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Mechanism of base-catalyzed autooxidation of corticosteroids containing 20-keto-21-hydroxyl side chain

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ABSTRACT

Corticosteroids and related compounds containing the 20-keto-21-hydroxyl side chain such as betamethasone, betamethasone 9,11-epoxide, dexamethasone, and dexamethasone 9,11-epoxide have been found to undergo facile autooxidation on the 1,3-dihydroxyacetone side chain of their D-rings under strong alkaline conditions to yield five main degradants (17-formyloxy-17-acid, 17-acid, 21-aldehyde, 20-hydroxy-21-acid, and 17-ketone). The rate of the autooxidation was correlated with the strength and concentration of the base used in the reaction. A novel mechanism for the observed autooxidation is proposed, in which the facile oxidation of the presumed enolate (resulting from the carbanion at the 21-position) by molecular oxygen is the key step. The proposed autooxidation mechanism, supported by LC–MS isotope experiments using $^{18}O_2$ as the oxidant, can satisfactorily explain the oxidative degradation patterns observed for corticosteroids containing the 20-keto-21-hydroxyl side chain.

1. Introduction

Forced degradation studies (or stress studies) under various degradative conditions are recommended by the International Conference on Harmonization (ICH) guidelines during pharmaceutical development of a drug candidate in order to assist in the understanding of the stability and/or degradation behavior/pathways of the drug candidate under long-term stability storage conditions.[1] Acid and base are typically employed to accelerate the evaluation of hydrolytic stability of a chemical entity; nevertheless, non-hydrolytic degradation may also occur and sometimes can become the dominant degradation process. For example, it has been reported that rofecoxib undergoes rapid oxidation under alkaline conditions; a mechanism involving oxidation of the rofecoxib enolate by molecular oxygen was proposed, which appears to be consistent with the presumption that free radical is not involved during the rather facile oxidation observed.[2] During our recent forced degradation studies of betamethasone (**1**, Fig. 1), an anti-inflammatory corticosteroid, and its related compounds under strong alkaline conditions, it became evident that betamethasone and its analogues containing the 20-keto-21-hydroxyl side chain undergo facile autooxidation. In this Letter, we present the evidence[3] for this relatively less known oxidative degradation process along with a proposed novel degradation mechanism in which the facile oxidation of the presumed enolate (resulting from the carbanion at the 21-position) by molecular oxygen is the key step. The proposed mechanism can satisfactorily explain the autooxidative degradation patterns reported for structurally similar corticosteroids containing the 20-keto-21-hydroxyl side chain during the past several decades.[4–7] A clear understanding of the autooxidation mechanism should greatly facilitate pharmaceutical development and/or improvement of drug products containing these corticosteroids as they continue to be a very critical class of therapeutic agents.

2. Initial forced degradation studies

For the initial forced degradation study of betamethasone under an alkaline condition, approximately 5 mg of betamethasone (**1**) was dissolved in 3 mL of acetonitrile, followed by addition of 100 μL of 1 N NaOH in water. The resulting solution was monitored at room temperature by LC–MS.[8] Two main oxidative degradants, betamethasone 17-formyloxy-17-acid (**10**, *m*/*z* 407) and betamethasone 17-acid (**11**, *m*/*z* 379),[9] were formed with the yields of ~10% and 20%, respectively, 60 min after the base was added (Fig. 2). The initial observation that **1** might be susceptible to autooxidation relatively easily under the alkaline condition led us to design a more systematic study in order to elucidate the oxidation mechanism. When the reaction was performed using a 1 N NaOH solution in methanol in place of the original 1 N NaOH aqueous solution, the autooxidation was found to proceed much faster: no **1** was detected in 30 min (Reaction 3 in Table 1). In addition to **11** (37% yield), a new oxidative degradant, betamethasone 21-aldehyde (**7**, in the form of its hydrate as detected by LC–MS), was observed along with the

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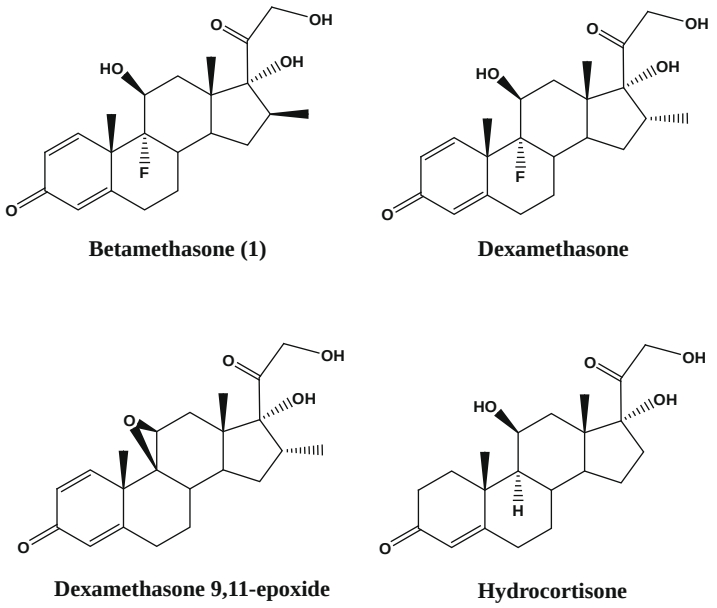


Figure 1. Structures of betamethasone and related compounds, dexamethasone, dexamethasone 9,11-epoxide, and hydrocortisone.

