Nucleophilic Vinylic Substitution of Halocoumarins and Halo-1,4-naphthoquinones with morpholine

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Reactions of morpholine with 4-halocoumarins **1**, 3-halocoumarins **3**, and 2-halo-1,4-naphthoquinones **8** yield two different products, one where halogen is replaced by a nucleophile at the same carbon and the other where the nucleophile is attached to the vicinal carbon away from that bearing the halogen. It is considered that reactions proceeds through nucleophilic vinylic substitution by comparision of the reaction products and deuterium exchange experiments. Plausible mechanisms for these routes are suggested.

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Introduction.

Nucleophilic vinylic substitutions [1a-g] have much in common with nucleophilic addition to electron deficient olefins (the Michael reaction [2a-b]). The first stage, namely the addition of a nucleophile to the double bond with formation of a carbanion, is the same in these two reactions. However the second stage is different. The carbanion combines with proton or electrophile in the Michael reaction, while in nucleophilic vinylic substitution a negatively charged leaving group is eliminated. Since leaving groups in nucleophilic vinylic substitutions are usually themselves electron withdrawing groups, the formation of a carbanion in the first stage is supposed to be more facilitated than typical Michael addition. It is found here that halogen at the β-position to the electron withdrawing group accelerates the reaction rate while halogen at α-position does not affect the rate significantly.

Compounds that have a double bond conjugated with an electron withdrawing group nearly always react by a nucleophilic mechanism [3]. α,β-Conjugated carbonyl systems add nucleophiles only at C-2 and/or C-4 with one exception of the addition to C-3 (anti-Michael addition) in the case of trimethylsilyl group attached β-position to amides in ynamides and enamides were treated with alkyl lithium [4].

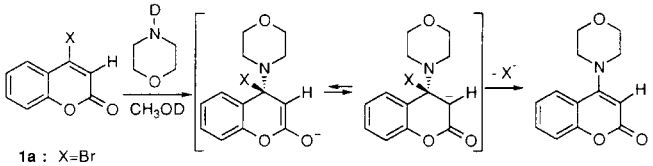
In coumarins, both 3- and the 4-position are the site of substitution but only at the 4-position can the Michael addition take place. Here favorable delocalization of the negative charge generated can be accomplished by enolization while at the 3-position the delocalization is much less favorable. In 1,4-naphthoquinone both the 2- and the 3-positions have characteristics of both α- and β-positions.

Attempts have been made to react monohalocoumarins or monohalo-1,4-naphthoquinones with morpholine in deuterated methanol to understand the reaction pathway.

Results and Discussion.

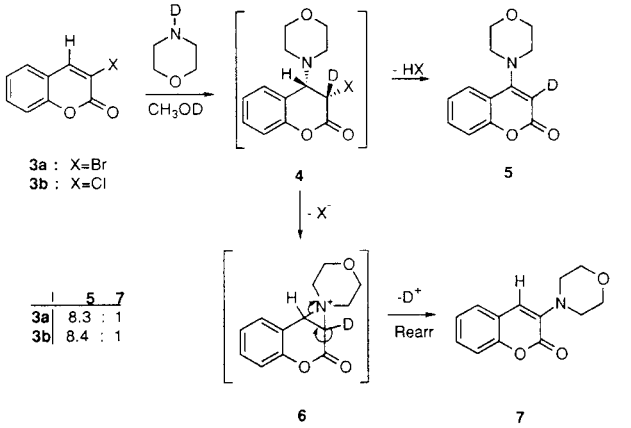
4-Bromocoumarin **1a** and 4-chlorocoumarin **1b**, namely β-halocoumarins [5], prepared from 4-hydroxycoumarin with triphenylphosphine-carbon tetrabromide (or carbon tetrachloride), undergo nucleophilic vinylic substitution with morpholine to give 4-morpholinocoumarin **2** as described in Scheme I. Furthermore, reaction in methanol-*d* solvent gave no 3-deuterated product. It indicates straight forward nucleophilic vinylic substitution since a certain deuterium exchange is expected in the case of a Michael addition followed by an elimination reaction.

