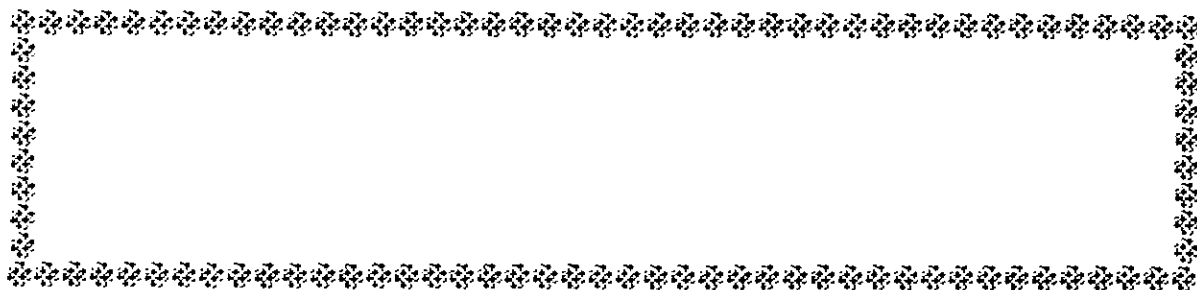# 行政院國家科學委員會專題研究計畫成果報告

計畫類別：☑個別型計畫　　□整合型計畫

計畫編號：NSC 88—2113—M—002-018

執行期間：87年 8 月 1 日至 88 年 7 月 31 日

個別型計畫：計畫主持人：陳昭岑

~~共同主持人：~~

整合型計畫：總計畫主持人：

子計畫主持人：

註：整合型計畫總報告與子計畫成果報告請分開編印各成一冊
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執行單位：台大化學系

中華民國 88 年 1 月 1 日

行政院國家科學委員會專題研究計畫成果報告　　(NSC Project Report)
計畫名稱：研發對於生物體上有重要性的縮氨酸化學感應器以及其它相關
　　　　　應用　　(Development of Chemosensors for Biologically Important
　　　　　Peptides and Other Related Applications)
計畫編號：　NSC 88-2113-M-002-018
執行期限：　87年8月1日　至　88年7月31日
主持人：陳昭岑　　國立臺灣大學化學系助理教授

（中文摘要）

本研究報告系根據研究一系列的 1,8- 雙取代菌蒽化合物在鋅粉/氨水或金屬還原試劑作用下的實驗結果。我們觀查到這個反應條件有很高的化學選擇性。當使用金屬還原試劑時，取代基在形成還原產物 – 4,5- 雙取代的 anthrone 只純粹扮演立體效應。然而，在鋅粉/氨水作用下，取代基不僅有立體效應亦有電子效應。這些因素對於反應的位置選擇性有相當重要的影響。取代基若能與相鄰的羰基形成氫鍵，那麼距離取代基較遠亦即立體障礙較小的羰基會被還原得到 1,8-取代 –9– anthrone。除此之外，我們研究亦發現當反應溶劑中的氧氣足以將反應的還原產物進一步氧化得到 dianthones 。總而言之，我們研究的研究不僅對於鋅粉/氨水在還原1,8- 雙取代菌蒽化合物的反應提供新的反應機制看法及正確無誤的化學結構鑑定。

（關鍵詞）

1,8- 雙取代菌蒽化合物；鋅粉/氨水；4,5- 雙取代的 anthrone；金屬還原試劑；位置選擇性；化學選擇性；立體效應；電子效應；氫鍵；dianthones 。