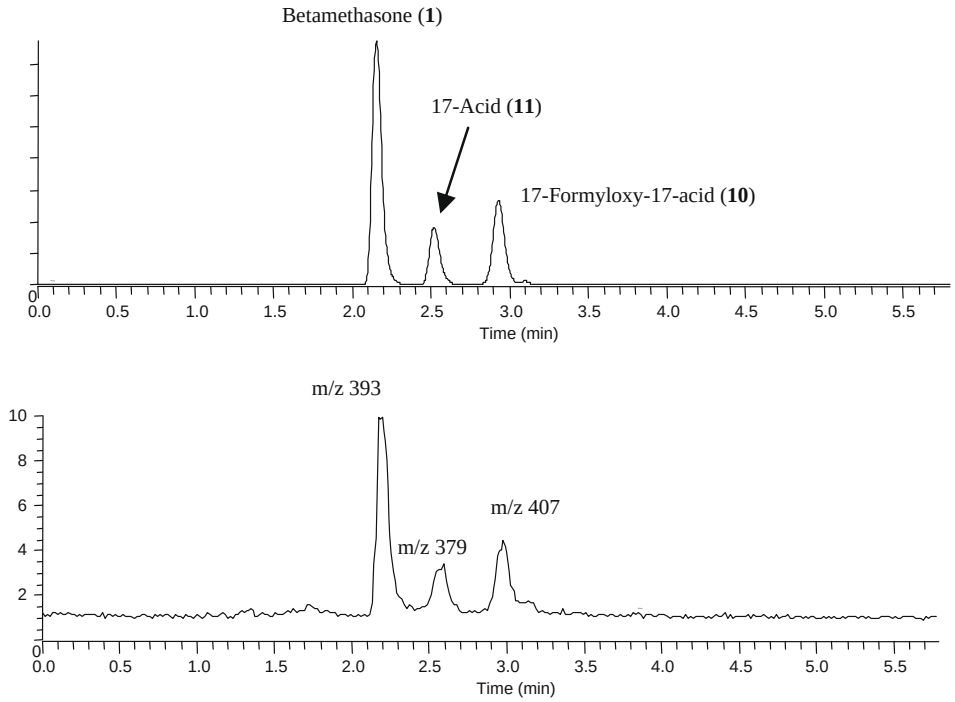


Figure 2. Autooxidation of betamethasone (**1**) under alkaline condition: ~5 mg of betamethasone (**1**) was dissolved in 3 mL of acetonitrile, followed by addition of ~100 μL of 1 N NaOH in water. LC–MS analysis was performed 60 min after the base was added.[6] Top: UV chromatogram at 240 nm. Bottom: the corresponding MS (total ion) chromatogram showing the molecular ions of the starting material (**1**, *m*/*z* 393) and the two oxidative degradants, betamethasone 17-formyloxy-17-acid (**10**, *m*/*z* 407) and betamethasone 17-acid (**11**, *m*/*z* 379).

