Pergamon

Tetrahedron Vol. 50, No. 29, pp. 8809-8814, 1994

0040-4020/94 $7.00+0.00

0040-4020(94)00487-0

The Mechanism of the Gibbs Reaction. Part 2[1]: The *Ortho* ⇌ *Ortho* 2,4-Cyclohexadiene-1-one Rearrangement of the Reaction Product of 2,6-Di-*tert*-butyl-4-chlorophenol and 2,6-Dichlorobenzoquinone N-chloroimine

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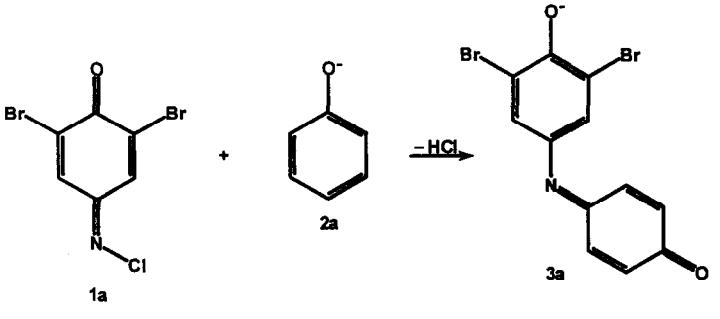
Abstract: The saturation transfers which were observed during the ^{1}H NOE difference measurements prove an *ortho* ⇌ *ortho* 2,4-cyclohexadiene-1-one rearrangement of the reaction product of 2,6-di-*tert*-butyl-4-chlorophenol and 2,6-dichlorobenzoquinone N-chloroimine. This process is an intramolecular rearrangement.

In 1927 H. D. Gibbs suggested the use of 2,6-dibromobenzoquinone N-chloroimine (**1a**) as a phenol assay reagent[2] (Scheme 1). According to his method, phenol (**2a**) reacts quantitatively with N-chloroimine **1a** in alkaline solution to give the indophenol anion **3a**, the concentration of which is established by colorimetric measurements.

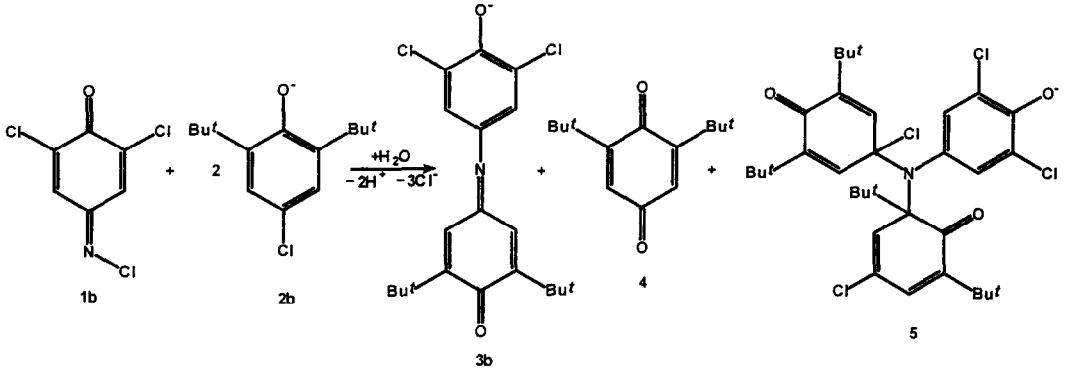


Scheme 1

Since then Gibbs reaction has been generally used[3-17], but **1a**[3-6] is replaced in most cases by the corresponding 2,6-dichloro compound **1b**[6-13]. The assay is usually positive even in the case when the phenol measured carries a substituent other than hydrogen at the *para* position, e. g., CH_2NH_2[4], $CH_2N(CH_3)_2$[4], CH_2OH[15], COOH[16], OCH_2Ph[4], alkoxy[4,8-10], Cl[4,8], Br[8] and I[8,10], or even F[10]. It is remarkable that among these *para* substituents there are several which are nucleofuges, i. e., they can be eliminated exclusively as an anion. There are some

controversial mechanistic considerations[2,6,15] and review[18], which have prompted us to reinvestigate this reaction in detail.

During our experiments the Gibbs reaction of several phenol derivatives were studied. In the present paper we focus on the reaction of 2,6-di-*tert*-butyl-4-chlorophenol (**2b**) with N-chloroimine **1b**. When the phenol **2b** was reacted with N-chloroimine **1b** in the molar ratio of 2.5:1, indophenol **3b** and 2,6-di-*tert*-butylbenzoquinone (4) were obtained together with compound **5** (Scheme 2).