Abstract:
A series of 1,8-disubstituted anthraquinones was investigated on the treatment of Zn dust/aqueous ammonia and metal hydride reducing agents. Highly chemoselectivity was observed. In the case of metal hydride reducing agents, the substituents imposed the purely steric effects on the formation of 4,5-disubstituted 9-anthrone. However, the electronic and steric nature of substituents exerted large influences on the regioselective reduction in the presence of Zn dust/aqueous ammonia. The substituents capable of forming hydrogen bondings with the flanked carbonyl group led to the reduction of the less steric congested the carbonyl group to give 1,8-substituted 9-anthrone. In addition, dissolving oxygen in the solvent was proved to further oxidize the anthrones formed at the earlier stage of the reaction to dianthrones. The studies not only provided new insights of the traditionally employed reduction methods for 1,8-disubstituted anthraquinones also unambiguous structural elucidation.
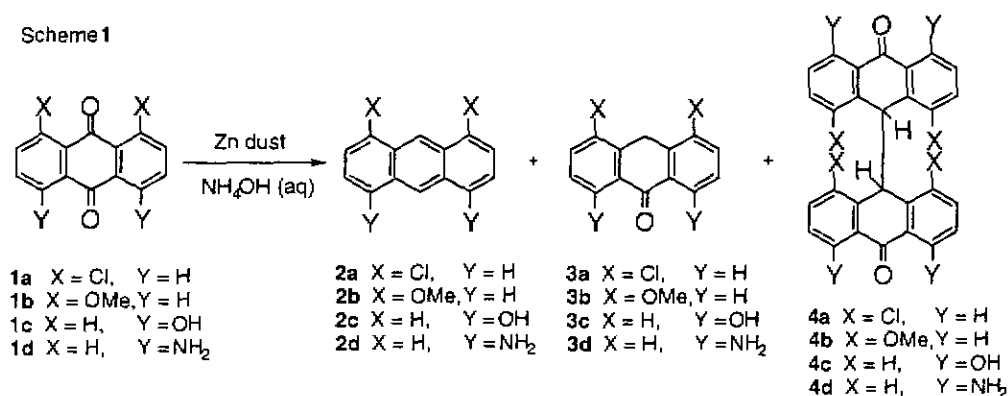
Key Words:
1,8-disubstituted anthraquinones; Zn dust/aqueous ammonia; metal hydride reducing agents; regioselective; chemoselectivity; steric effects; electronic effects; hydrogen bondings; dianthrones.

Reduction of anthraquinones have been widely used to prepare anthracenone and anthracene derivatives in applications of biological activity studies[1-6] and organic materials synthesis.[7-8] For past few decades, considerable reagents and conditions[9-18] have been developed to reduce anthraquinones regioselectively. For instances, structural modifications of anthracenones to avoid the severe inflammation and staining of the skin still remain as a great challenge. *However, it is not always clear that whether the ascribed structures of many reduced products are correct.[19-21] The proof of structures heavily relies on the analysis of spectroscopic data.[13,18] Excess of Zinc dust in aqueous ammonia solution and lithium alumina hydride (LAH), which were used to reduce substituted anthraquinones to corresponding anthracences or anthracenone, gave conflicting reports on the long assigned structures.[19-21] These observations prompted us to reinvestigate these reactions. Indeed, we report herein a systematic exploration of the relationships between the nature of substituents and regiocontrol in series of 1,8-disubstituted anthraquinones at the presence of zinc dust/aqueous ammonia. Reduction of these anthraquinones with LAH was also performed for the comparison of chemoselectivity with zinc dust/aqueous ammonia condition.

The situation with 1,8-disubstituted anthraquinones is confused by the fact that the first reduction may occur at the keto group flanked by the *peri* substituents or that remote from them. Thus, various 1,8-disubstituted anthraquinones (**1a-e**) were subjected to the Zn dust/aqueous ammonia reducing condition (scheme **1**). The use of excess zinc dust (5-8 equiv) accompanied by heating led to optimized yields and short reaction time.

Scheme 1

1a X = Cl, Y = H	**2a** X = Cl, Y = H	**3a** X = Cl, Y = H	
1b X = OMe, Y = H	**2b** X = OMe, Y = H	**3b** X = OMe, Y = H	
1c X = H, Y = OH	**2c** X = H, Y = OH	**3c** X = H, Y = OH	**4a** X = Cl, Y = H
1d X = H, Y = NH$_2$	**2d** X = H, Y = NH$_2$	**3d** X = H, Y = NH$_2$	**4b** X = OMe, Y = H
			4c X = H, Y = OH
			4d X = H, Y = NH$_2$