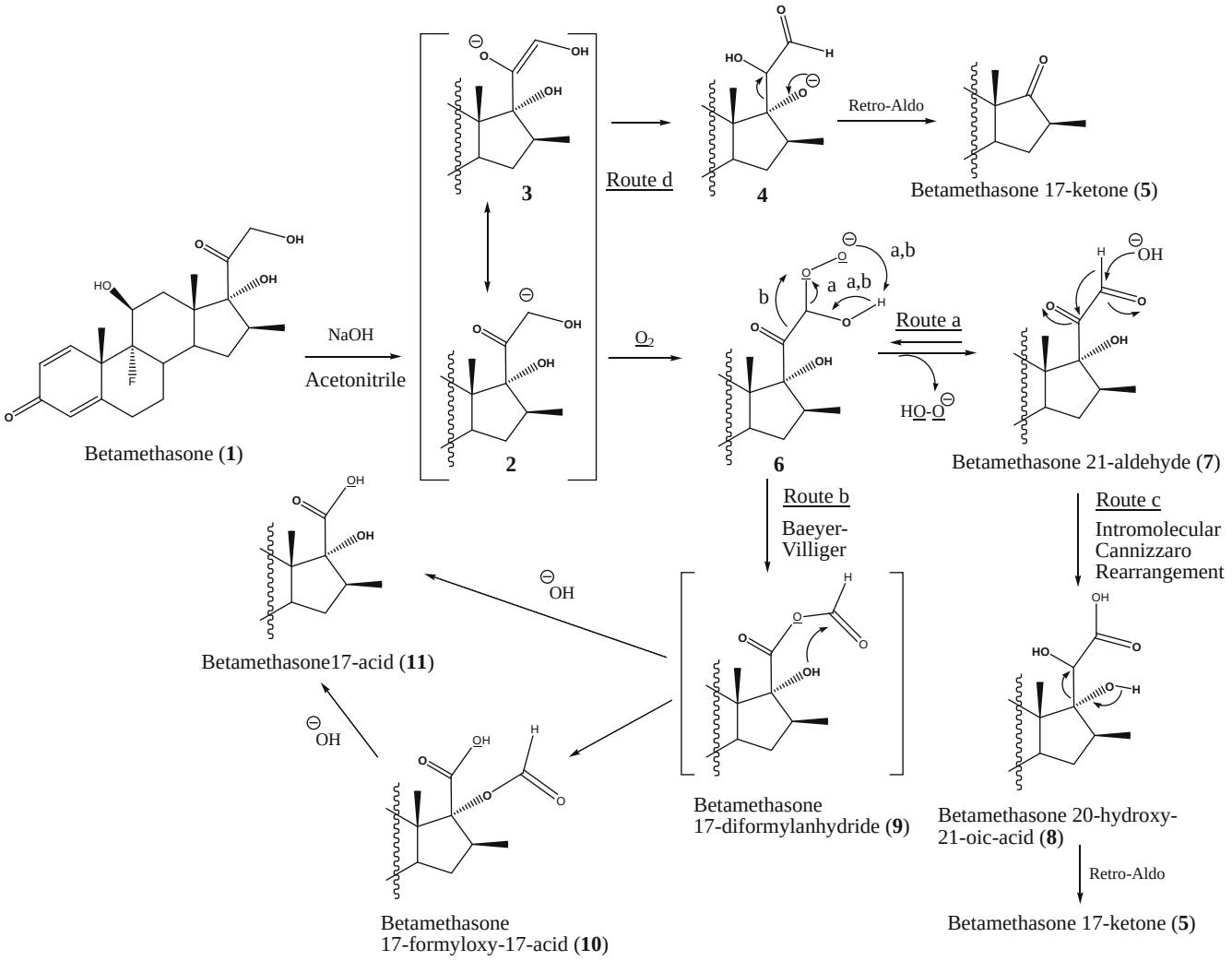
isomer of its hydrate form (**7** and **8**, in a ratio of ~1:3, were formed in 46% yield collectively) and 17-ketone (**5**, 17%). Further study suggested that this isomer (**8**) of betamethasone 21-aldehyde hydrate is very likely betamethasone 20-hydroxy-21-acid which would be formed from 21-aldehyde via hydration and a subsequent intramolecular Cannizzaro rearrangement (Scheme 1). Edmonds et al. reported the conversion of dexamethasone 21-aldehyde to dexamethasone 20-hydroxy-21-acid in strong alkaline aqueous solution.[6] Indeed, when a 1.5 mL solution of **7** in acetonitrile was treated with 50 μL of 1 N NaOH in methanol at room temperature, **7** was completely converted to **8** within ~10 min.

When subjected to the same stress condition mentioned above, three steroids such as betamethasone 9,11-epoxide, dexamethasone, and dexamethasone 9,11-epoxide which are structurally related to **1** were found to undergo the same base-catalyzed autooxidation. In order to verify that molecular oxygen is the oxidizing agent, we repeated the reaction with **1** using the NaOH solution in methanol under the condition in which oxygen was largely excluded by bub-

Table 1
Based-catalyzed autooxidation of betamethasone (**1**): impact of the strength of the base

Reaction[a]	Base used[b]	Betamethasone% (**1**) reacted	Distribution of degradation products			
			17-Ketone (**5**)	21-Aldehyde (**7**)/20-hydroxy-21-acid (**8**)[c]	17-Formyloxy-17-acid (**10**)	17-Acid (**11**)
1	Triethylamine	0	—	—	—	—
2	LiOH	~20%	10%	ND	ND	90%
3	NaOH	>99%	17%	46%	ND	37%
4	KOH	100%	11%	6%	3%	80%
5	NaOMe	100%	24%	8%	ND	68%

[a] All bases were dissolved in solutions of MeOH at a concentration of ~1 M. An aliquot of the base (50 μL) was added to a 1 mL solution of **1** in acetonitrile (1 mg/mL) and the reaction was monitored at room temperature by LC–MS[8] 30 min after the base was added. The molar concentration ratio of the base and **1** is ~20:1.
[b] The strengths of the bases are in the following order: NaOMe > KOH > NaOH > LiOH > triethylamine.[10]
[c] Under the current LC–MS condition, **7** and **8** co-eluted. With a modified LC–MS method, **7** and **8** were found to form in a ratio of ~1:3 in Reaction 3.