Scheme I



3-Bromocoumarin **3a** and 3-chlorocoumarin **3b** [5], namely α-halocoumarins to the carbonyl group, undergo substitution reaction in methanol-*d* to 3-deuterio-4-morpholino- **5** (77% from **3a** and 78% from **3b**) and 3-morpholinocoumarin **7** (9.3% from each **3a** and **3b**) at a much slower rate than 4-halocoumarins as depicted in Scheme II. The product distribution ratio of **5**/**7** is 8.3 for **3a** and

Scheme II

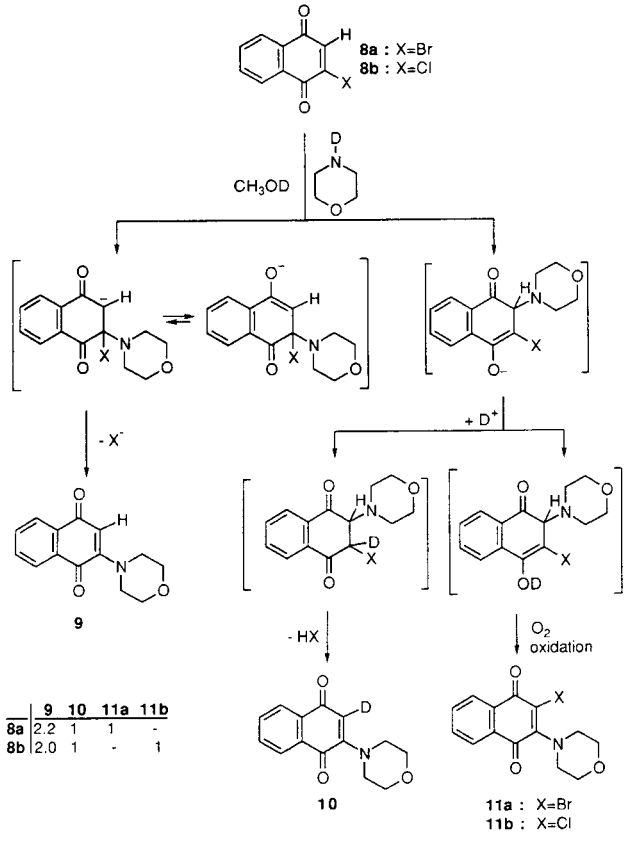


8.4 for **3b**. When the same reaction is carried out in methanol, products are **2** and **7** respectively.

When halogen was placed at the α-position to the carbonyl group in **3**, activation of the α-carbon is usually too low to enable substitution *via* addition-elimination. Michael type addition is however possible, the morpholine being attached to the β-carbon. Then hydrogen bonding to the β-carbon is eliminated with the α-halogen, forming a product in which morpholine is attached to the β- rather than to the α-carbon atom [1a] because complete deuterium exchange is observed in methanol-*d*. It is further suggested by complete deuterium exchange that formations of Michael adduct **4** and subsequent dehydrohalogenation to **5** is also stereospecific as anti-addition [6a-b] and anti-elimination. Otherwise, deuterium exchange can only be partial.

The minor pathway leading to **7** is contrary to the HSAB theory [7a-c]. However, after Michael-type addition of morpholine, the adduct **4** contains vicinal halogen and nitrogen. Nitrogen attacks the α-carbon bearing halogen to form an aziridinium intermediate **6** [8a-c]. Loss of more acidic α-deuterium over that of β-hydrogen results in product **7**. This pathway also accounts for the lack of deuterium exchange in methanol-*d*. The ratio of **5**/**7** (8.3) is the relative rate of addition-elimination over the aziridinium intermediate.

