Catalytic Dehalogenation of Halogenated Pyridine Donors under DOW-Phenol Conditions

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Various halogenated pyridines (2-fluoropyridine, 2-chloropyridine, 2-bromopyridine, 3-bromopyridine, 2,5-dibromopyridine, and 3,5-dibromopyridine) are subject to catalytic reduction and substitution under DOW-phenol conditions; copper(I) benzoate is shown to play a key role in these processes. In the absence of copper(I), the halogenated pyridines do not react with benzoic acid, while after precipitation of copper(I) halide the dehalogenation process stops. Marked differences are observed between the copper(I)-catalyzed dehalogenation of the halopyridines and the previously reported dehalogenation of halogenated aromatics. While the copper(I)-catalyzed substitution of haloaryl compounds by benzoate makes only a minor contribution to the overall dehalogenation process, substitution of halopyridine compounds is at least as important as the reduction reaction. Furthermore, the reaction with halopyridine compounds is regioselective, in contrast to that with halogenated aryl compounds.

Introduction

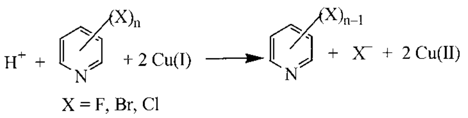
Many halogenated hydrocarbons are hazardous due to their tendency to accumulate in the body and the resultant damage of nerves and hepar.[1] Halogenated hydrocarbons are widely used as solvents and monomers for polymer production. Furthermore, halogenated compounds are produced in various combustion processes, including (natural) wood burning and the combustion of waste. TCDD, 2,3,7,8-tetrachlorodibenzo[1,4]dioxin, known as the "Seveso dioxin", is a well-known representative of the latter group.[1] Halogenated compounds have also played a role in parasite control (DDT).[2] The transformation of halogenated hydrocarbons into less harmful compounds is still a challenge in chemistry. Among the methods currently used industrially, electrochemical dehalogenation and decomposition by iron catalysts are well-known processes.[3,4] A recent discovery was that chlorinated and brominated hydrocarbons can be catalytically reduced under DOW-phenol conditions,[5] and this was confirmed in our investigation of the role of different apical donors on the DOW-phenol process.[6] We have investigated this process in some detail and report here the scope of this novel catalytic reaction.

Results

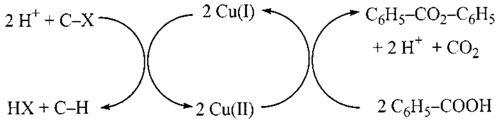
The catalytic reduction of halogenated hydrocarbons under DOW-phenol conditions consists of two steps:

(i) Copper(I) is oxidized by the halogenated pyridines to copper(II) [Equation (1)].

(ii) Copper(II) is reduced to copper(I) during the thermal decomposition of copper(II) benzoate (DOW-phenol reaction) [Equation (2)].

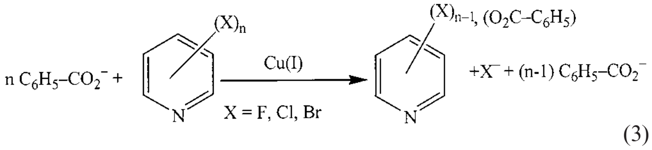


(1)



(2)

Another possible route for the dehalogenation of the halogenated pyridines is the nucleophilic substitution of a halogen atom by a benzoate [Equation (3)].



(3)

During a catalytic cycle, a halogen in a carbon−halogen bond is substituted by a benzoate and, in acidic solution, one molecule of HX is produced. The reaction stops when all halogenated substrates are reduced or substituted, or when the copper catalyst has completely precipitated as the Cu[I] halide.

Table 1 gives an overview of the results obtained in the thermal decomposition of the copper(II) benzoates with apical donors. Apart from the expected DOW-phenol product, i.e. phenyl benzoate, pyridine, *ipso*-benzoate substituted

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Table 1. Overview of the results for the thermal decomposition of the pure complexes [Cu_2(benzoate)$_4$(n-X-pyridine)$_2$] at 230 °C (HPLC and LC-MS)

Apical donor	DOW Phenol	Cu^{I} products			Benzoic acid
	phenyl benzoate	pyridine	n-ArCO$_2$-pyridine	n-HO-pyridine	
2-F-pyridine[a]	3.6	0.3	42.1	3.9	25.9
2-Cl-pyridine	7.0	1.0	36.5	3.1	25.8
2-Br-pyridine	4.4	2.2	32.1	2.9	23.8
3-Br-pyridine	12.2	9.3	13.9	3.2	10.2
2,5-Br$_2$-pyridine	0.5[b]	0.5	28.6	3.3	20.8
3,5-Br$_2$-pyridine	1.9	1.4	25.2	3.2	9.8