Scheme 1. Proposed mechanism for the base-catalyzed autooxidation of betamethasone and related degradation reactions. The two acids (**8** and **11**) should exist as their carboxylate forms in the basic stress conditions.

bling all the reagent solutions with nitrogen for ~3 min and the reaction was then carried out under a nitrogen atmosphere. Under this essentially anaerobic condition, oxidation of betamethasone (**1**) was mostly inhibited for 30 min at room temperature.

3. Strength of the base and solvent effect

Based on the results from the initial base stress studies outlined above, it appeared that the strength of the base, which should be impacted by the reaction medium, might play a critical role in the facile autooxidation observed. Hence, four bases of different strengths, triethylamine, LiOH, KOH, and NaOMe, were also evaluated in the base-catalyzed autooxidative degradation. The results as summarized in Table 1 show that the autooxidation is correlated to the strength of the bases used:[10] triethylamine, a weak base, did not give any reaction; with LiOH, a relatively weak alkali metal base, ~20% of **1** was consumed; NaOH, KOH, and NaOMe, all very strong bases, caused all of **1** to react.

All the reactions described so far were carried out in a medium consisting of mostly acetonitrile, an aprotic solvent, with a tiny

fraction of either of the protic solvents, that is, water and methanol, introduced as part of the base solutions. The solvent effect toward the autooxidative degradation catalyzed by NaOH was evaluated with two additional aprotic solvents, acetone and tetrahydrofuran (THF), versus MeOH, a protic solvent. When the forced degradation was performed in MeOH instead of acetonitrile while the concentration of the base remained the same, essentially no reaction was observed within 2 h. When the same reaction was carried out in acetone and THF, respectively, similar reaction product distribution and reaction rates (vs Reaction 3 in Table 1) were observed in 30 min. It is known that the strength of an alkali metal base such as NaOH becomes much stronger in an aprotic environment than in a protic one, primarily due to the fact that hydroxide is not solvated in the aprotic medium.[10] The non-reactivity in MeOH can probably be largely attributed to the much reduced basicity of NaOH in the protic environment. Therefore, the results from the solvent effect study are consistent with those shown in Table 1.

4. Ratio of the base and. betamethasone: impact on the reaction rate and degradation product distribution

The ratio of the base used and betamethasone (**1**) was also studied and three different ratios of the base (1 N NaOH solution in methanol) were used. The reaction rate and degradation product distribution as revealed by LC–MS were compared at different times after the reactions were initiated by addition of the base solutions. The results showed that the rate of the autooxidation increased as more base was used, although the difference between the reactions with the molar ratios of 0.4:1 and 0.8:1 (NaOH and **1**) did not appear to be obvious enough at 50 min (Fig. 3). At the highest amount of the base (4:1) used, only ~2% of **1** remained after just 5 min. In addition, the product distribution also changed significantly: the initially formed 17-formyloxy-17-acid (**10**) had disappeared while 21-aldehyde (**7**)/20-hydroxy-21-acid (**8**) and 17-acid (**11**) continued to increase. On the other hand, 17-ketone (**5**), which was not detected under the lower levels of the base, occurred in significant quantities. Betamethasone 17-ketone (**5**) could be generated by strong base under an anaerobic condition through a retro-aldo pathway that was reported for hydrocortisone.[5] Nevertheless, **5** could also be an oxidative degradant of **1** or one of its degradants such as enol aldehyde based on our experience.[11] In the current study, although it is difficult to tell exactly how **5** was formed as to through which pathway(s), it appears that the majority of **5** should come from the retro-aldo pathway. This speculation is consistent with the current observation that the formation of **5** increased when the highest amount of the base was used (Fig. 3) and/or stronger bases were used (Table 1). In addition, the retro-aldo pathway leading to the formation of **5** could be operative in two places in the current study (Scheme 1): (1) starting from the 21-carbanion of betamethasone (**2**) through 'Route d' and (2) starting from betamethasone 20-hydroxy-21-acid (**8**).

5. Isotope experiments with $^{18}O_2$

Other than 17-ketone (**5**), other degradants observed in the current study are all known oxidative degradants. In order to provide further evidence that the degradation occurred is indeed a base-catalyzed autooxidation, that is, oxidation inflicted upon directly by molecular oxygen,[12] isotope experiments with $^{18}O_2$ were performed using NaOMe in methanol as the base. When compared with the control experiment in which the regular $^{16}O_2$ was used at the molar ratio of NaOMe/**1** at 0.8:1, the $^{18}O_2$ isotope experiment clearly showed that ^{18}O was incorporated into the two oxidative