Scheme 2

The structure of compound **5** was determined by ^{1}H and ^{13}C NMR methods (see Fig. 1)[19]. During ^{1}H NOE difference measurements (at T=264 K) irradiation of the vinyl protons (δ 4.85 ppm) and the *tert*-butyl groups (δ 0.92 ppm) of the 2,4-cyclohexadiene-1-one moiety resulted in saturation transfer to the other vinyl proton (δ 6.82 ppm) and *tert*-butyl group (δ 1.21 ppm) of the same ring respectively. Moreover irradiation of the *tert*-butyl signal at 0.92 ppm resulted in NOE at both vinyl protons of the 2,4-cyclohexadiene-1-one too.

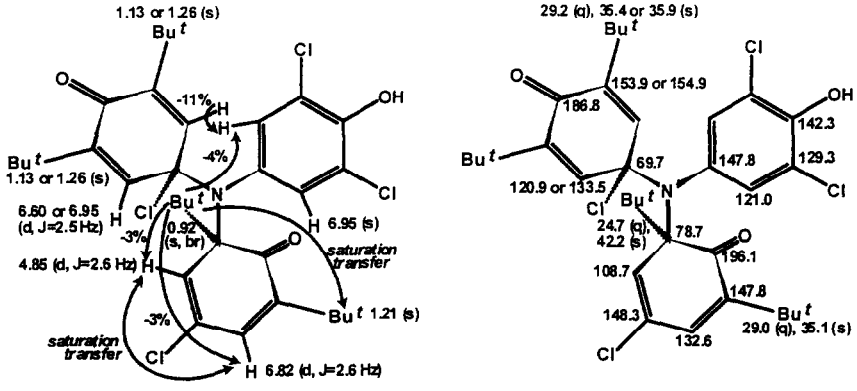
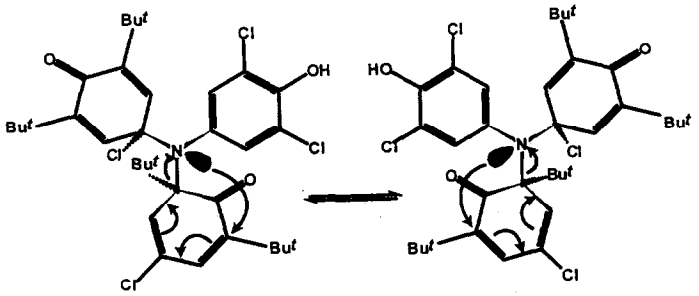


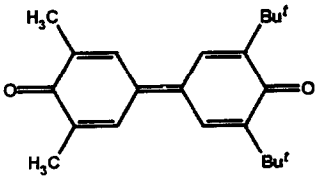
Figure 1.

Irradiation of the vinyl protons of the 2,4-cyclohexadiene-1-one moiety of compounds **5** in the reaction mixture resulted in no saturation transfer to the aryl protons of phenol **2b** and similarly at the irradiation of the aryl protons of **2b**, no effect was observed on the vinyl protons of compound **5**. These results can be interpreted by an intramolecular *ortho* ⇌ *ortho* 2,4-cyclohexadiene-1-one rearrangement of compound **5**.
The results of the ^{1}H NOE measurements (Fig. 1) refer also to the fact, that the steric structure of compound **5** is favourable for an intramolecular rearrangement. Namely the electron pair of the nonbonding orbital of the nitrogen atom is in a proper orientation to bring a nucleofilic attack on the double bond next to the carbonyl group, inducing the rearrangement of the double bonds and fission of the C-N bond (Scheme 3)[20].