In 1,8-dihydroxylanthraquinone case (**1c**), neutralization of the reaction solution with dilute HCl prior to extraction with organic solvents proved to be beneficial for the products purification. In case of **1a-b**, we obtained anthracence derivatives (**2a-b**) and isomeric 4,5-disubstituted-9(10H)-anthracenone (**3a-b**), along with the products that were consistent with the 4,4',5,5'-tetramethoxy-9, 9'(10H, 10'H) bianthrone (**4a-b**). On the basis of reported ^{1}HNMR and IR data, the chemical structures of **2a-b** and **3a-b** were established. X-ray diffraction analysis of **3a** further confirmed the structural assignment, which showed clearly that **3a** existed in the keto form in the solid state.[22] Although the formation of bianthrone compounds was reported in literature by different reaction conditions,[16,23-28] structural elucidation of bianthrones, especially the regio positions of substituents, deserved some attention. Isolation of **4a** as the major product in 44% yield is very surprising and not found in previous reports. Mass spectra of **4a -b** showed very intense molecular ion peaks at m/e 524 and 507 respectively. These data were in agreement with a dianthrone structure. A singlet appearing at δ 5.97 with correct integration of the peak area was evidenced and assigned to the methine proton in **4a**. The methoxy groups and the methine protons in **4b** were also observed as sharp singlets, with the proper proton counts, at δ 3.57 and 5.78, respectively, further confirming the symmetrical structure of the dimerizaton product. However, no characteristic absorptions for protons peri to a carbonyl group, which normally appeared at d 8.26 as a doublet of doublets. There were at δ 7.63 (for **4a**) and δ 7.34 (for **4b**) as doublets instead. The carbonyl absorptions exhibited at 1680-1670 cm^{-1} in infrared spectra of **4a-b**. To ascertain regiochemistry of the substituents, X-ray diffraction analyses of **4a-b** were performed and clearly indicated the position of substituents (figure 1). Neither isomeric 1,8-dichloro-9-anthracenone nor 1,1',8,8'-tetrachloro-9,9'-bianthrone was obtained from the reduction. There appeared to be distinct differences in product distribution between our reducing system and the conventionally employed Zn dust/aqueous ammonia condition.[8,18] One explanation for the difference in reactivity is the use of less equivalents of reducing agents (4 equiv *vs.* more than 15 equiv.). In the cases of **1c -d**, the products were **3c**, **3d**, **4c** and **4d** exhibiting different regiochemistry from their counterparts **3a**, **3b**, **4a** and **4b** in addition to anthracene derivatives. The total isolated yields for the reduction of **1b-c** were relatively low probably due to the decomposition of the reaction

mixture since the solutions got darken as the reaction progressed.[28-29] Mass spectra of **4c-d** displayed very weak molecular ions at m+1/e 451 and 447 and prominent fragments at 225, 233 respectively. Compound **4c** was reported in the literature by oxidizaton of the corresponding anthracenone with singlet oxygen or salem complex[29] and its structure was established by the X-ray diffraction analysis. Examination of ^{1}HNMR and IR spectra of **4c-d** revealed some discrepancy from their counterparts, **4a-b**. The observed chemical shift values of methine protons in **4c** and **4d** appearing rather upfield shifted at δ 4.56 and 4.31 respectively, compared with those of **4a** and **4b**. Moreover, the chemical shifts in the aromatic region of **4c** (recorded in $CDCl_3$) and **4d** (recorded in acetone-d_6) were observed in the range of δ 6.3-7.4 and δ 6.0-7.0 with very similar coupling and chemical shift patterns. A downfield shift singlet at δ 11.69 indicated hydrogen-bonded phenolic protons in **4c**. Low frequency absorptions of the carbonyl groups at 1630-1620 cm^{-1} in infrared spectra were consistent with the hydrogen-bonded carbonyl groups. On the basis of these spectroscopic data **4c** and **4d** were assigned to be the 1,1',8,8'-tetrasubstituted dianthrones. The carbon-carbon bonds could be formed with high regiocontrol fashion under the zinic dust reducing condition. Attempts to grow a single crystal of **4d** for X-ray diffraction analysis was unsuccessful. Subjection of the parent anthraquninone (**1e**) to this reducing condition failed to give **3e** and **4e**. Recovered most of starting materials and few anthracene.

