

Solvent Effects in the Autoxidation of 2,5-Dimethylpyrrole

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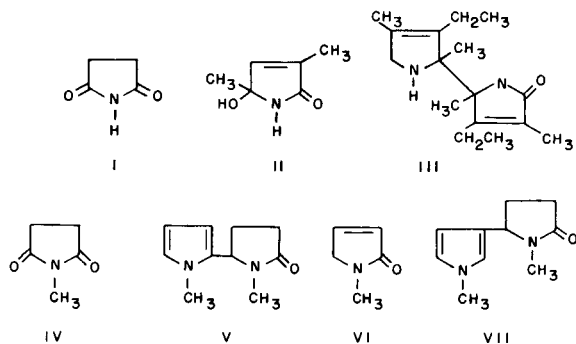
Received November 21, 1985

The mechanism of the autoxidation of *C*-alkylpyrroles is suggested to proceed by way of a charge transfer mechanism. Kinetic measurements for the autoxidation of a representative *C*-alkylpyrrole, 2,5-dimethylpyrrole, are presented which are consistent with this hypothesis.

J. Heterocyclic Chem., **23**, 1095 (1986).

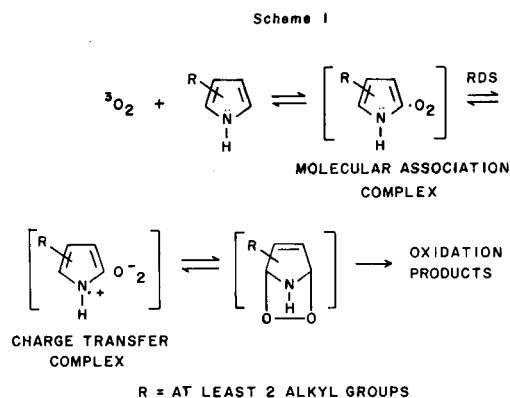
Although the reactions of pyrroles with singlet oxygen has been studied intensely over the last two decades, there has been little recent interest in the reactions of pyrroles with ground state triplet oxygen [4,5]. This is surprising in view of the ubiquity of the pyrrole nucleus in nature. For example, the products of alkylpyrrole autoxidation have been associated with problems ranging from fossil fuel stability to certain neuropsychiatric disorders [6-9].

Ciamician and Silber reported that the autoxidation of pyrrole in water produces a large amount of black polymer along with an unidentified product (empirical formula $C_{12}H_{14}N_2O_5$) and a minor amount of succinimide (I) [10]. Hoft, Katritzky and Nesbit were able to isolate and characterize two different types of products from the autoxidation of alkylpyrroles [11,12]. Thus, the autoxidation of 2,4-dimethylpyrrole in benzene produces β -hydroxylactam (II), while a similar autoxidation of 2,4-dimethyl-3-ethylpyrrole yielded the oxygenated dimer (III). Smith and Jenson reported a detailed study of the autoxidation of *N*-alkylpyrroles and have characterized four oxidation products derived from 1-methylpyrrole (IV-VII) [13]. The available experimental evidence suggested that *N*-alkylpyrroles undergo reaction with triplet oxygen by a free radical initiated oxidation process.



We have previously reported both spectroscopic and kinetic investigations of the autoxidation of *C*-alkylpyrroles [14-16]. On the basis of the results from this work, we are led to propose the mechanism depicted in Scheme 1 for the initial stages of the autoxidation of *C*-alkylpyrroles. As shown in Scheme 1, the first step of the autoxidation

involves the reversible formation of a molecular association complex between the alkylpyrrole and dissolved oxygen. This hypothesis is supported by previously published UV spectroscopic data; in addition, such association complexes between triplet oxygen and electron-rich molecules are well-known [14,17].



The rate determining step depicted in Scheme 1 utilizes the alkylpyrrole as an electron donor and oxygen as an electron acceptor. Such a mechanistic sequence qualitatively explains why electron-rich pyrroles autoxidize so much faster than pyrrole itself or then pyrroles substituted with electron withdrawing groups [18,21]. Additionally, this scheme accounts for the observation that there exists a correlation between the pyrrole anodic oxidation potential and the pseudo-first-order rate constant for the autoxidation [15]. Similar redox processes have been implicated in the oxidation of dihydroflavins with triplet oxygen [22,23].