[a] 250 °C (no reaction occurred at 230 °C); 3.4% of benzene was also produced. − [b] No phenyl benzoate was observed, but a mixture of the precursor *o*-, *p*-, and *m*-benzoyloxybenzoic acids; *ortho*-selectivity: 66.7%.

pyridines, and hydroxypyridine are obtained. Dehalogenation appears to be essentially complete in these experiments. The results demonstrate the scope of the reaction: F-, Cl-, and Br-substituted pyridine ligands undergo reduction and substitution by benzoate under DOW-phenol conditions. Substitution follows the order F > Cl > Br in the series of 2-halopyridine ligands, with relative molar amounts of the substituted products amounting to 99%, 94%, and 87%, respectively. The reduction shows an opposite trend, with relative amounts of pyridine of 1%, 6%, and 13%, respectively. In the case of 3-bromopyridine, the reduction and substitution processes both account for approximately 50% of the overall reaction. Similar behavior is observed for the dibromopyridine donors: the observed monobenzoyloxypyridine compounds are the result of a reduction and substitution cycle. A double reduction process yields pyridine, while a double substitution yields dibenzoyloxypyridine. Both are observed by LC-MS, albeit at very low levels. Hydroxypyridine products, resulting from hydrolysis, are also detected. Phenol, i.e. the hydrolysis product of phenyl benzoate, is not observed. In the case of 2-fluoropyridine, a significant amount of benzene is also obtained, which is probably formed as a decomposition product due to the relatively high temperature (250 °C).

Discussion

Comparing the different pyridine substrates, three issues need clarification: 1) the order of the halogens in both substitution and reduction, 2) the order of reactivity in the series of brominated pyridines with respect to their regiochemistry, and 3) the observation that phenol, the hydrolysis product of phenyl benzoate, is not present in the reaction mixtures, while the hydroxypyridines are present in all the mixtures.

A possible explanation for these issues emerges from the proposed mechanism.[5] One electron is donated by Cu^{I} to the carbon−halogen bond, possibly involving the temporary formation of a cuprate. A second Cu^{I} donates an electron to the carbon, leading formally to a carbanion stabilized by two Cu^{II} centers. The resulting halide might form a Cu^{II}·X·Cu^{II} bridge. The Cu^{II}-stabilized carbanion is then protonated by benzoic acid and eliminated from the Cu^{II} coordination sphere. Alternatively, a benzoate might act as a nucleophile after the donation of the first electron to the carbon−halogen bond, leading to net overall nucleophilic substitution of the original halogen by a benzoate. In this case, the role of Cu^{I} is to improve the leaving group ability of the halogen. The tentative mechanism is shown in Figure 1.

Important features are the properties of the reactive intermediates and transition states, i.e. the radicals and carbanions derived from the substrates. Quantum mechanical calculations are a useful tool for the investigation of the properties of such species. Semi-empirical calculations (PM3) were used for an efficient comparison of the entire series. DFT calculations (BP level) on the series of monohalogenated pyridines gave essentially the same results. Computational details are given in the Exp. Sect.. Table 2 lists the computed electrostatic charges on the corresponding C-atoms of the 2- and 3-halogenated pyridines.

2-Fluoropyridine has by far the highest positive charge, +0.858, on the C2 atom, followed by 2-chloro- and 2-bromopyridine, with charges of +0.504 and +0.305. 3-Bromopyridine, on the other hand, has a negative charge on the C3 atom (−0.634). If the nucleophilic substitution can be correlated with the positive charge on the relevant carbon atoms, the proposed order by PM3 would be: 2-fluoropyridine > 2-chloropyridine > 2,5-dibromopyridine (2) > 2-bromopyridine > 3-bromopyridine > 2,5-dibromopyridine (5) > 3,5-dibromopyridine. This order is indeed observed for the series of 2-halopyridines. 2,5-Dibromopyridine is a special case with its two different carbon−bromine bonds. The C2 atom is positively charged, this charge being roughly equal to that on the C2 atom of 2-bromopyridine, while its C5 atom is even more negatively charged than the C3 atom of 3-bromopyridine. Therefore, 2,5-dibromo- and 3,5-dibromopyridine fit well in this sequence, being intermediate between the 2-bromo- and 3-bromopyridines.