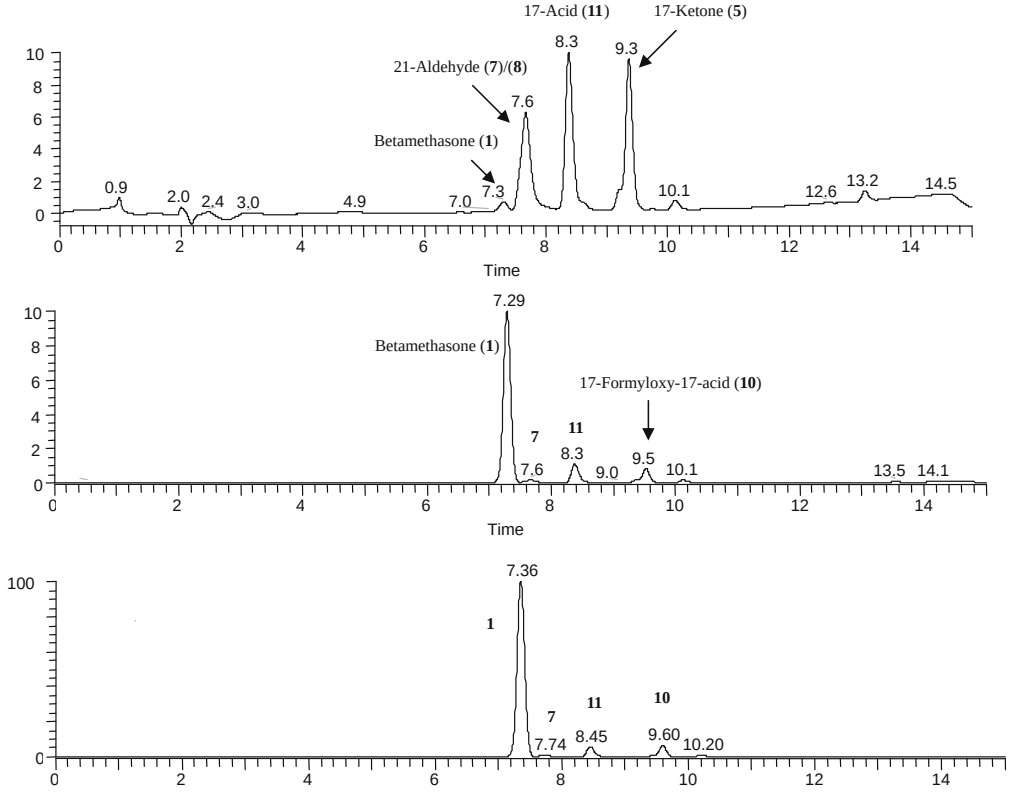


Figure 3. Autooxidation of betamethasone (**1**) using different amounts of base (1 N NaOH solution in methanol). The molar ratio of NaOH and **1** (1 mg/mL in acetonitrile) is approximately 0.4:1, 0.8:1, and 4:1, respectively, from the bottom panel to the top panel. LC–MS analyses[6] were performed at different times after the base was added to the respective reaction solutions: 50 min for the reactions at the bottom and the middle panels and 5 min for the reaction at the top panel.