Scheme III



	9	10	11a	11b
8a	2.2	1	1	-
8b	2.0	1	-	1

2-Bromo-1,4-naphthoquinone **8a** or 2-chloro-1,4-naphthoquinone **8b**, reacts with morpholine to yield 2-morpholino-1,4-naphthoquinone **9** and 2-bromo-3-morpholino-1,4-naphthoquinone **11a** or 2-chloro-3-morpholino-1,4-naphthoquinone **11b**. The product distribution ratio of **9**/**11a** is 45.6/13.5 and that of **9**/**11b** is 55.1/16.7. Deuterium exchange in methanol-*d* is expressed as **9**:**10**:**11** is 2:1:1 shown in Scheme III.

We are very much tempted to think that a parallelism between coumarins and naphthoquinones exists. From deuterium exchange experiment and its comparison with the case of 3-halocoumarins, it is suggested that three different paths might be followed by the above reaction. While Carmeron presented two different paths [9] that nucleophile attacked on halogenated carbon or on the vicinal carbon. Hewgill and Mullings suggested two other different paths [10a,b] that Michael addition occurred and was followed by β-elimination or oxidation.

Product **9**, about 1/2 of all products, was formed by direct nucleophilic vinylic substitution. Product **10**, about 1/4 of all products, was obtained through a Michael addition followed by elimination. For the formation of **11a** or **11b**, about 1/4 of all products, it was explained by Michael addition followed by oxidation [11a-b]. Thus the ratio of **9**:**10** and **11** depends on the position of the initial morpholine attack whether on vicinal carbon or halogen-bearing carbon. The ratio of **10**:**11** is the relative rate of elimination and oxidation after Michael addition.

EXPERIMENTAL

Melting points were determined in capillary tubes (Thomas Hoover melting point apparatus) and are uncorrected. The pmr spectra were recorded on either a 60 MHz Varian EM60 or a 300 MHz Varian Gemini 300 spectrometers. The cmr spectra were recorded on a 75 MHz Varian Gemini 300 spectrometer. Chemical shifts are given in ppm using TMS as the internal reference. Elemental analyses were performed on a Perkin-Elmer 240 DS element analyzer. Mass spectra were determined with a Hewlett Packard model 5988A spectrometer. For column chromatography, the silica gel 60 (Merck 200-230 mesh) was used. The tlc analysis was performed on silica gel 60 plates (0.25 mm or 1 mm layer, GF-254, Merck).

4-Bromocoumarin (**1a**) and 4-Chlorocoumarin (**1b**).

To a dried flask, 1.62 g of 4-hydroxycoumarin (10 mmoles), 2.62 g of triphenylphosphine (10 mmoles) and 5 ml of chloroform were charged. Solution of 3.31 g carbon tetrabromide (10 mmoles) and 3.5 ml of chloroform was added dropwise over 30 minutes at room temperature. The reaction mixture was heated to reflux and held for 2 hours. Most of solvent was removed at reduced pressure and 5 ml of carbon tetrachloride was added to the residue. The mixture was filtered to remove insoluble phosphine oxide. After removal of the solvent at reduced pressure, the remaining solid was purified by column chromatography to ob-

tain **1a** (1.51 g, 67%) [12a]. Compound **1b** was prepared as in the preparation of **1a** except that equimolar carbon tetrabromide was replaced by excess carbon tetrachloride (72%).

Compound **1a** had mp 89.5-91.5° (91.5° [12b]); pmr (deuteriochloroform) 7.78 (d, d, 1H), 7.57 (t, d, 1H), 7.30 (m, 2H), 6.80 (s, 1H).

Compound **1b** had mp 93.5-94.5° (91-92°[12c], 93-94° [12d]); pmr (deuteriochloroform) 7.88 (d, d, 1H), 7.63 (t, d, 1H), 7.38 (m, 2H), 6.62 (s, 1H); cmr (deuteriochloroform): 159.0, 152.9, 149.7, 133.3, 125.5, 124.9, 117.0, 115.5, 115.4.

