	**11:12**=3:7, 86% (**3**=13%)
NAΔDA (**4**)	5 *eq.* Ag_2O, acetone, RT, 10 m	**14:15:17:18**=1:2:2:3, 8% (**4**=35%)
	1.2 *eq.* DDQ, THF, −40 °C, 1 h	**16:17:18**=3:2:3, 8%
	1 *eq.* Ag_2O, MeOH, RT, 1 h[b]	**18**=40%

[a] Ethanethiol was added after the specified time.
[b] In the absence of ethanethiol, SM=starting material.



Scheme 1. Oxidative nucleophilic trapping studies with NADA and NADOPAME.