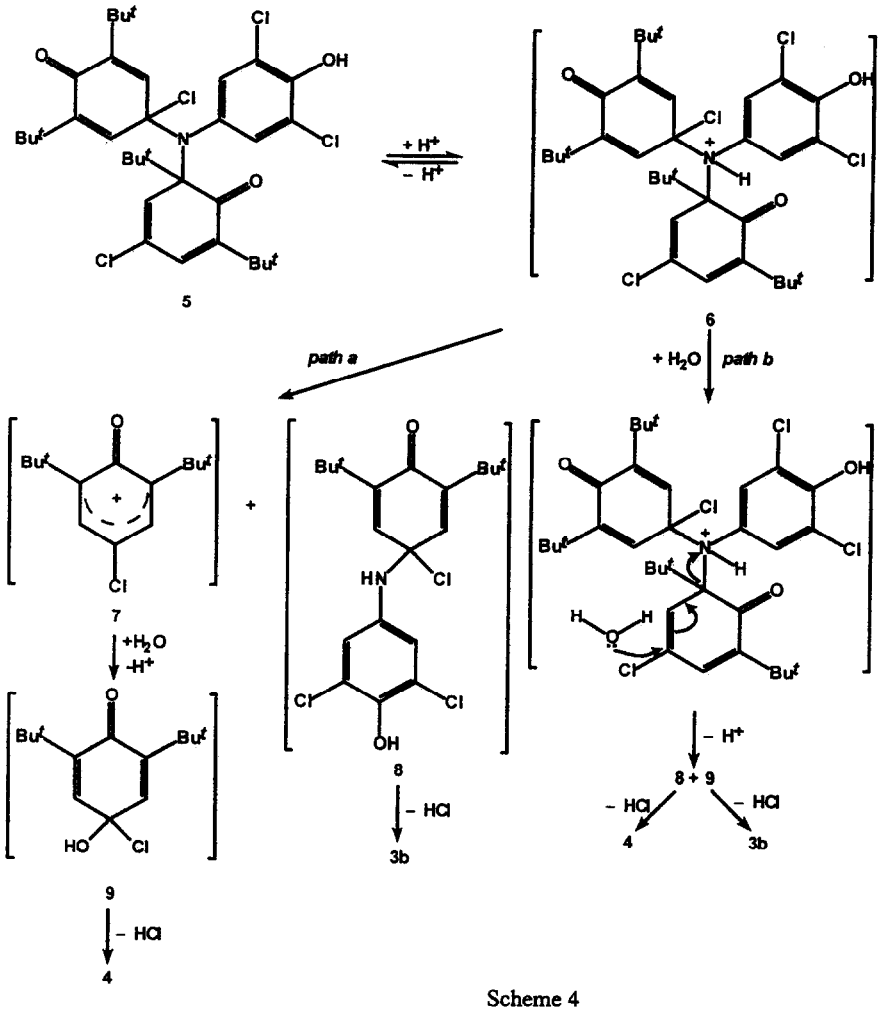


Scheme 3

Compound **5** is acid-sensitive. Protonated the nitrogen atom the molecule will split into indophenol **3b** and quinone **4**. We assume two possible pathways for the acidic decomposition (Scheme 4). According to ***path a***, a spontaneous heterolysis of the protonated amine **6** occurs, giving phenoxenium ion[21] **7** and the amine **8**. The former will be transformed first into quinol **9** and then quinone **4** is formed by the less of hydrochloric acid. From the amine **8** on other hand indophenol **3b** will be formed by the elimination of hydrochloric acid. Another possibility (***path b***) may be that a water molecule attacks at the carbon atom containing chlorine in the 2,4-cyclohexadiene-1-one part of molecule **6**. This results in the rearrangement of the double bonds and the fission of the C-N bond. The products of this step are again the amine **8** and quinol **9**, from wich the final products **4** and **3b** are formed respectively, as described above. When instead of hydrochloric acid another proton-donor was given to the solution, which itself or the conjugate base of which could react as a nucleofile (e.g. 2,6-dimethylphenol **2c**), again indophenol **3b** was produced, but instead of quinone **4** compound **10** was resulted.



10



Scheme 4

Experimental Section

The ^1H NMR and ^{13}C NMR spectra were recorded by a Bruker AC 250 spectrometer equipped with an ASPECT computer, at frequencies of 250.1 and 62.9 MHz, respectively. The NMR spectra were recorded in acid free 1,1,2,2-tetrachloroethane-d_2 (TCE) or in $CDCl_3$ with tetramethylsilane (TMS) and TCE (73.8 ppm) as the reference standards. In the experiments ^1H, ^1H-^1H COSY, ^1H NOE, ^{13}C, DEPT, selective INEPT[22], proton coupled ^{13}C(Gated), selective proton decoupled ^{13}C, ^{13}C-^1H COSY methods were applied[23]. The ^1H NOE difference measurements (at T = 264K) were done after the ^{13}C NMR measurements and the solution were diluted 2.0-2.5 times of its volume and were deoxygenated with argon gas.