Reaction of **1a** or **1b** with Morpholine in Methanol-d_4.

To 100 mg (0.44 mmole) of **1a** or **1b** in 5 ml of methanol-d_4 was added 80 µl (0.92 mmole) of morpholine. The reaction mixture was heated to 55° for 5 minutes and sample was taken for nmr spectrum. The peak at 6.80 ppm assigned to the 3-hydrogen of **1a** disappeared while a new peak at 5.80 assigned to 3-hydrogen of **2** appeared in the ratio of **4**:**6**. The reaction was virtually complete in 25 minutes. No deuterium exchange was observed. The mixture was worked up to give 89.4 mg (87%) of **2** after chromatography on silica gel. While **2** (72%) and trace of starting material from **1b** were isolated.

Compound **2** had mp 139-141°, (139-141° [12c]); pmr (deuteriochloroform) 7.2-7.8 (m, 4H), 5.8 (s, 1H), 3.85-4.2 (m, 4H), 3.2-5 (m, 4H).

3-Bromocoumarin (**3a**) and 3-Chlorocoumarin (**3b**).

Compounds **3a** and **3b** were prepared by following known methods [13a-13b]. Compound **3a** had mp 110-101° (110° [13c]); pmr (deuteriochloroform) 8.2 (s, 1H), 7.2-7.8 (m, 4H). Compound **3b** had mp 121-122° (122.5° [13b]); pmr (deuteriochloroform) 7.9 (s, 1H), 7.3-7.6 (m, 4H) [13d].

Reaction of **3a** or **3b** with Morpholine.

To 150 ml of methanol was dissolved 25 g (0.11 mole) of **3a** and 33.2 g (0.38 mole) of morpholine. The reaction mixture was heated to reflux and held for 24 hours. The solvent was removed at reduced pressure and the residue was dissolved in dichloromethane and washed twice with 1*M* hydrochloric acid solution followed by washing twice with water. The organic layer was separated and dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was purified by column chromatography to yield 19.8 g (77%) of 4-morpholinocoumarin **2**, 2.4 g (9.3%) of 3-morpholinocoumarin **7** and 1.1 g (4.4%) of unreacted **3a**. Compound **3b** reacts with morpholine as described above to yield 4-morpholinocoumarin **2** (78%), **7** (9.3%) and unreacted **3b** (4.4%).

Compound **7** had mp 151-153°; pmr (deuteriochloroform) 7.35 (m, 4H), 6.9 (s, 1H), 3.8-4.0 (m, 4H), 3.15-3.3 (m, 4H); ms: (70 eV) m/z 231 (M^+, 28), 213 (9), 200 (49), 188 (12), 187 (21), 174 (19), 173 (18), 172 (24), 160 (24), 147 (11), 146 (100), 145 (26), 144 (14), 118 (27), 90 (19), 89 (32), 77 (10).

Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.50; H, 5.67; N, 6.06. Found: C, 67.44; H, 5.64; N, 6.09.

Reaction of **3a** or **3b** with *N*-Deuteriomorpholine in Methanol-d_1.

To 5.5 ml of methanol-d_1 was added 200 mg (0.89 mmole) of **3a** or **3b** and 5.48 mmoles of deuterated morpholine solution. And the rest of the reaction conditions were the same as for the above reaction of **3a** or **3b** with morpholine. The products from **3a** were 3-deuterio-4-morpholinocoumarin **5** (74%), **7** (9.0%) and unreacted **3a** (3.1%). The products from **3b** were 3-deuterio-4-morpholinocoumarin **5** (75%), **7** (8.8%) and unreacted **3a** (3.6%).

Compound **5** had pmr (deuteriochloroform): 7.61 (m, 1H), 7.51 (m, 1H), 7.23-7.31 (m, 2H), 3.94 (t, 4H), 3.26 (m, 4H).

2-Bromo-1,4-naphthoquinone (**8a**) and 2-Chloro-1,4-naphthoquinone (**8b**).

