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REACTIVITY OF METHYL DERIVATIVES OF NITROGENOUS HETEROCYCLES IN VAPOR-PHASE CATALYTIC OXIDATION

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A study has been made of the reactivity of methylpyridines, methylpyrazines, and methylquinolines in oxidation in the vapor phase in the presence of β-VO $(PO_3)_2$. Relationships have been found between the overall reaction rates of heterocyclic compounds and the charge on the ring nitrogen, and between the partial oxidation rate and the charge on the ring carbon atom adjacent to the methyl group. The partial oxidation rate of methylpyridines is given to a first approximation by the Hammet-type expression $\ln W_a = -3.5 + 4.6\ \Sigma\sigma$, with a correlation coefficient of 0.93.

The vapor phase oxidation of methylheterocycles with atmospheric oxygen over vanadium catalysts forms the basis of the industrial production of heteryl aldehydes, which are intermediates in the synthesis of biologically active compounds. In order to establish the most important structural features governing the reactivity of heterocyclic compounds in oxidation, and to obtain further information on the reaction mechanisms under comparable conditions, the oxidation of representatives of three classes of nitrogen heterocycles has been studied, namely pyridines, diazines, and quinolines. In the pulsed vapor-phase oxidation of these compounds (Table 1) in the presence of vanadyl β-polyphosphate at 400°C, the principal reaction products are the monoaldehyde and oxides of carbon. Under these conditions, 4-MP, 2,3-DMP, 2,5-DMP, 3,4-DMP, 2-MQ, and 4-MQ give predominantly the partial oxidation products, whereas oxidation of 3-MP, 3,5-DMP, and DMPZ results in extensive oxidation. The rates of total and partial oxidation W_a of the remaining compounds are similar. Comparison of the total oxidation rates (W_{tot}) of the pyridine bases shows that introduction of methyl substituents into the pyridine ring increases the overall reaction rate, but there is not clear relationship between the reactivity of the pyridines and the number of methyl groups present.

Under impulse conditions, the total conversion rate of monomethylpyridines and the amounts of aldehydes formed on oxidation over β-$VO(PO_3)_2$ decreases in the isomer sequence 4- > 2- > 3-, just as when vanadium oxide catalysts are used [1].

It is noteworthy that the sequence of reactivities of 2-, 3-, and 4-MP obtained under conditions which restrict the occurrence of subsequent reactions is similar to the rate of deuteration of the methyl groups in these compounds [2], and also to their reactivity in prototropic reactions, for example with sodamide [3]. In the quinoline series, 4-MQ also undergoes vapor phase oxidation more readily than 2-MQ both in total and partial oxidation (Table 1). These facts lead to the conclusion that the limiting step in the heterogeneous catalytic

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TABLE 1. Rates and Selectivity of Oxidation and Methylheterocyclic Compounds over Vanadyl Polyphosphate

Compound	Compound oxidized	Specific rates, μmole/(m² sec)		Selectivity in pyridinealdehydes, %
		W_{tot}	W_a	
1	Pyridne (P)	2,9	—	—
2	2-Methylpyridine (2-MP)	4,8	3,0	60
3	3-Methylpyridine (3-MP)	3,0	0,3	3
4	4-Methylpyridine (4-MP)	5,0	3,3	67
5	2,3-Dimethylpyridine (2,3-DMP)	3,9	3,2	81
6	2,4-Dimethylpyridine (2,4-DMP)	4,6	2,2	48
7	2,5-Dimethylpyridine (2,5-DMP)	3,9	1,7	44
8	2,6-Dimethylpyridine (2,6-DMP)	4,8	3,2	66
9	3,4-Dimethylpyridine (3,4-DMP)	5,6	3,7	65
10	3,5-Dimethylpyridine (b,5-DMP)	2,6	0,3	8
11	2,4,6-Trimethylpyridine (2,4,6-TMP)	3,7	1,8	47
12	2-Methyl-5-ethylpyridine (MEP)	3,0	1,6	56
13	Methylpyrazine (MP)	1,3	1,3	100
14	2,5-Dimethylpyrazine (DMPZ)	2,0	0,5	27
15	2-Methylquinoline (2-MQ)	2,4	2,1	89
16	4-Methylquinoline (4-MQ)	3,9	3,1	80

oxidation of nitrogen heterocycles has an ionic mechanism, and the rate of this step is dependent on the mobility of hydrogen in the methyl group.