As shown in Scheme 1, the charge transfer complex is postulated to be in equilibrium with an endoperoxide intermediate. Such endoperoxides are believed to be intermediates in the photochemical dye-sensitized oxidation of pyrroles [24]. Such a common intermediate for both sensitized photooxidation and autoxidation could thus account for the observation that many photochemical oxidations and autoxidations produce the same type of oxidation products [25,26,27].

Table 1
Kinetic, Thermodynamic and Frequency Factors for the Autoxidation of 2,5-Dimethylpyrrole

| Solvent [a] | Temp (°C) | k (sec ⁻¹ × 10 ⁶) [b] | E _a (kcal/mole) | ΔG [‡] (kcal/mole) | ΔS [‡] (e.u.) | log A |
|------------------------|-----------|--|----------------------------|-----------------------------|------------------------|-------|
| dodecane | 60 | 0.86 | | | | |
| dodecane | 65 | 1.21 | | | | |
| dodecane | 70 | 1.70 | 16.9 | 29.2 | -37.9 | 5.0 |
| 1,2,4-trichlorobenzene | 60 | 4.02 | | | | |
| 1,2,4-trichlorobenzene | 65 | 6.47 | | | | |
| 1,2,4-trichlorobenzene | 70 | 8.10 | 17.4 | 28.1 | -33.4 | 6.0 |
| nitrobenzene | 60 | 12.22 | | | | |
| nitrobenzene | 65 | 15.95 | | | | |
| nitrobenzene | 70 | 26.24 | 19.1 | 27.4 | -26.5 | 7.7 |

[a] The dielectric constant for dodecane, 1,2,4-trichlorobenzene, and nitrobenzene are ~2ⁱ, ~3.9ⁱⁱ, and ~35ⁱⁱⁱ, respectively. i) Kodak Laboratory Chemical Catalog. ii) "Physical Properties of Chemical Compounds", American Chemical Society, Washington, DC, 1955, p 138. iii) "Physical Properties of Chemical Compounds", American Chemical Society, Washington, DC, 1955, p 345.

[b] The reproducibility of results was tested by repeating measurements in dodecane and 1,2,4-trichlorobenzene, and the results coincided within 5%.

In order to further test the mechanism proposed in Scheme 1, the scope of our earlier kinetic study was extended [15]. 2,5-Dimethylpyrrole was used as a representative alkylpyrrole. The autoxidation was found to be first-order in 2,5-dimethylpyrrole. Three solvents of widely different polarity were used for the pyrrole autoxidations. The E_a, ΔG[‡], log A, and ΔS[‡] values reported in Table 1 were derived from the observed pseudo-first-order rate constants.

Examination of Table 1 reveals that as the solvent polarity increases the observed energy of activation (and enthalpy of activation) for the autoxidation reaction also increases. However, the increase in the energy of activation is compensated for by an increase in the entropy of activation (*i.e.*, ΔS[‡] becoming more positive). The net effect of increase in solvent polarity is a decrease in the free energy of activation and hence an increase in the rate constant for the autoxidation reaction.

The data presented in Table 1 is consistent with the mechanism presented in Scheme 1 in the following manner:

i) The observed entropy of activation and log A values are consistent with those reported for other reactions which are believed to involve two reactant molecules forming one product molecule [28].

ii) It is assumed that the transition state for the rate determining step is late (*i.e.*, the transition state is more polar than the reactants). Therefore, an increase in solvent polarity would be expected to stabilize the transition state to a greater extent than the reactants. Thus, an increase in the rate constant for the autoxidation with increasing solvent polarity would be expected.