Compounds **8a** and **8b** were prepared by following known methods [14a-14b]. Compound **8a** had mp 137.5-140.5° (136-139° [14a]); pmr (deuteriochloroform): 7.7-8.3 (m, 4H), 7.5 (s, 1H). Compound **8b** had mp 115-116° (115-116° [14c]); pmr (deuteriochloroform): 7.6-8.1 (m, 4H), 7.1 (s, 1H).

Reaction of **8a** or **8b** with Morpholine.

To a solution of 159 mg (0.67 mmole) of **8a** or **8b** in 5.0 ml of methanol was added 59 µl (0.67 mmole) of morpholine. The reaction mixture was stirred at room temperature for 10 minutes and concentrated at reduced pressure. The residue was dissolved in chloroform and washed with water. The organic layer was dried, evaporated and purified by chromatography on silica gel to yield 74.4 mg (46%) of 2-morpholino-1,4-naphthoquinone **9**, 29.1 mg (14%) of 2-bromo-3-morpholino-1,4-naphthoquinone **11a** and 41 mg (26%) of recovered **8a**. The products obtained from **8b** were **9** (55%), 2-chloro-3-morpholino-1,4-naphthoquinone **11b** (17%), and unreacted **8b** (18%).

Compound **9** had mp 150-151° (152.5-153.5° [15a]); pmr (deuteriochloroform): 7.99 (m, 2H), 7.65 (m, 2H), 5.98 (s, 1H), 3.84 (t, 4H), 3.48 (t, 4H); cmr (deuteriochloroform): 183.7, 182.9, 153.6, 134.0, 132.7, 132.6, 132.2, 126.7, 125.6, 112.0, 66.4, 49.2.

Compound **11a** had mp 130-131° (128-129° [15b]); pmr (deuteriochloroform): 8.12 (m, 1H), 8.02 (m, 1H), 7.70 (m, 2H), 3.88 (t, 4H), 3.64 (t, 4H).

Compound **11b** had mp 153-155° (152° [15c]); pmr (deuteriochloroform): 8.11 (m, 1H), 8.00 (m, 1H), 7.70 (m, 2H), 3.87 (t, 4H), 3.63 (t, 4H).

Reaction of **8a** or **8b** with *N*-Deuteriomorpholine.

To a solution of 42.0 mg (0.18 mmole) of **8a** or **8b** in 0.5 ml of methanol-d_4 was added 15.5 µl (0.18 mmole) of morpholine. The reaction mixture was kept at room temperature for 10 minutes and the resulting reaction mixture was separated by preparative tlc upon elution with hexane/ethyl acetate (3/1) to obtain mixture of **9** and **10** 21.7 mg (50%), 9.2 mg (16%) of **11a** and 9.7 mg (23%) of unreacted **8a**. The products given from **8b** were mixture of **9** and **10** (51%), **11b** (15%) and unreacted **8b** (18%).

Compounds **9** and **10** obtained from **8a** had pmr (deuteriochloroform): 8.03 (m, 2H), 7.67 (m, 2H), 6.03 (s, 1H, *ca.* 67% of the expected intensity), 3.88 (t, 4H), 3.50 (t, 4H).

Compounds **9** and **10** obtained from **8b** had pmr (deuteriochloroform): 8.03 (m, 2H), 7.67 (m, 2H), 6.03 (s, 1H, *ca.* 70% of the expected intensity), 3.88 (t, 4H), 3.50 (t, 4H).

Deuterium Exchange of **2**, **7** and **9**.

Into a nmr tube 1 ml of methanol-d_4, 20 mg of **2** or **7** or **9** and 10 µl of morpholine was added. The tube was held at room temperature for five days and the nmr spectrum was taken. Intensities of proton signal at 5.80, 6.90 or 6.03 ppm assigned as the 3-hydrogen for **2**, the 4-hydrogen for **7** or 3-hydrogen for **9** did not change.

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