The variations in the reactivity of monomethylpyridines in vapor phase catalytic oxidation are usually regarded as being due to the superimposition of conjugational and inductive effects. With methyl groups in the 3-position, there is no +M effect (the increased basicity of pyridine consequent upon the introduction of a methyl group into this position is attributed mainly to the +I effect), and the reactivity of 3-MP is similar to that of toluene. However, in 2- and 4-MP conjugation is increased to such an extent that some authors have assumed that the formation of quinoid structures is possible [3], the hydrogen of the methyl group thereby becoming highly mobile. However, as a result of the high electronegative inductive effect of the heteroatom at the 2-position, the shift in electron density at this position is reduced, and reactivity of the 2-CH_3 group is less than that of the 4-CH_3 group. Furthermore, according to nonempirical quantum chemical calculations [4], 2-MP should also be more stable overall then 4-MP.

In the oxidation of di- and trimethylpyridines over a vanadium phosphate catalyst, this sequence of reactivities of the methyl groups is maintained, i.e., the rates of conversion of the CH_3 group to CHO decrease in the sequence 4- > 2- and 6- > 3- and 5-. Similar behavior has been found in the oxidation of pyridine bases over vanadium oxide catalysts [5].

Since, in nitrogen heterocycles, interaction with acidic sites on the catalyst surface is most likely, to a first approximation it is desirable in assessing the effects of adsorptive interactions on reactivity to compare the reactivities of these compounds with their basicity.

An experimental measure of the basic properties of molecules in the vapor base is proton affinity (PA). However, the literature data on the PA of nitrogen heterocycles is highly ambiguous [6, 7]. For example, even using the same method of measurement, for pyridine the values vary from 908.7-943.0, and for 2-MP from 922.5-961.4 kJ/mole. We therefore resorted to a theoretical measure of basicity, namely the value of the negative charge on the nitrogen atom (q_N), as calculated by the MO LCAO PPDP/2 method, which provides a good description of the electron density distribution in organic molecules [8].

For all the compounds examined, as q_N is increased, the overall reaction rate increases (Fig. 1). For compounds 1-14, this relationship may be described by a trinomial equation, with a correlation coefficient of 0.89:

$$\ln W_{tot} = -2.4-21.7q_N+0.7\Sigma E_s^\circ;$$
$$S=0.18;\ F=34.5,$$

where ΣE_s° is the sum of the steric coefficients [9], which characterize steric hindrance in the reaction of the N-heterocycle with the catalyst, involving the nitrogen atom. The points for 2- and 4-MQ do not lie on this plot.

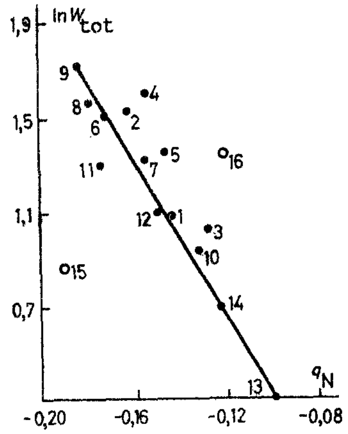

Fig. 1

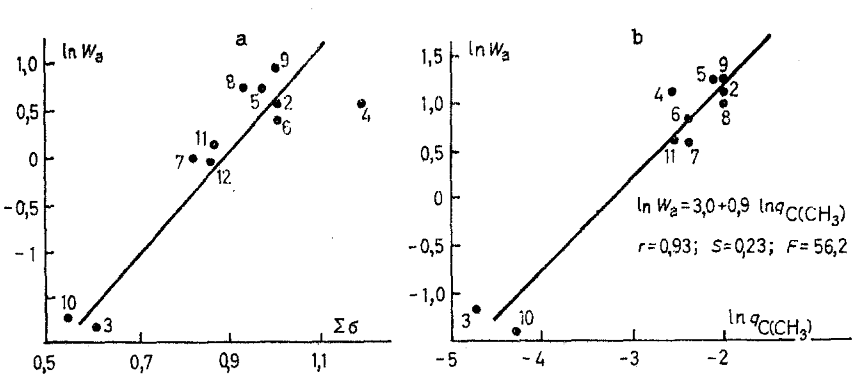

Fig. 2

Fig. 1. Plot of W_{tot} against the charge on the nitrogen atom.

