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一、中文摘要

本計畫主要是利用鋅粉在氨水的作用條件下，針對 1,8-取代昆 化合物還原反應進行研究。同時，提出可能的反應機構來合理解釋此還原反應的位置選擇性及雙 化合物的形成。我們的研究結果指出取代基的電子效應，而不是電子效應，對於此還原反應的反應活性及位置選擇性扮演相當重要的角色。

關鍵詞：1,8-取代昆 位置選擇性，雙 化合物，電子效應，立體效應。

Abstract

Reduction of 1,8-disubstituted anthraquinones (**1a-d**) mediated by zinc dust/$NH_{3(aq)}$ was studied and the plausible mechanism was proposed to rationalize the regioselectivity and the formation of bianthracenones. The results indicate that the electronic effects, instead of the steric effects, of *peri* substituents play crucial roles for the control of reactivity and regioselectivity in the reduction.

Keywords: 1,8-disubstituted anthraquinones, regioselectivity, bianthracenones, electronic effects, steric effects。

二、緣由與目的

Anthracene derivatives are frequently used as rigid spacers to incorporate functional units of interests[1-4] and the sensory readout units to signal the presence of analytes.[5-8] On the other hand, the anthracenone moiety is an important pharmacophore; for example, 1,8-dihydroxyanthracenone (which is known as the antipsoriatic agent anthralin) and its derivatives are often used as a remedy for the treatment of skin psoriasis.[9-13] In the past few decades, reduction of anthraquinones has been carried out by using many kinds of reagents in various conditions[14-23] to give either anthracenes or anthracenones. The structural proof of isomeric anthracenones heavily relies on the analysis of spectroscopic data. However, controversy over the ascribed structures of many reduced products arises from time to time. The methods using zinc dust in aqueous ammonia[24-26] or lithium aluminum hydride[24-26] are notorious in these regards, giving conflicting reports on the assigned structures.

In connection with our study of chemosensors, we found that reduction of 1,8-disubstituted anthraquinones using zinc dust in aqueous ammonia showed different regioselectivities depending on the electronic nature of substituents. Moreover, the formation of bianthracenone, which has been elusive

to previous observations in similar reaction conditions, was evidenced.

三、結果與討論

As shown in Scheme 1, reduction of 1,8-disubstituted anthraquinones **1a-d** occurred either at the carbonyl group flanked by the *peri* substituents or at that remote from the substituents. By heating with zinc dust (less than 5 equivalents) in aqueous ammonia (50 °C for 7 h) under N_2 balloon, 1,8-dichloroanthraquinone **1a** was reduced to give 4,5-dichloro-10*H*-anthracen-9-one **2a** (20%), 4,4',5,5'-tetrachloro-10*H*,10'*H*-bianthracene-9,9'-dione **3a** (41%) and 1,8-dichloroanthracene **4a** (19%). Reduction of 1,8-dimethoxyanthraquinone **1b** occurred in a similar fashion, albeit 8 equivalents of zinc dust and longer reaction hours (20 h) were required. However, anthraquinones **1c** and **1d** bearing OH and NH_2 substituents were reduced at the remote carbonyl groups to afford 1,8-disubstituted-9-anthracenones and 1,1',8,8'-tetrasubstitued-9,9'-bianthracenones (**5c**, **5d**, **6c** and **6d**).[27] The parent anthraquninone (X = H) was inert to $Zn/NH_{3(aq)}$ under the similar reaction conditions. These results indicated that the substituents certainly played a crucial role for control of reactivity and regioselectivity in the reduction.

Structural elucidation of the isolated products, especially the positions of substituents, deserves some attention. The 4,5-disubstituted-10*H*-anthracen-9-ones showed the characteristic resonance of H-1 (and H-8) at relatively low fields (δ 8.27 in compound **2a** and δ 7.95 in compound **2b**) due to the deshielding effect of the adjacent carbonyl group, whereas the aromatic protons in 1,8-disubstituted-10*H*-anthracen-9-ones **5c** and **5d** had the chemical shifts around 6.47-7.41 ppm. An X-ray diffraction analysis confirmed the structure of **2a**, which existed as a keto form in the solid state.