Reaction of 2,6-di-*tert*-butyl-4-chlorophenol (2b) with 1b. To a solution of **1b** (31 mg, 0.15 mmol) in *tert*-butanol (10 mL), a solution of $Na_2B_4O_7$ (225 mL, 6 x 10^{-3} M) was poured, then a solution of **2b** (90 mg, 0.37 mmol) in *tert*-butanol (30 mL) was added. The mixture was kept at ambient temperature (25°C) for 20-25 minutes then the solution was shaken with hexane (100 mL), the pH was adjusted to 6.5-7.0 (6.5 mL, 0.5 M

HCl) and after repeated shaking, the two layers were separated. The extraction was repeated with 100 mL of solvent. The organic extracts were combined, washed with water (2x100 mL), dried over anhydrous sodium sulphate and concentrated to 4-5 mL at reduced pressure (water bath temperature 30-35°C). After addition TCE (0.5 mL) the rest of hexane was removed. The molar ratio of the products **3b**:**4**:**5** was 1:1:2 by ^{1}H NMR. **4** ^{1}H NMR δ 6.49 (s, 2H), 1.26 (s, 18H); ^{13}C NMR δ 188.4 (C-4), 187.5 (C-1), 157.7 (C-2 and C-6), 129.9 (C-3 and C-5), 35.4 (*tert*-butyl, s), 29.3 (*tert*-butyl, q). The stability of **5** was markedly affected by the acidity of the solvent, but in water and acid-free TCE the rate of conversion to indophenol **3b** could be significantly suppressed (no significant transformation was detected at 250 K during 3 days). ^{1}H NMR spectra of the indophenol **3b** is sensitive to both acids and changes in temperature. Since the transformation of compound **5** to quinone **4** and indophenol **3b** is an acid producing step, the δ_H values of **3b** depend on time ^{1}H NMR spectra of **3b** were recorded within 20 minutes at 298 K:7.25 (s, br, 1H), 7.05 (s, br, 2H), 6.85 (d, *J*=2.5 Hz, 1H). After compound **5** was converted to indophenol **3b**, dichloromethane (30 mL) was added to the solution, then it was washed first with $Na_2B_4O_7$ (0.05 M, 2x10 mL) and subsequently with water (10 mL), dried and the dichloromethane was removed by evaporation under reduced pressure. **2,6-bis-(1,1-dimethylethyl)-4-[(3,5-dichloro-4-hydroxyphenyl) imino]-2,5-cyclohexadien-1-one (3b)**: ^{1}H NMR δ 6.97 (d, *J* = 2.5 Hz, 1H), 6.89 (s, 2H), 6.77 (d, *J* = 2.5 Hz, 1H), 1.31 (s, 9H), 1.22 (s, 9H); ^{13}C NMR δ 187.3 (C-1), 159.5 (C-4), 154.4 and 153.4 (C-2 and C-6), 145.5 and 142.6 (C-1' and C-4'), 134.1 and 120.8 (C-3 and C-5), 121.5 (C-3' and C-5'), 121.3 (C-2' and C-6'), 35.7 (*tert*-butyl, s), 35.2 (*tert*-butyl, s), 29.3 (*tert*-butyl, q).

Reaction of compound 5 with 2,6-dimethylphenol (2c). Compound **5** was prepared as described above in two experiments, the solutions (TCE) were combined. To this solution, phenol **2c** (30 mg, 0.25 mmol) was given and it was left at room temperature for 40 min. Dichloromethane (100 ml) was given to the solution and it was washed with NaOH (4x75 ml, 0.1 M) and water (2x50 ml). After evaporation the residue was column-chromatographed on silica gel with eluents in the following order: hexane/benzene 8:2, hexane/benzene 1:1 and benzene. **10** ^{1}H NMR ($CDCl_3$) δ 7.64 (s, 2H), 7.60 (s, 2H), 2.10 (s, 6H), 1.29 (s, 18H); ^{13}C NMR δ 187.3 (s), 186.6 (s), 150.9 (s), 139.6 (s), 136.1(s), 135.7 (s), 128.7 (d), 125.9 (d), 36.1(s), 28.7 (q), 17.2 (q).

Acknowledgement

The authors thank Dr. B. Podányi for helpful discussion on this theme.

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19. The structure of the unstable compound **5**, existing only in solution was elucidated as follows : the signals of **5** were assigned as a part of multicomponent systems in which the signals of the known compounds (phenol **2b**, indophenol **3b** and quinone **4**) were selected by adding (them prepared in a different route) into the solution investigated.
20. As an alternative to the ionic mechanism described above, the rearrangement observed could be explained by the combination of the radical pair formed by a homolytic fission of the C-N bond in the solvent cage. Similar rearrangement of 2,6-bis(1,1-dimethylethyl)-6-bromo-4-cyano-2,4-cyclohexadiene-1-one was described proposing an intermolecular radical mechanism (Rieker, A.; Zeller, N.; Kessler, H. *J. Am. Chem. Soc.* **1968**, *90*, 6566-6567.).
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23. Softwares from Bruker Library were used.

(*Received in UK* 21 *December* 1993; *revised* 31 *May* 1994; *accepted* 3 *June* 1994)