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Regioselectivity of conjugate additions to monoalkyl-1,4-benzoquinones

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Abstract: The regioselectivity of the reaction of conjugate addition of thiols, amines, methanol and hydrogen chloride with the monoalkyl-1,4-benzoquinones avarone and 2-*tert*-butyl-1,4-benzoquinone was investigated. It was shown that the regioselectivity of the reaction is influenced by the electrophilicity of position 5 in unprotonated 2-alkylquinones, the increased electrophilicity of position 6 in acidic medium, and by the acidity of the intermediate hydroquinones.

Keywords: quinone, avarone, conjugate addition, regioselectivity.

INTRODUCTION

Although conjugate addition is a well studied reaction of *p*-quinones, certain ambiguities regarding the regioselectivity observed in the reaction of substituted quinones still remain. It is generally accepted that in 1,4-benzoquinones having an electron-donor substituent, the most reactive position is 5, and in quinones with an electron-acceptor or an unsaturated substituent, the most reactive position is either 6 or 3.[1–4] In our efforts to prepare new derivatives of the naturally occuring quinone avarone **I** (Fig. 1)[5–7] by conjugate addition, differences in regioselectivity were observed. In this study, the results obtained using thiols, amines and alcohols as nucleophiles are presented. The reactivity of 2-*tert*-butyl-1,4-benzoquinone **II** (Fig. 1), as a model compound, was also investigated for comparison.

EXPERIMENTAL

Conjugate addition was carried out under standard conditions.[7] In a typical experiment, to a solution of 1.6 mmol of the quinone in 50 ml ethanol-water 1:1, 1.6 mmol of the nucleophile were added. To improve the reactivity of aliphatic thiols, the solution was made weakly alkaline (4.5 % $NaHCO_3$) and the reaction was carried out under nitrogen to prevent polymerisation of the quinone. Since the redox potential of amino- and alkoxy- derivatives is low,[8] oxidation of the intermediate hydroquinones either by the starting quinone or by

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atmospheric oxygen occurs. In the reaction with alcohols, acid catalysis was applied (anh. $ZnCl_2$).[9] Chloro derivatives were also obtained under acidic conditions using hydrogen chloride in chloroform.[9]

The structure of the obtained quinones was determined using ^{1}H-NMR and ^{13}C-NMR spectroscopy. In the ^{1}H-NMR spectra of all 5- substituted products there are always two singlets in the spectral region corresponding to the quinone moiety, whereas in the spectrum of 6-substituted products there are two doublets with $^4J \approx 2.2$ Hz. For the analysis of the ^{13}C-NMR spectra, previously detemined increments were used.[9] The full characterization and biological activity of the synthesized derivatives will be published elsewhere.

RESULTS AND DISCUSSION

The reaction of quinones with nucleophiles occurs by the mechanism of conjugate addition followed by oxidation of the intermediate hydroquinone by either the starting quinone or by atmospheric oxygen (Fig. 1).[1]