The regioselective outcome seemed to be dictated by the *peri* substituents on the anthraquinones, where the ability of forming hydrogen bondings with the carbonyl groups would lead to the formation of isomeric 4,5-disubstituted anthrones and 4,4',5,5'-tetrasubstitued bianthrones rather than 1,8-disubstituted and 1,1',8,8'-tetrasubstituted counterparts. Similar regioselectivity was observed for 1-hydroxyanthraquinone in the presence of zinc dust/acetic acid solution.[9] If the 1-hydroxyanthraquinone was acylated before reduction, the reversed regioselectivity was found, the carbonyl group adjacent to the acyloxy group reduced preferably. It seemed reasonable to infer that the chelated linkage between the substituents and the carbonyl group rendered the carbonyl group immune from reduction. The steric effects of substituents seem not the only factor played in the regioselectivity.

Formation of dianthrones was not documented in the literature under the zinc dust /aqueous ammonia condition although Caluwe P. *etal.* reported the formation of dianthrone derived from anthrone upon the treatment of 1,8-dimethoxy anthraquinone with lithium aluminum hydride (LAH).[16] The structure of the resulting bianthrone was assigned to the isomeric 1,1',8,8'- tetramethoxydianthrone on the analysis of the spectroscopic data. We found that the regioassignment is incorrect based on our spectroscopic data and the X-ray single crystal analysis. This findings drove us to reinvestigate the regioselectivity of LAH on **1a-c**. The 4,5-disubstitution pattern of anthracenones was established by the support from the spectroscopic properties for the reduction of **1a-c**. Along with these anthracenones as the major products, dianthrones were also isolated. The characteristic methine protons all appeared as a sharp singlet around δ 5.8-5.7 indicating 4,4'5,5'-tetrasubstituted regiochemistry. It took us a surprise that regioselectivity of the product, 4,4'5,5'-tetrahydroxydianthrone (**5**), in the case of **1c** was different from what we observed in the Zn/aqueous ammonia method. We then employed sodium borohydride (NaBH$_4$)[18] to reduce **1c** and **5** was obtained again along with 4,5-dihydroxy anthracenone (**6**). Attempts to reduce **1d** with the treatment of either LAH or NaBH$_4$ failed to afford identiable products. It was proposed that the conversion into anthrones required elimination of one alkoxyaluminum hydride moiety from the meso 9,10-dihydroanthracene-9,10-bis(lithium oxyaluminum hydride. The stereooutcome of these metal hydride reduction agents depended highly on the steric effects of the peri substituents. These effects exerted their decisive influence on the primary addition products of quinones with metal hydrides and the following elimination of one alkoxyaluminum hydride (or water) promoted by the base (hydride) attack at the axial proton of 10-position (away from the substituents.) of the corresponding diols.[16] However, this proposed mechanism for the formation of peri-substituted anthracenones cann't explain the regioselectivity observed in our Zn/NH$_4$OH studies. We are at present in no position to offer active species or an alternative mechanism to explain the results. The electronic effects of substituents probably exerted strong influences on the redox potential of the carbonyl groups flanked by the substitutents. Moreover, the chelating ability of substituents either to the carbonyl groups or the metal probably protected the

keto group from being reduced and rendered the more excess of keto group got reduced preferentially.