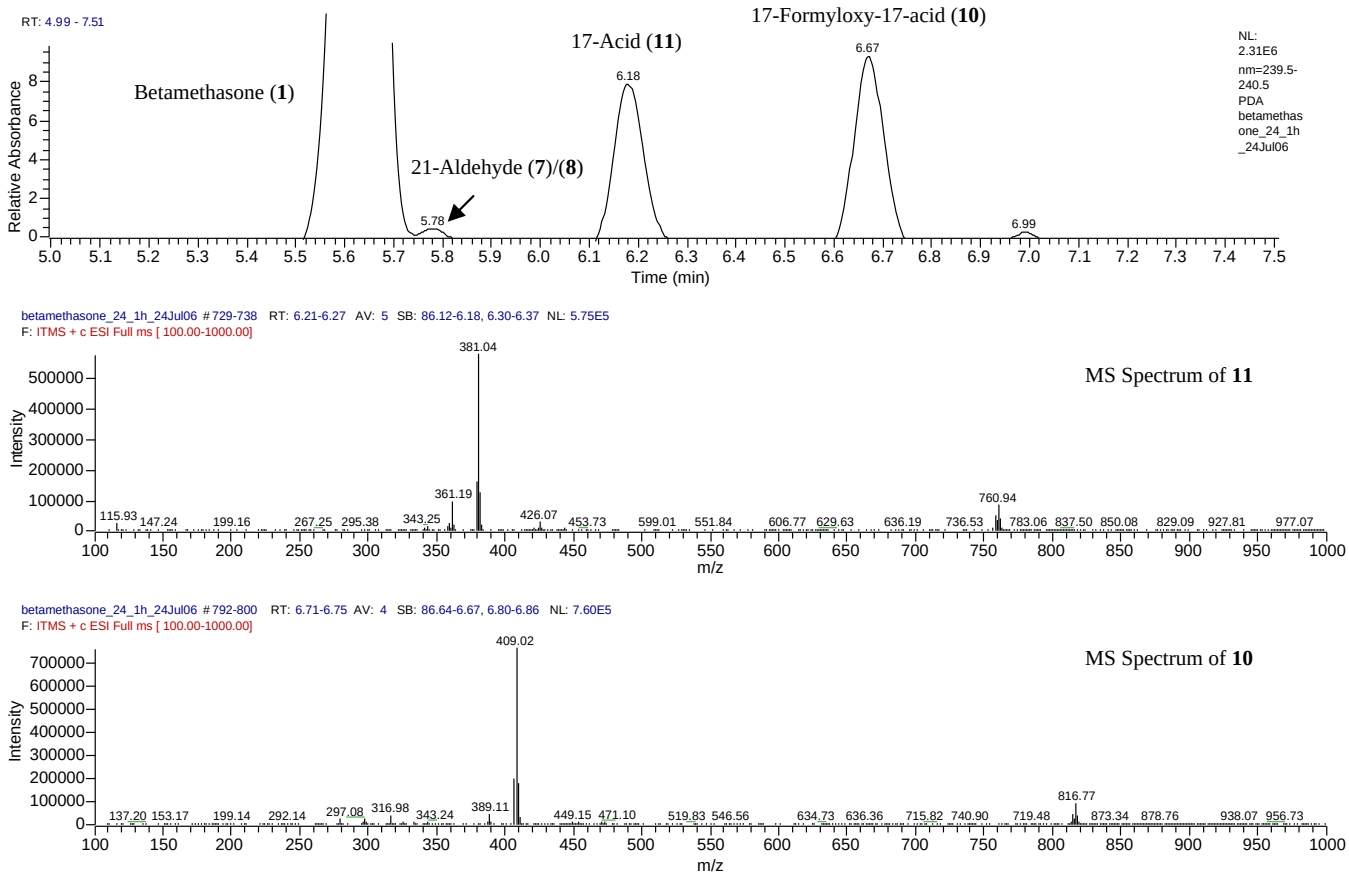


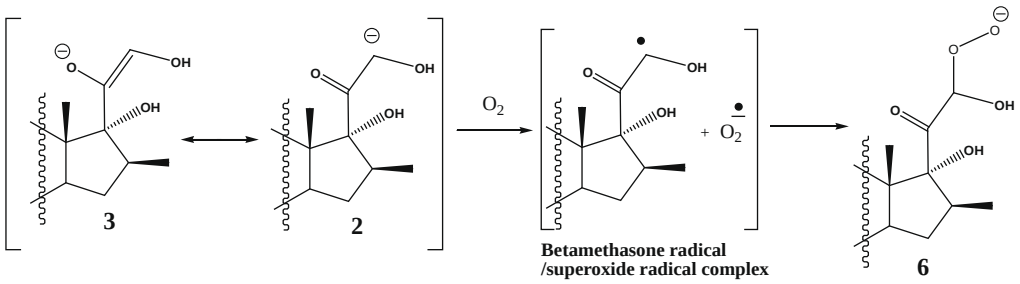
Figure 4. LC–MS analysis of the autooxidation isotope experiments using $^{18}O_2$. A 5 mL solution of betamethasone (**1**) in acetonitrile (1 mg/mL) and a 0.5 M NaOMe solution in methanol were gently bubbled with $^{18}O_2$ for a few min; an aliquot of 10 μL of the NaOMe solution was then injected into the sealed solution of **1**, followed by shaking of the resulting solution for a couple of times. LC–MS analysis was performed 60 min after the base was added.[6] Top: UV chromatogram at 240 nm showing the starting material (**1**), 21-aldehyde (**7**)/20-hydroxy-21-acid (**8**), 17-acid (**11**), and 17-formyloxy-17-acid (**10**), respectively. Middle: MS spectrum of the 17-acid peak displaying the ^{18}O isotope molecular ion at *m*/*z* 381. Bottom: MS spectrum of the 17-formyloxy-17-acid peak displaying the ^{18}O isotope molecular ion at *m*/*z* 409.

degradants, 17-formyloxy-17-acid (**10**) and 17-acid (**11**) since they displayed the corresponding M+2 mass peaks as their molecular ions (Fig. 4). On the other hand, the 21-aldehyde peak did not show ^{18}O incorporation. In a separate isotope experiment in which higher molar ratio of the base was used (20:1), 17-ketone (**5**) was formed as expected; however, ^{18}O was not incorporated into the structure of **5** due to the fact that the original molecular ion of **5** at *m*/*z* 333 was still observed (results not shown). The results from these isotope experiments not only clearly demonstrate the nature of the autooxidation observed but also provide solid evidence required for elucidating the underlying mechanism.