If the reduction can be correlated with the negative charge on the corresponding pyridine anion, then the order predicted by PM3 calculations would be: 3-pyridine anion (−1.489) ≈ 5-bromo-3-pyridine anion (−1.467) ≈ 2-bromo-5-pyridine anion (−1.464) > 2-pyridine anion (−0.893) ≈ 5-bromo-2-pyridine anion (−0.840). This order

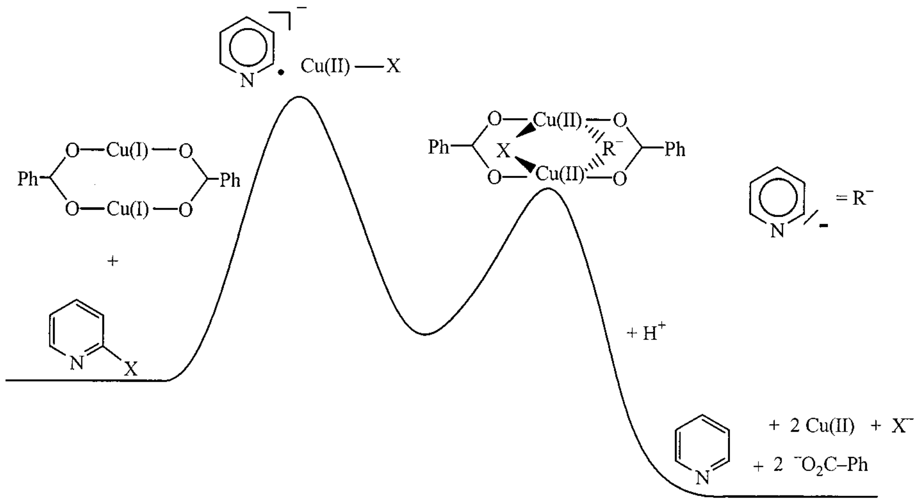

Figure 1. Proposed mechanism for the reduction of halogenated pyridines under DOW-phenol conditions

Table 2. Electrostatic charges of the halogenated pyridines, pyridyl radicals, and pyridine anions; computations were carried out at the PM3 and BP levels

pyridine substrate	PM3 electrostatic charge	BP electrostatic charge
2-fluoropyridine	+0.858	+0.718
2-chloropyridine	+0.504	+0.437
2-bromopyridine	+0.305	+0.413
3-bromopyridine	−0.634	−0.299
2,5-dibromopyridine 2-position 2,5-dibromopyridine 5-position −0.651	+0.338	
3,5-dibromopyridine	−0.747	
2-pyridyl radical	−0.089	+0.038
3-pyridyl radical	−0.439	−0.299
2-bromo-5-pyridyl radical	−0.428	
5-bromo-2-pyridyl radical	+0.084	
5-bromo-3-pyridyl radical	−0.497	
2-pyridine anion	−0.893	−0.793
3-pyridine anion	−1.489	−1.188
2-bromo-5-pyridine anion	−1.464	
5-bromo-2-pyridine anion	−0.840	
5-bromo-3-pyridine anion	−1.467	

indeed explains the different reduction yields, i.e. of 9.3% for 3-bromopyridine and of 2.2% for 2-bromopyridine. A similar pattern is observed for 2,5-dibromopyridine (0.5%) and 3,5-dibromopyridine (1.4%), although the double reduction yields are rather low. This also leads to speculation concerning the major product derived from the two dibromopyridines; that arising from 2,5-dibromopyridine should be 2-benzoyloxypyridine (28.6%), whereas the corresponding product from 3,5-dibromopyridine should be 3-benzoyloxypyridine (25.2%).

Conclusion

(i) Semi-empirical quantum chemical calculations are an excellent tool for interpreting the observed order of the halogens in the substitution reaction of 2-halopyridines; the opposite order for the reduction might be a simple consequence of the preference for substitution, while the next steps (pyridyl radical, pyridine anion) become increasingly independent of the leaving group in the proposed mechanism.

(ii) The difference between the regioisomers 2-bromo- and 3-bromopyridine can be adequately explained, both in terms of substitution and reduction.

(iii) At first sight, it might seem surprising that the hydrolysis products hydroxypyridines are observed, while phenol is not. However, with the benzoyloxypyridines intramolecular base hydrolysis is possible, whereas with phenyl benzoate it is not.