Fig. 2. Plots of $\ln W_a$ against the induction contant (a) and the charge on the carbon adjacent to the methyl group (b).

As is well known, the heteroatom in pyridine may be regarded as a substituent introduced into the benzene ring in place of the CH fragment. In this case, the rate of formation of monoaldehydes in the oxidation of compounds 2-12 is satisfactorily approximated by a Hammet-type equation with σ-constants describing the electron-acceptor properties of the heteroatom (Fig. 2a):

$$\ln W_a = -3.5+4.6\Sigma\sigma;\ r=0.93;\ S=0.41.$$

In the case of 2,3- and 2,4-DMP, the sigma constants used were the sums $\sigma_{N_2} + \sigma_{n\text{-}CH_3}$ and $(\sigma_{N_4} + \sigma_{n\text{-}CH_3})$, as in [11].

Since these σ-constants were calculated [12] from the rate of replacement of chlorine by alkoxy-groups in pyridines, it may be that their use here indicates a similarity in the transmission of electronic effects in nucleophilic substitution and in vapor-phase catalytic oxidation at the stage of interaction with the catalyst.

From the values of the reaction constant ρ, obtained from the $\ln W_a$–σ plots, two conclusions may be drawn with respect to the mechanism of the partial oxidation of methylheterocycles: 1) Oxidation of the CH_3 group to CHO is a nucleophilic reaction, and 2) the surface complex in the transition state is largely ionic in character.

These features of the mechanism of the oxidation of methylpyridines appear to hold true both for vanadyl phosphate and vanadium–molybdenum oxide systems.

The description of oxidative reactions of other methylheterocycles in a single series with methylpyridines by a Hammet-type equation has not so far been possible as a result of the absence from the literature of σ-constants which take fully into account electronic interactions in these compounds.

The positive values of the parameter ρ obtained for the partial oxidation of methylpyridines lead to the conclusion that the reaction proceeds the more readily as the electron density at the ring carbon adjacent to the methyl group is reduced. It has in fact been found that an adequately linear $\ln W_a$–$\ln q_{C(CH)_3}$ plot is obtained for methylpyridines (Fig. 2b).

Correlational analysis shows that the principal features determining the overall reactivity of methylheterocycles in vapor-phase catalytic oxidation are the basic properties of the heteroatom, and in partial oxidation to the aldehydes, the most important factor is the electron density at the ring carbon atom attached to the methyl group, which is dependent on the electron-acceptor properties of the heteroatom.

Taking some diazines and quinolines as examples, we have shown that the incorporation of methylheterocyclic compounds of different types into an overall reaction series appears to require the use of multifactorial correlational relationships which take into account the basic properties and the structural features of the compounds to be oxidized, which have a considerable influence on the mechanism of the oxidation reaction.

Since such information is not at present available to us, a quantitative description of the rates of catalytic oxidative reactions using the approaches developed here has been obtained for pyridine derivatives only.

EXPERIMENTAL

Oxidations were carried out in a microreactor (3 cm × 1.2 mm) in the pulsed mode. The catalyst volume was 0.5 ml, and the free volume of the reactor was packed with quartz. The preparation and properties of the catalyst have been described previously [13].*

The grain size of the catalyst and the inert packing with 0.25-0.5 mm. The impulse volume was 0.4 μl, and the air flow 40 ml/min. The reaction products were analyzed chromatographically on a column with a stationary phase containing 2.5% of Reoplex 400 and 10% SE-301 on Chromosorb W-AW (40-60 mesh). The column temperature was 120-160°C.

Before use, the compounds were dried over KOH and redistilled over CaH_2. 2-MP, 4-MP, and 1,6-DMP were first purified by crystallization of their complexes with $Mn(CNS)_2$, $CaCl_2$, and urea, respectively.

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