6. Proposed mechanism of the autooxidation by molecular oxygen

Based on all the results obtained, in particular those from the critical isotope experiments, the mechanism of the base-catalyzed degradation is proposed in Scheme 1. In this mechanism, once the carbanion (**2**) is generated through deprotonation by the base, oxidation of the presumed enolate (**3**, resulting from **2**)/carbanion (**2**) by molecular oxygen should give the key peroxide anion intermediate (**6**). Starting from this point, further degradation via 'Route a' would produce 21-aldehyde (**7**) during which process hydrogen peroxide anion (HOO^-) should leave as a by-product. On the other hand, further degradation via 'Route b' would yield the Baeyer–Villiger-type degradant, 17-diformylanhydride (**9**). Due to the fact that **10** and **11** were formed more quickly in the early stage of the reaction than **7** (Fig. 3), it appears that 'Route b' should be the predominant pathway for the formation of **10** and **11**. Under the current alkaline condition, the anhydride (**9**) would undergo a quick rearrangement of the formyl group from the 21-position to the 17-position to give 17-formyloxy-17-acid (**10**) and/or a direct cleavage to yield 17-acid (**11**). The evidence for a 17-diformylanhydride moiety in **9** and the subsequent rearrangement of the formyl group was reported in a study of a pharmaceutical product which contains dexamethasone as the active pharmaceutical ingredient.[13] With the reaction progressing and/or conducted at a higher ratio of the base, **10** should be further degraded to **11** through deformylation. The formation of 17-ketone (**5**), which becomes more significant with stronger and/or more base, is most likely through the known retro-aldo mechanism via 'Route d';[5] nevertheless, it is also possible that some of **5** may result from retro-aldo of **8** as discussed above.

The critical step of the carbanion/enolate oxidation by molecular oxygen proposed in this mechanism is similar to what was proposed by Harmon et al. in their study of autooxidation of rofecoxib enolate by molecular oxygen,[2] although the latter study was conducted in aqueous solutions. One of the key observations in the current study is that the base-catalyzed autooxidation is very fast, which is a strong supporting evidence for the mechanism of the oxidation of carbanion/enolate by molecular oxygen that has already been dissolved in the reaction solvent (acetonitrile). The probability for a free radical-mediated mechanism can be excluded since it needs an induction period which should result in a slow



Scheme 2. The caged free radical mechanism, alternate to the direct pathway as shown in Scheme 1, for the formation of the peroxide intermediate (**6**).

reaction; the same conclusion was also reached by Harmon et al.[2] One inevitable question regarding the direct formation of the hydroperoxide anion (**6**) from carbanion (**2**)/enolate (**3**) is that such a process[14] would violate the spin conservation rule.[15–17] The proposed answer to this paradoxical concern is that **2** would transfer a single electron to molecular oxygen to form a pair of a carbon free radical and superoxide free radical in a 'caged' environment, followed by spin inversion and then combination to produce **6** (Scheme 2). However, regardless of which pathway may be operative, the net result is a very efficient oxidation of **2**/**3** by molecular oxygen which appears to display no induction period during the oxidation. It has been shown in the current study that the rate of the carbanion/enolate oxidation by molecular oxygen is positively correlated to the strength and concentration of the base used. When the base strength is strong (particularly in aprotic solvent) and concentration is high enough, the carbanion/enolate autooxidation appears to be instantaneous (Fig. 3).

Although autooxidation of carbanion/enolate has been studied and reviewed in the literature,[18–20] it seems that its relevancy has been overshadowed by the predominant free radical mechanism as the latter mechanism would automatically be applied by default even though the evidences may be clearly against it.[21] Part of the reason may be that the majority of the work in autooxidation of carbanion/enolate has been conducted with strong alkoxide bases such as potassium *t*-butoxide in organic solvents;[18,20] therefore, the relevance of the work may not become obviously applicable during pharmaceutical development process in which the stability of drug substances is frequently assessed in aqueous media. For example, Hansen and Bundgaard studied degradation pattern of hydrocortisone (Fig. 1) in aqueous solutions at pH between 0 and 11.[5] In basic solution, they found the formation of three oxidative degradants, hydrocortisone 21-aldehyde, 20-hydroxy-21-acid, and 17-acid. More recently, Edmonds et al. reported the formation of the corresponding 21-aldehyde, 20-hydroxy-21-acid, and 17-acid degradants from autooxidation of dexamethasone (the authors' term for autooxidation is aerial oxidation) under various alkaline pH conditions.[6] In both cases, no detailed mechanistic explanation was given regarding the oxidative degradation. Edmonds et al. did compare the oxidation with and without laboratory lighting and found no difference, which eliminated the possibility for the involvement by singlet oxygen.[22] By going through the results obtained by these authors,[4–7] it is apparent that the mechanism proposed here (Scheme 1) can be readily applied to the oxidation of corticosteroids containing 20-keto-21-hydroxyl side chain including hydrocortisone and dexamethasone in various alkaline conditions, in particular at higher pH region where the observed autooxidation is fairly efficient.