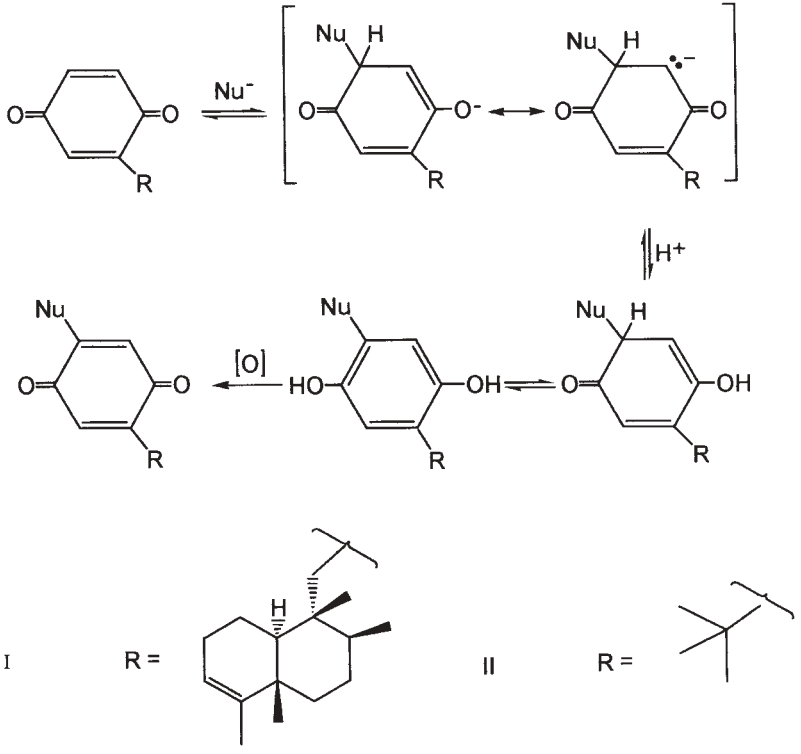

Fig. 1. Mechanism of conjugate addition to quinones. Only the reaction at position 5 is represented.

From the results given in Table I, it can be concluded that with good nucleophiles the reaction occurs predominately or exclusively at the most electrophilic position 5, while poor nucleophiles are usually introduced in position 6. Aliphatic thiols are the most reactive of all the applied classes of nucleophiles and only 5-substituted products were obtained. Thiophenol is less nucleophilic and some of the 6-substituted product was also obtained. The reaction with aliphatic amines afforded both types of products, but the reaction of aromatic amines, which are poorer nucleophiles, took place only at position 6. The reac-

tion with methanol, which is also a weak nucleophile, followed the same substitution pattern. The 3-substituted products were never formed in these reactions.

TABLE I. Yields of substituted quinones under standard reaction conditions and the respective melting points

Derivative	Yield/%		M.p./ºC	
	5[a]	6[a]	5[a]	6[a]
Isopropylthioavarone	44	0	Oil	–
Propylthioavarone	55	0	Oil	–
Isobutylthioavarone	65	0	Oil	–
Butylthioavarone	90	0	Oil	–
tert-Butylthioavarone	53	0	Oil	–
Phenylthioavarone	68	7	134–136	100–102
Isopropylthio-2-*tert*-butyl-1,4-benzoquinone	19	0	Oil	–
Propylthio-2-*tert*-butyl-1,4-benzoquinone	32	0	Oil	–
Isobutylthio-2-*tert*-butyl-1,4-benzoquinone	23	0	Oil	–
Butylthio-2-*tert*-butyl-1,4-benzoquinone	21	0	Oil	–
tert-Butylthio-2-*tert*-butyl-1,4-benzoquinone	15	0	Oil	–
Phenylthio-2-*tert*-butyl-1,4-benzoquinone	17	0	Oil	–
Aminoavarone[7]	50	25	84–85	78–80
Methylaminoavarone[7]	33	19	161–164	152–155
Ethylaminoavarone[7]	43	35	110–112	122–124
Butylaminoavarone	21	19	Oil	Oil
Phenylaminoavarone	0	12	–	Oil
p-Hydroxyphenylaminoavarone	0	20	–	Oil
Amino-2-*tert*-butyl-1,4-benzoquinone	44	0	140	–
Butylamino-2-*tert*-butyl-1,4-benzoquinone	23	21	95	102
Phenylamino-2-*tert*-butyl-1,4-benzoquinone	0	49	–	Oil
p-Hydroxyphenylamino-2-*tert*-butyl-1,4-benzoquinone	0	71	–	77–79
Methoxyavarone[9]	0	65	–	94
Methoxy-2-*tert*-butyl-1,4-benzoquinone	0	53	–	84–85[10]
Chloro-3',4'-dihydroavarone[9]	90	0	66	–
Chloro-2-*tert*-butyl-1,4-benzoquinone	91	0	101	–

[a]Positions 5 and 6 in the molecule of 2-*tert*-butyl-1,4-benzoquinone correspond to positions 4' and 3', respectively, in the molecule of avarone.