Finally, we would like to comment on the behavior of the halopyridines as compared with that of the haloaromatics. With the latter, no indication was found for a major contribution of the nucleophilic substitution reaction and no regioselectivity was observed.[5] An appealing explanation is that the benzene ring is an electron-rich aromatic system in comparison with the pyridine ring. Therefore, nucleophilic substitution is more likely to occur on the electron-poor pyridine system than on benzene. Moreover, the reaction mixtures composed of benzoic acid, Cu^I benzoate, and a haloaryl compound are rather acidic, whereas the mixtures composed of benzoic acid, Cu^I benzoate, and a halopyridine are basic, at least locally. The final step in the reduction requires a proton. Therefore, the reduction should be easier in the more acidic environment. Fortunately, halogenated pyridines are not produced in very large quantities because the observed regioselectivity has to be considered as a disadvantage for an environmental technology.

Experimental Section

Materials and Analytical Procedures: Copper(II) benzoate was prepared from copper(II) sulfate and sodium benzoate. All other compounds were purchased from Sigma or Aldrich and were used without further purification. − **Pyrolyses:** The pure copper(II) benzoate salts with the apical donors (150 mg in each case) were heated for 7 h at 230 °C in sealed silica tubes. The tubes were filled under argon. Since in the case of copper(II) benzoate with 2-fluoropyridine no reaction occurred at 230 °C, this experiment was repeated at 250 °C. After cooling to ambient temperature, the tubes were opened and the products were analyzed by HPLC. In the case of the halogenated pyridines, the products were also analyzed by LC-MS. − **Electrospray MS:** Positive-ion ESI-MS data were obtained on an HP1100 quadrupole LC-MS system (Agilent Technologies, Waldbronn, Germany). Mass spectra were obtained in full scan mode from $m/z = 50-1000$ amu at a fragmentor voltage of 70 V and a capillary voltage of 3000 V. The drying gas flow was 10 L/min and the drying gas temperature was 350 °C. − **Reversed-Phase HPLC:** For reversed-phase HPLC, the black solids produced were dissolved in acetonitrile (2 mL) and then injected into an HP 1090 chromatograph with a Nucleosil 120−5 C18 column (500 × 4 mm) at 50 °C. The products were eluted with a gradient made up of different mixtures of eluents A and B [eluent A: 1 M H_3PO_4 (45 mL), conc. acetic acid (2 mL) and 1 M NaOH (35 mL) were added to water (1500 mL) and the pH of the solution was adjusted to 3.2 with 1 M NaOH; after the addition of acetonitrile (200 mL) the mixture was made up with water to give 2000 mL of eluent A; eluent B: 1 M H_3PO_4 (20 mL), conc. acetic acid (2 mL), and 1 M NaOH (60 mL) were added to water (60 mL) and the pH of the solution was adjusted to 6.6 with 1 M NaOH; after the addition of acetonitrile (1200 mL) the mixture was made up with water to give 2000 mL of eluent B]. A DAD (L-3000 Hitachi) was used for detection at 254 nm.

Computational Details

All calculations were carried out using the Titan molecular modeling suite of programs.[8] All molecules and fragments were geometry-optimized using the semi-empirical PM3 method. These structures were used as input data for a geometry optimization at the BP level (DFT), using the LACVP* basis set for Br and 6−31 G* for all other elements. DFT calculations were carried out only for the monohalogenated pyridines. The DFT results were in full accord with the PM3 results.

Acknowledgments

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[1] C. Bliefert, *Polychlorierte Dibenzodioxine, Dibenzofurane und Biphenyle*, VCH, Weinheim, **1994**, p. 276.

[2] C. Bliefert, *Pestizide*, VCH, Weinheim, **1994**, p. 332.

[3] D. Schmal, P. J. Van Duin, A. De Jong, *Elektrochem. Energ. Umwelttech.* **1991**, *124*, 241.

[4] S. V. Ho, D. E. McKenzie, R. G. Orth, *Patent WO 9704868*, **1997**.

[5] W. Buijs, *Cat. Today* **1996**, *27*, 159.

[6] W. Buijs, P. Comba, D. Corneli, Y. Mengerink, H. Pritzkow, M. Schickedanz, *Eur. J. Inorg. Chem.* **2001**, 3143−3149, preceding article in this issue.

[7] W. Buijs, *J. Molec. Cat. A: Chemical* **1999**, *146*, 237.

[8] Wavefunction, Inc., 18401 Von Karman Avenue Suite 370, Irvine, CA 92612, USA; Schrödinger, Inc., 1500 SW First Avenue, Suite 1180, Portland, OR 97201, USA.

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