In summary, we have proposed a mechanism for the autooxidation of corticosteroids containing 20-keto-21-hydroxyl side chain under alkaline conditions in which direct oxidation of the presumed carbanion/enolate at the 21-position by molecular oxygen is the critical step leading to the formation of the key 21-peroxide anion intermediate (such as **6**). Subsequent pathways from **6** would satisfactorily explain the product distribution among 17-ketone (**5**), 21-aldehyde (**7**), 20-hydroxy-21-acid (**8**), 17-formyloxy-17-acid (**10**), and 17-acid (**11**) under various conditions. The formation of the degradants, analogous to **5**, **7**, **8**, **10**, and **11** from a large number of structurally related corticosteroids such as hydrocortisone and dexamethasone, under alkaline conditions has been reported during the past several decades.[3–5] The current proposed mechanism is able to provide a reasonable explanation for this decades-old observation, despite the fact that our studies were performed in a largely organic solvent environment. Water is a strong protic solvent and as such, its presence will lower the intrinsic basicity of a base leading to slower reaction rate, rendering the carbanion/enolate-mediated autooxidation less obvious but more susceptible to confusion with free radical-mediated autooxidation. It appears that the direct autooxidation of carbanion/enolate by molecular oxygen may play a much more significant role in the oxidative degradation of compounds that contain 'acidic' CH protons.

Acknowledgments

We would like to thank Dr. T. M. Chan's group at Schering-Plough Research Institute for performing all the NMR experiments.

Supplementary data

^{1}H and ^{13}C NMR results of betamethasone 17-acid, betamethasone 21-aldehyde, and betamethasone 17-ketone are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.05.074.

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8. All the reactions studied in this Letter were monitored by LC–MS and/or high-resolution LC–MS. The characterization of the degradants formed during all the forced degradation studies was done through one of the two ways: (1) For the majority of the degradants formed, comparative LC–MS analyses were performed against authentic reference compounds available in-house. (2) In cases where authentic compounds were not available, high-resolution LC–MS characterization was further confirmed by 1D and 2D NMR determination. All

the compounds generated in this study were found to be within 3 ppm of their theoretical formulas by high-resolution LC–MS. The LC–MS analyses were performed under ESI positive mode either on a Thermo Electron Surveyor HPLC system coupled with a PDA detector and an MSQ Plus MS detector or on a Thermo Electron Surveyor HPLC system coupled with a PDA detector and an LTQ MS detector or a high-resolution Orbitrap MS detector, with the MS conditions similar to those published by our group previously: Li, M.; Chen, B.; Lin, M.; T.-M. Chan; Rustum, A. *Tetrahedron Lett.* **2007**, *48*, 3901–3905. The LC conditions of the LC–MS methods used are summarized as follows. (1) For the conditions used in Figure 2, the chromatographic elution was effected isocratically on a Supelco Supercosil ABZ-plus column (25 cm × 4.6 mm ID, 5 μm) with a mobile phase consisting of 55% of A (0.2% acetic acid) and 45% of B (acetonitrile) at a flow rate of 2.0 mL/min. (2) For the conditions used in Figure 3 and Table 1, the chromatographic elution was effected on a Supelco Supercosil ABZ-plus column (25 cm × 4.6 mm ID, 5 μm) with a gradient generated between mobile phase A (0.1% TFA in water) and B (0.1% TFA in acetonitrile) at a flow rate of 1.3 mL/min according to the following program: 0–10 min, 30–60%B; 10.1–15 min, 30%B. (3) The conditions used in Figure 4 were similar to those used in Figure 3 and Table 1, except that the flow rate was 2.0 mL/min and the gradient program was slightly different: 0–10 min, 30–75%B; 10.1–15 min, 30%B.

9. A different nomenclature has been used in the literature for the majority of the degradants mentioned in this Letter. We prefer to use a more descriptive and self-explanatory name such as betamethasone 21-aldehyde. All the compound names we used are listed below along with other conventional names (if available) and the IUPAC names: betamethasone (**1**), (11β,16β)-9-fluoro-11,17,21-trihydroxy-16-methylpregna-1,4-diene-3,20-dione; betamethasone 17-ketone (**5**): (11β,16β)-9-fluoro-11-hydroxy-16-methylandrosta-1,4-diene-3,17-dione; betamethasone 21-aldehyde (**7**), betamethasone glyoxal, 21-dehydrobetamethasone, (11β,16β)-9-fluoro-11,17-dihydroxy-16-methylpregna-1,4-diene-3,20-dione-21-al; betamethasone 20-hydroxy-21-acid (**8**), betamethasone glycolic acid, (11β,16β)-9-fluoro-3-oxo-11,17,20-trihydroxy-16-methylpregna-1,4-diene-21-oic acid; betamethasone 17-formyloxy-17-acid (**10**), (11β,16β,17α)-9-fluoro-17-(formyloxy)-11-hydroxy-3-oxo-16-methylandrosta-1,4-diene-17-carboxylic acid; betamethasone 17-acid (**11**), (11β,16β,17α)-9-fluoro-11,17-dihydroxy-3-oxo-16-methylandrosta-1,4-diene-17-carboxylic acid.
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22. We did not see any difference in our own studies either with or without laboratory lighting.