The more or less pronounced tendency of poor nucleophiles to react at position 6 can be explained by two causes. The reaction conditions for such nucleophiles are often acidic, since it is necessary to increase the quinone electrophilicity, and so, position 6 becomes more activated (Fig. 2). It should be noted that on increasing the acidity of the reaction medium to pH 5 (acetate buffer) the yield of 3'-phenylthioavarone was doubled, the overall

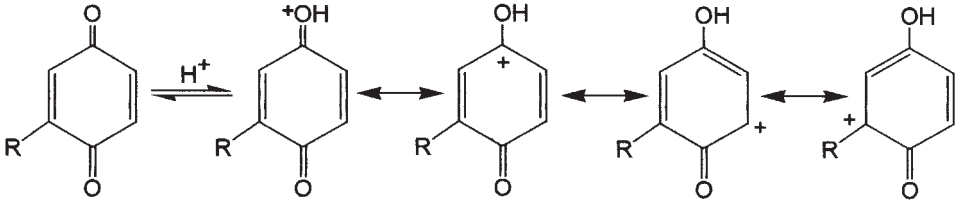

Fig. 2. Activation of position 6 in 2-alkylquinones by protonation.

yield being unchanged. However, the reaction with aromatic amines has the same outcome under both acidic and neutral conditions, so that the regioselectivity can not be a consequence of acid catalysis only. The factor governing the regioselectivity in this case could be the acidity of the 5- and 6-substituted 2-alkylhydroquinones, because in the second step of the reaction deprotonation takes place, and it is to be expected that the reaction would proceed faster *via* the more acidic intermediate. The acidity constants (pK_{a1}) were estimated for some of the intermediate hydroquinones using the Hammett σ_{meta} substituent constants, special σ constants for *para*-substituents in phenols, and apparent σ_{ortho} constants for phenols.[11] According to the available data, *tert*-butyl, methylthio, dimethylamino, amino, methoxy and chloro substituents were taken into account. The estimated pK_{a1} values of some of the 5- and 6-substituted 2-*tert*-butylhydroquinones are given in Table II. With chloro, methylthio and amino substituents, the 5-substituted derivatives are more acidic, whereas with dimethylamino and methoxy derivatives, the 6-substituted ones are. The reaction products were indeed quinones substituted in the 5 position with alkylthio and chloro groups and in the 6 position with the methoxy group. Mixtures were obtained with amino and alkylamino derivatives with the 5-substituted products prevailing with amino substituents (the 5-substituted hydroquinone is more acidic) and almost equal amounts of both isomers with alkylamino substituents, where the 6-substituted hydroquinone is more acidic.

TABLE II. Estimated pK_{a1} values of 5- and 6-substituted 2-*tert*-butylhydroquinones

Substituent	5-	6-
Methylthio	9.38	9.74
Chloro	8.54	9.50
Amino	9.89	10.05
Dimethylamino	10.86	10.39
Methoxy	10.05	9.81

In conclusion, the regioselectivity of conjugate addition to 2-alkyl-1,4-benzoquinones is governed by several opposing effects: the electrophilicity of position 5 of unprotonated quinones, the increased electrophilicity of position 6 in acidic medium and the acidity of the intermediate hydroquinone.

As the biological effects of quinones including avarone are based in part on their ability to generate oxygen radicals,[12] but also on the addition of cellular nucleophiles to the

quinone moiety,[13,14] the obtained results might also be helpful for a better understanding of the mechanisms of their biological activity.

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ИЗВОД

РЕГИОСЕЛЕКТИВНОСТ КОНЈУГОВАНЕ АДИЦИЈЕ НА МОНОАЛКИЛ-1,4-БЕНЗОХИНОНЕ

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Проучавана је региоселективност конјуговане адиције тиола, амина, метанола и хлороводоника на моноалкил-1,4-бензохиноне аварон и 2-*tert*-бутил-1,4-бензохинон. Показано је да на региоселективност реакције утичу електрофилност положаја 5 непротонованих 2-алкил-хинона и повећана електрофилност положаја 6 у киселој средини, као и киселост интермедијерних хидрохинона.

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