The structures of bianthracenones **3a**, **3b**, **6c** and **6d**[28-29] were also unambiguously determined by X-ray diffraction analyses. The mass spectra of **3a** and **3b** showed very intense signals at *m/z* 524 and 507, respectively, corresponding to their molecular ion peaks. In the ^{1}H NMR spectra, a sharp singlet with 2-proton counts, appearing at δ 5.97 for **3a** and δ 5.78 for **3b**, were attributable to the methine protons (H-10 and H-10'). The mass spectra of **6c** and **6d** displayed very weak molecular ion peaks at *m/z* 451 and 447 (M^++1) and prominent fragments at *m/z* 225 and 223, respectively. The methine protons in 1,1',8,8'-tetrasubstitued-9,9'-bianthracenones **6c** and **6d** occurred at relatively higher fields of δ 4.56 and 4.31 by comparison with those in 4,4',5,5'-tetrasubstitued-9,9'-bianthracenones **3a** and **3b** (at δ 5.97 and δ 5.78).

In order to understand how the bianthracenones were formed in high regioselectivity, the time course experiments were conducted to monitor the reduction of 1,8-dichloroanthraquinone with $Zn/NH_{3(aq)}$/benzene by ^1H NMR spectroscopy. Benzene was introduced as a reaction medium to avoid the interference of precipitates during the reaction course.

At selected intervals, aliquots were taken from the organic layer and the ^1H NMR spectra were recorded (Figure 1). After the first 30 min, two doublets appeared at δ 3.15 and at δ 6.38. Upon addition of one drop of D_2O, the signal at δ 3.15 disappeared and the doublet at δ 6.38 became a singlet. This spectroscopic evidence indicated an intermediate of 4,5-dichloro-10-hydroxy-10*H*-anthracen-9-one (**7a**), which was further proved by an X-ray analysis. The carbonyl group *peri* to the chlorine substituents was selectively reduced to a hydroxyl group.

As the reaction proceeded, the gradual disappearance of the peaks at δ 3.15 and 6.38 was accompanied by the growing signals at δ 4.21 and 8.27, which was responsible for the concomitant formation of anthracenone **2a**. Accordingly, 1,8-dichloroanthraquinone was completely converted to anthracenone **2a** within 2 h and a small amount of over-reduced product, 4,5-dichloro-9,10-dihydro-9-anthracenol (**8a**), was detected as evidence of the new resonances appearing at δ 5.66 (d, H-9), 4.17 (dd, H-10) and 2.07 (d, OH). Surprisingly, no bianthracenone **3a** was observed after 6 h presumably due to little oxygen dissolved in the benzene solution.

We thus purged benzene with oxygen and ran time course experiment again (Figure 2). After 6 h, a new peak at δ 5.97 corresponding to the methine protons of **3a** appeared as our anticipation. By following the ratio of the signal at δ 4.21 for the methylene protons of **2a** to the signal at δ 5.97 for the methine protons of **3a**, we concluded that bianthracenone **3a** was formed at the expense of anthracenone **2a**. In another experiment, we also demonstrated that **2a** in aqueous ammonia, with or without the presence of $ZnCl_2$, were successfully converted to **3a** (85% isolated yield) as long as the reaction media contained enough oxygen.

The regioselectivity of reductions mediated by $Zn/NH_{3(aq)}$ was likely dictated by the electronic nature of *peri* substituents on the anthraquinones instead of steric effects. The substituents on the *peri* positions might exert a significant electronic effect to alter the redox potential of the adjacent carbonyl group.[30] We thus proposed a plausible reaction mechanism, as exemplified in Scheme 2, to account for the formation of anthracenones and bianthracenones.

Zinc metal first gave one electron to one of the carbonyl group with lower redox potential to form a radical anion intermediate **A**, which yielded 4,5-dichloro-10-hydroxy-10*H*-anthracen-9-one (**7a**) after sequential protonation, second electron-transfer and protonation. The reaction proceeded further to give anthracenone **2a** in the presence of excess Zn. The pivotal compound **2a** could be either oxidized by oxygen to give bianthracenone **3a**, or reduced by Zn to give anthracene **4a** via an intermediary anthrol **8a**.

The reduction of 1,8-dimethoxyanthraquinone **1b** with $Zn/NH_{3(aq)}$ was considered to follow the pathway similar to that of **1a**, giving anthracenone **2b**, bianthracenone **3b** and anthracene **4b**. The chelating ability (intramolecular hydrogen bondings) of hydroxyl (or amino) substituents might be attributable to the different regioselectivity observed in the reduction of 1,8-dihydroxyanthraquinone **1c** (or 1,8-diaminoanthraquinone **1d**).[11a] The chelated carbonyl group[31b] was either protected from reduction, or the remote carbonyl group was rendered to preferentially accept electrons transferred from zinc.