iii) The observed variation in the entropy of activation can be accommodated within the postulated charge transfer mechanism. It is known that the intermolecular

distance between the reactants in certain redox processes is at least partially influenced by solvent polarity. Generally, for a given redox reaction, an increase in solvent polarity will result in an increase in the intermolecular distance between the redox partners [29]. If this were the case for the autoxidation of 2,5-dimethylpyrrole, then an increase in the intermolecular distance between the pyrrole and oxygen with increased solvent polarity would be expected. Thus, the observed increase in ΔS[‡] can be rationalized with the subsequent minimization of Van der Waals interactions during formation of the transition state.

iv) A major contribution to the observed energy of activation for the autoxidation reaction is presumably a consequence of the generation of the oxidized pyrrole and the reduced oxygen in the presence of a solvation layer appropriate for the neutral reactant molecules [30]. Therefore, the change in solvation environment upon transition state formation can account for the observed differences in activation energy.

EXPERIMENTAL

A typical kinetic experiment is described below. A 500 ml three neck round bottom flask was equipped with a reflux condenser, a rubber septum, magnetic stir bar, and an oxygen inlet valve. The three neck flask was then immersed into a Sargent-Welch kinetic water bath Model S-84810 such that the water level extended up to the precise midpoint of the neck of the flask. An air driven magnetic stirrer was submerged and under the round bottom flask. The reaction flask was shielded from light during the course of the experiment.

The water bath was warmed to the reaction temperature and the temperature maintained at ±0.1° with insulation and a Sargent-Welch Model ST Thermonitor. The solvent was allowed to come to thermodynamic equilibrium with the bath while being maintained under a constant oxygen atmosphere. The pyrrole was introduced into the round bottom flask such that a concentration of 400 ppm (weight of nitrogen/volume of solvent) was achieved. Constant stirring was applied during the course of the experiment [31]. The extent of the pyrrole autoxidation was

monitored by capillary column GC analysis of aliquots of the reaction mixture.

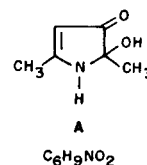
A Varian gas chromatograph model 3700 with a flame ionization detector (FID) and equipped with a 50-m 0.21 mm i.d. wall-coated open tubular (OV-101) fused silica capillary column was used. A carrier gas flow of 1 ml/minute was combined with an inlet split ratio of 60:1 and a temperature program with an initial hold at 110° for 5 minutes, a ramp of 4°/minute, and a final temperature of 260°. The chromatogram was recorded and integrated on a Hewlett-Packard Model 3390A reporting integrator.

The psuedo-first-order rate constants were calculated from the slope of a linear regression plot of the change in pyrrole concentration (natural log) versus the time (seconds). In general, the correlation coefficients were $\geq .98$. When dodecane was used as solvent the pyrrole was consumed to the extent of 30-50%. In all other solvent systems the pyrroles were consumed to the extent of 50-100%.

2,5-Dimethylpyrrole is commercially available and was used without further purification. Capillary gc revealed that the pyrrole had 98% purity. The solvents used were Aldrich Gold Label or Fisher Certified and were used without further purification.

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- [16] We have used 2,5-dimethylpyrrole as a representative alkylpyrrole in our studies on autoxidation. The autoxidation of 2,5-DMP in dodecane (in the dark) produces a large amount of intractable red-brown sediment. Based on elemental analysis, ir and magic angle ^{13}C nmr we have tentatively assigned structure A, or a polymeric form of structure A, as the major oxidation product.



Capillary gc analysis of the autoxidation reaction mixture has failed to detect any intermediates during the course of the reaction.

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[18] In aprotic solvents alkylpyrroles generally have oxidation potentials ($\sim .8\text{V vs. SCE}$) that are very close in energy to the reduction potential of triplet oxygen ($\sim .8\text{V vs. SCE}$) [19,20]. However, *N*-alkyl or pyrroles that contain withdrawing groups have oxidation potentials much more negative than $-.8\text{V vs. SCE}$ [19,21]. Therefore, the autoxidation of these pyrroles would not be expected to occur by way of the electron-transfer initiated autoxidation depicted in Scheme I.

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[31] In the absence of stirring the observed rate constants are approximately 10% less than those observed when vigorous stirring is maintained. In all experiments, every attempt was made to insure that vigorous stirring was maintained during the autoxidation.