Diathrone has been obtained as a byproduct in the reduction of anthraquinones.[6] In rationalizing this observation, it was suggested that dimer formation proceeded by way of self-condensation of an intermediate anthrone. An alternative route involving pinacol-type reduction of anthrone followed by elimination of water also seemed plausible. No solid evidence was shown. Since we isolated dianthrones as major prodcuts in some cases investigated in our studies, we would like to understand how the dianthrones was formed. We decided to take aliquots to monitor the reduction of 1,8-anthraquinone with the Zn/aqueous NH_3 by ^{1}HNMR. However, we were unable to make good sense of spectroscopic data acquired during the reaction due to the precipitation of products. We then dissolved 1 in benzene and recorded the ^{1}HNMR spectra of the reaction aliquots every hour. We found that 3 was formed within an hour in almost quantitative yield from the analysis of ^{1}HNMR. After 5h reaction time, small amount of side product was observed and assigned to 4,5-dichloro-9,10-dihydro-9-anthrol. No dianthrone was evidenced presumably due to little oxygen dissolved in benzene solution. Based on this assumption, we then purged benzene with oxygen and ran the reaction again. The product distribution is very different from the former one. 3a was formed in small amount after 2h and new product was observed. After addition of one drop of D_2O, one of the doublets appearing at δ 3.13 disappeared and the other doublet at δ 6.39 became a singlet. The product was then isolated and assigned to 4,5-dichloro-9-hydroxy-10-anthrone (7) on the basis of spectroscopic data. No dihydro diol, which was frequently observed in the $LiAlH_4$ or $NaBH_4$ reduction of anthraquinones, was formed in the reaction. As the reaction proceeded, the formation of 4a was observed in the spectrum. By following the peak ratio of methylene proton absorption at δ 4.21 of 3a and methine proton absorption at δ 5.97 of 4a, we found that 4a was formed at the expense of 3a. After 7h, no appreciable 3a was observed and the ratio of 4a and 7 was constant. Furthermore, 4a was isolated in good yield 85% when we subjected the pure 3a in aqueous ammonia with or without $ZnCl_2$. Based on all these evidences, it appeared likely

that the dianthrone was the oxidized product of anthrones in the presence of dissolving oxygen in the reaction solution.

Our studies provided new insights on the reduction of 1,8-disubstituted anthraquinones with Zn dust in aqueous ammonia as well as unambiguous structural elucidation. The nature of substituents played an important role in the regiochemistry of the reaction. In some cases, steric more congested dianthrones (**4a, 4b, 5**) were isolated despite the apparently unfavorable interaction. Detailed studies of physical properties of these dianthrones and the mechanism of this highly regioselective reduction are underway.