A previous work of Caluwe *et al.* has demonstrated that the reduction of 1,8-dimethoxyanthraquinone with $LiAlH_4$ gives a side product assigned as "1,1',8,8'-tetramethoxy-10*H*,10'*H*-bianthracene-9,9'-dione". As this side product exhibits the ^1H NMR spectral data similar to that of bianthracenone **3b**, we suggest the previous assignment should be corrected as 4,4',5,5'-tetramethoxy-10*H*,10'*H*-bianthracene-9,9'-dione. Indeed, our reinvestigation (Scheme 3) on the reduction of 1,8-dimethoxyanthraquinone with $LiAlH_4$ (20 molar proportions in THF, 0 °C, 2 h) showed a major product of 4,5-dimethoxy-9-anthracenone **2b** (32%) and a minor product of bianthracenone **3b** (19%). On treatment with $LiAlH_4$ or $NaBH_4$ (in MeOH, 0-5 °C, 1 h), 1,8-dihydroxyanthraquinone (**1c**) was similarly converted to 4,5-dihydroxy-9-anthracenone (**2c**) and 4,4',5,5'-tetrahydroxy-10*H*,10'*H*-bianthracene-9,9'-dione (**3c**) with methine proton signals at δ 5.65, differing from the products **5c** and **6c** obtained by using zinc dust.

The generally accepted 1,4-conjugate elimination mechanism, first proposed by Cristol,[13] is often used to account for the selectivity observed in metal hydride reduction of anthraquinone derivatives. The 9,10-anthracenediol intermediate **B** (or its metal alkoxide analogs) could eliminate a H_2O molecule to give 9-anthracenol **C**, which underwent a tautomerization to give 9-anthracenones **2b** and **2c**. The oxidative dimerization of **2b** and **2c** would afford the corresponding bianthracenones **3b** and **3c**. The regiochemical outcome of these

metal hydride reductions apparently depended highly on the steric effects of the *peri* substituents. Due to such a steric effect, elimination of H_2O (or the analogs) from the diol intermediate **B** occurred preferentially by removal of H-9 rather than H-10.

四、結論

In summary, our current study provided a new insight into the reduction of 1,8-disubstituted anthraquinones. The regiochemistry in the reduction using $Zn/NH_{3(aq)}$ was manipulated by the electronic nature of the substituents, whereas the regiochemistry in the reduction using metal hydrides was controlled by the steric effect of the substituents. We also provided an efficient method to prepare the sterically demanding 4,4',5,5'-tetrasubstituted 9,9'-bianthracenones with $Zn/NH_{3(aq)}$ in the presence of excess oxygen. The structures of anthracenone (**2a-c** and **5c-d**) and bianthracenones (**3a-c** and **6c-d**) were rigorously determined by spectral and X-ray analyses, and thus clarified the long-standing controversy of structural assignments. The proposed reaction mechanism for the reduction using zinc dust (Scheme 2) was supported by the time course experiments and the isolation of 10-hydroxy-9-anthracenone **7a** and 9-anthracenol **8a**.