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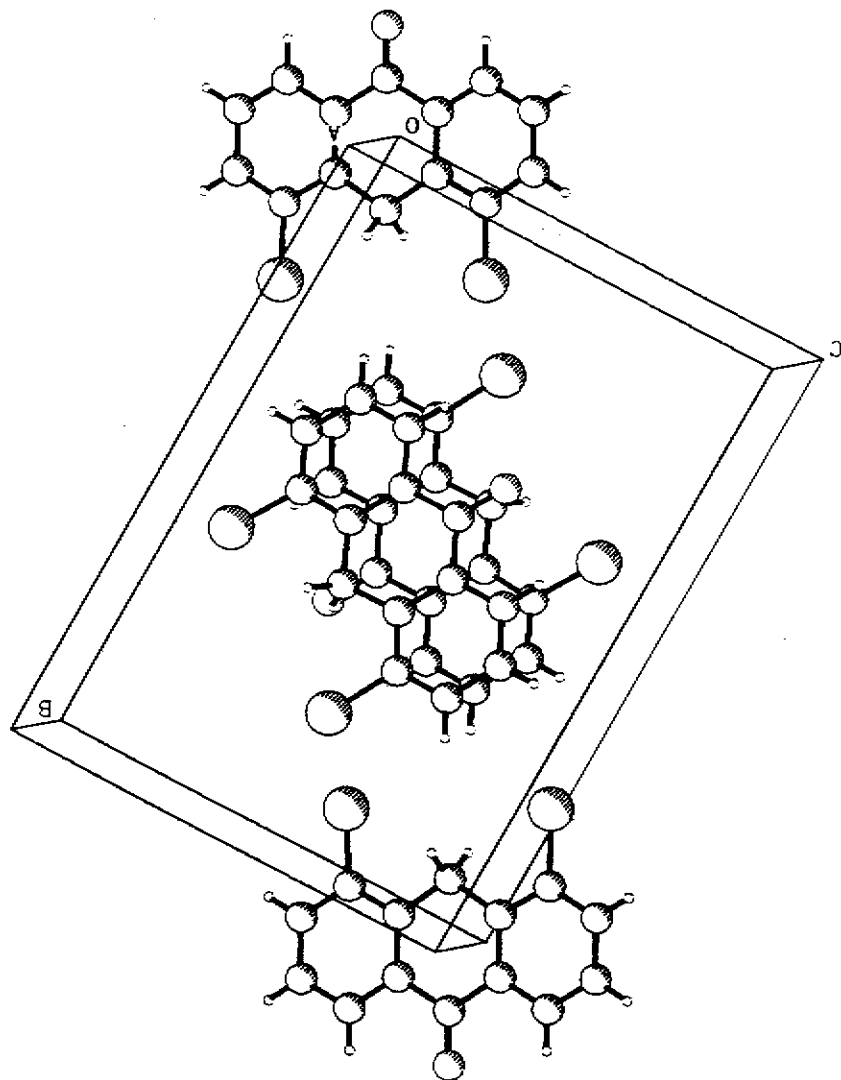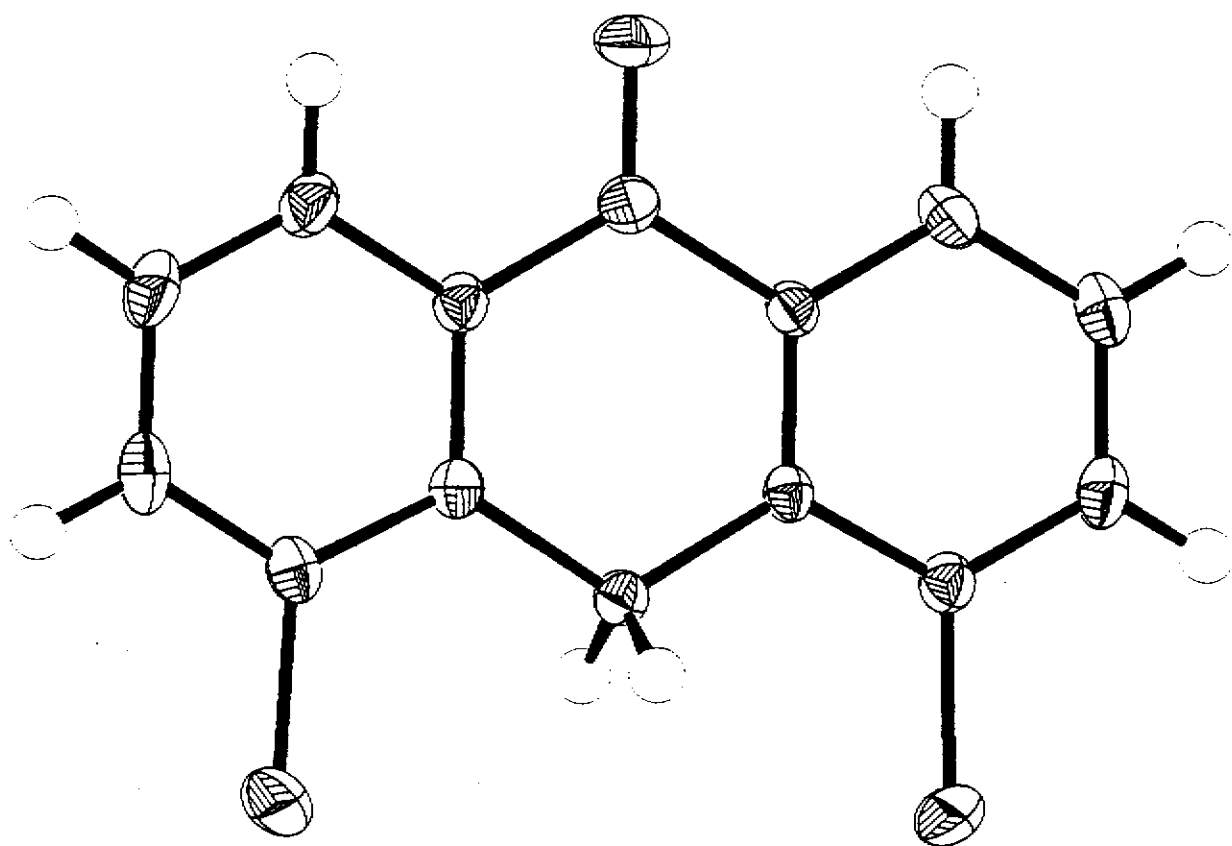
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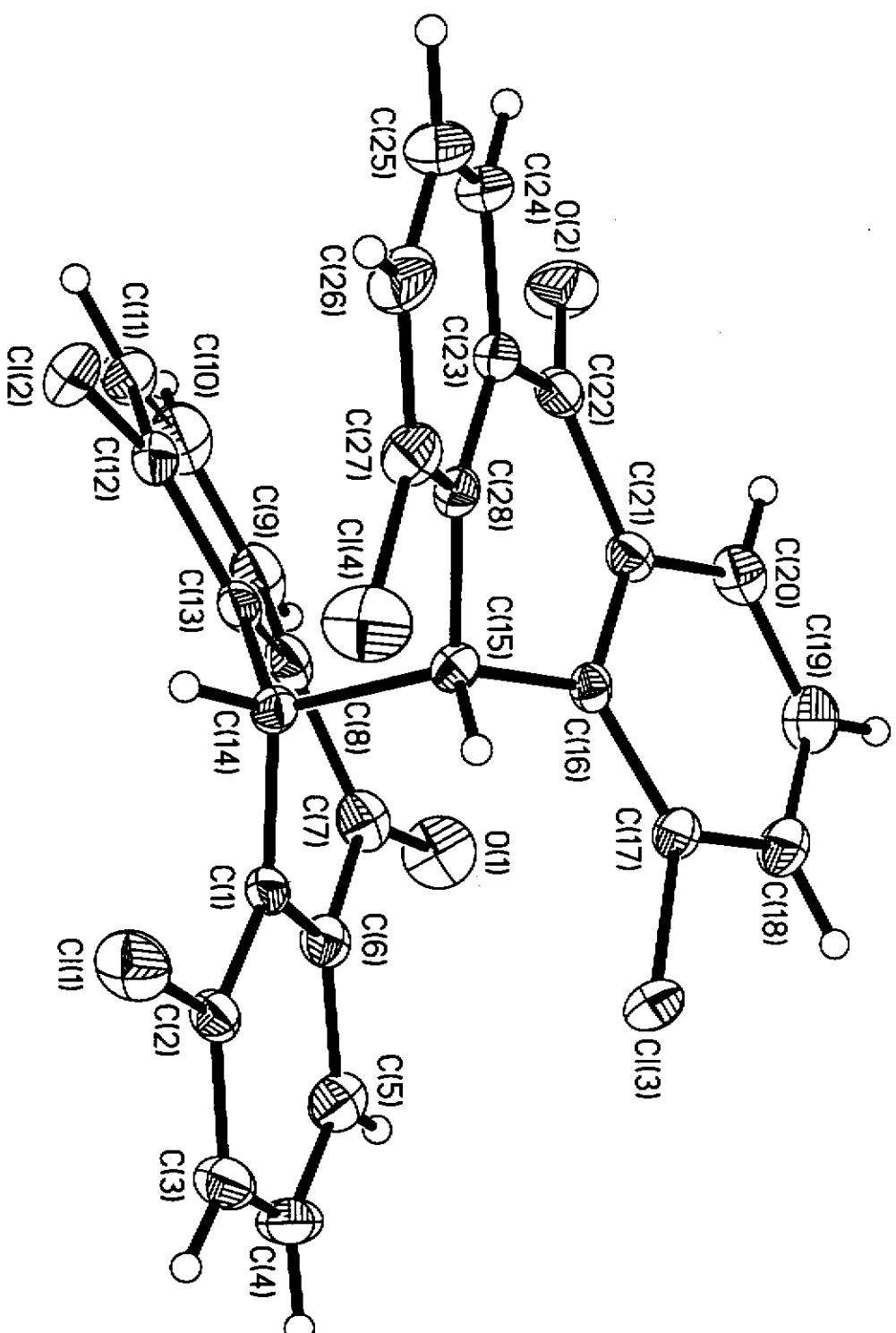
Fig. 3.2 ORTEP of Complex

Fig. 1: The molecular structure of IC6203, thermal ellipsoids drawn at the 30% probability level.