五、參考文獻

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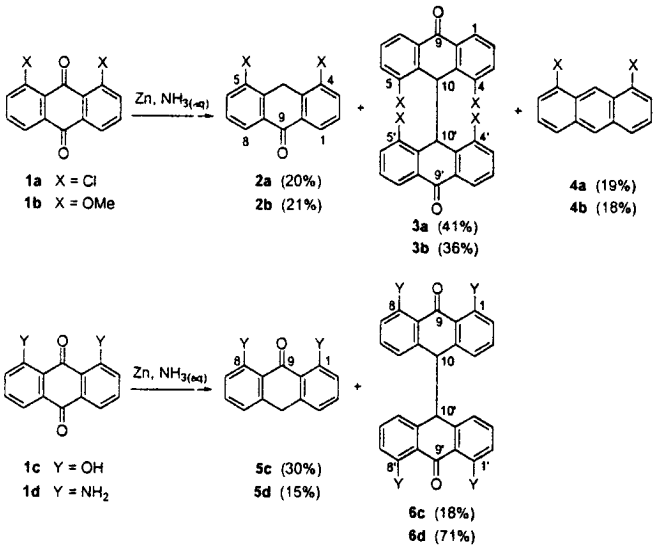
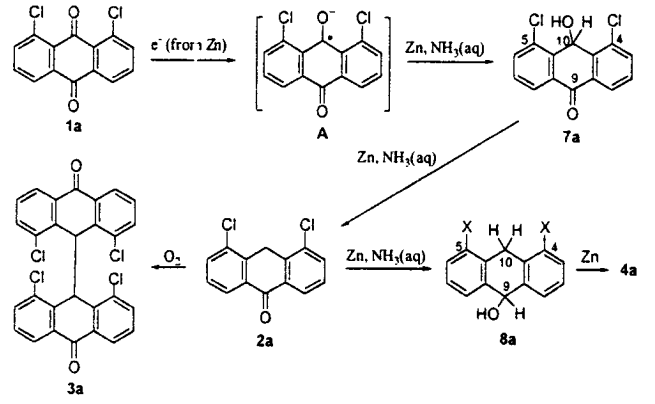
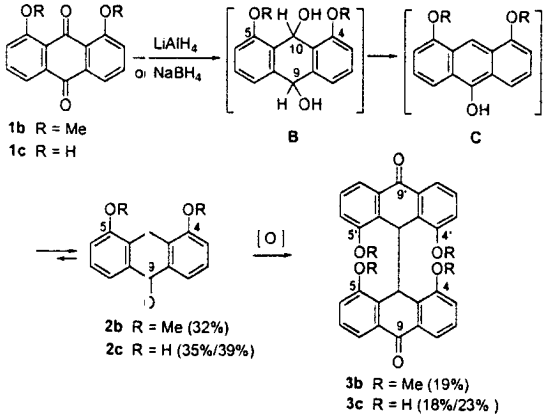
Scheme 1.



Scheme 2.



Scheme 3.



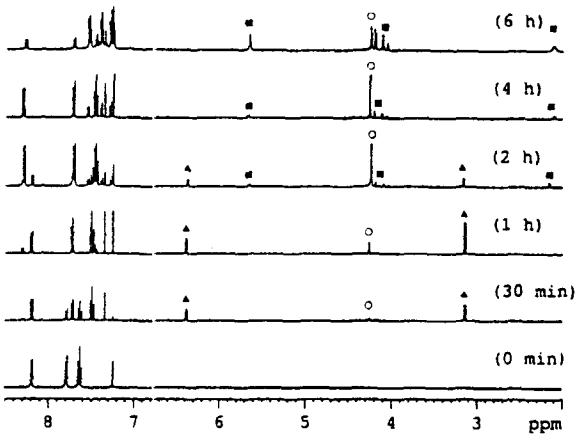


Figure 1. The stacked plot of ^{1}H NMR time course experiments of reduction of **1a** with Zn/$NH_{3(aq)}$/benzene. The signals appearing at δ 3.15 (d) and δ 6.38 (d) denoted with solid triangles (▲) correspond to the hydroxyl and the carbinyl protons of 4,5-dichloro-10-hydroxy-10*H*-anthracen-9-one (**7a**). The signal showing at δ 4.21 (s) denoted with open circles (○) corresponds to the methylene protons of anthracenone **2a**. The signals showing at δ 5.66 (d), δ 4.17 (dd) and δ 2.07 (d) denoted with filled squares (■) correspond to the carbinyl, hydroxyl and methylene protons of 4,5-dichloro-9,10-dihydro-9-anthracenol (**8a**).

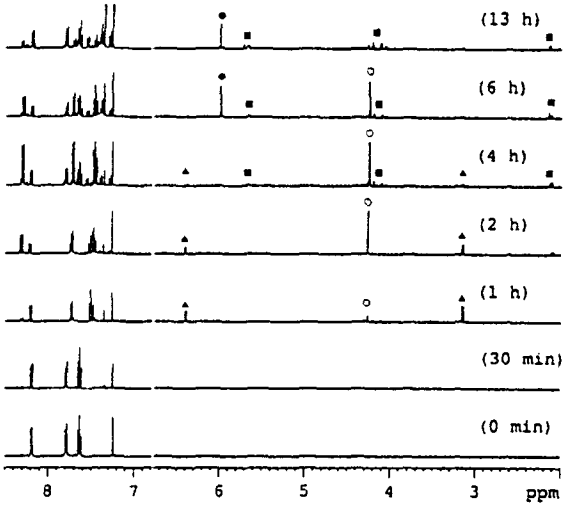


Figure 2. The stacked plot of ^{1}H NMR time course experiments of reduction of **1a** with Zn/$NH_{3(aq)}$/benzene purged with oxygen. The new peak appearing at δ 5.97 (s) denoted with filled circles (●) corresponds to the methine protons of **3a**.