# Rates and Mechanisms of Indole and 3-Methylindole Polymerization
## in Cation Exchange Resin Beads

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Batch extraction and polymerization of indole and 3-methylindole (skatole) with acidic cation exchange resins functioned as pseudo first-order reactions. Activation energies of 3.4 and 5.7 kcal/mole indicated greater steric hindrance to skatole polymerization, as would be expected from 2,2' bonding of skatole compared to 3,2' bonding for indole. Linear polymerization occurred, although a heterocyclic ring opened at the trimer stage of poly(indole). 2-Methylindole did not polymerize.

General acid-base catalysis caused unreproducible partial depolymerization when the polymers were extracted from resin beads. Thus, compounds chromatographically separated probably were of lower degree of polymerization than were the polymers formed in the resin matrix.

A dimer hydrochloride rapidly precipitates when skatole in ether is treated with dry hydrogen chloride and when skatole is added to 15% aqueous hydrochloric acid (3,4). Indole forms a dimer or trimer or a mixture of the two, depending upon experimental conditions (5-8). Indole dimer is bonded 3,2', whereas skatole dimer bonds 2,2' (9-12). Our nmr data verified the previously postulated cis addition of skatole.
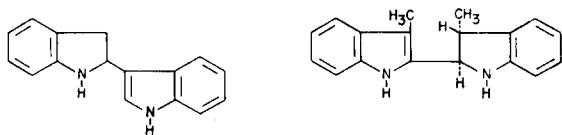
Heterocyclic ring opening occurs in indole trimer formation (13).

No oligomers higher than skatole dimer and indole trimer have been reported. Schmitz-DuMont and his collaborators (14,15) showed that the relative solubilities of dimer and trimer hydrochlorides determine the ratios of products formed in aqueous solution. Since the hydrochlorides would be less soluble in organic solvents, the implication is that skatole dimer and indole trimer represent the upper limits of polymerization. The cation exchange resin matrix, however, proved to be a medium which permitted higher degrees of polymerization than did water or such organic solvents as ether and benzene.
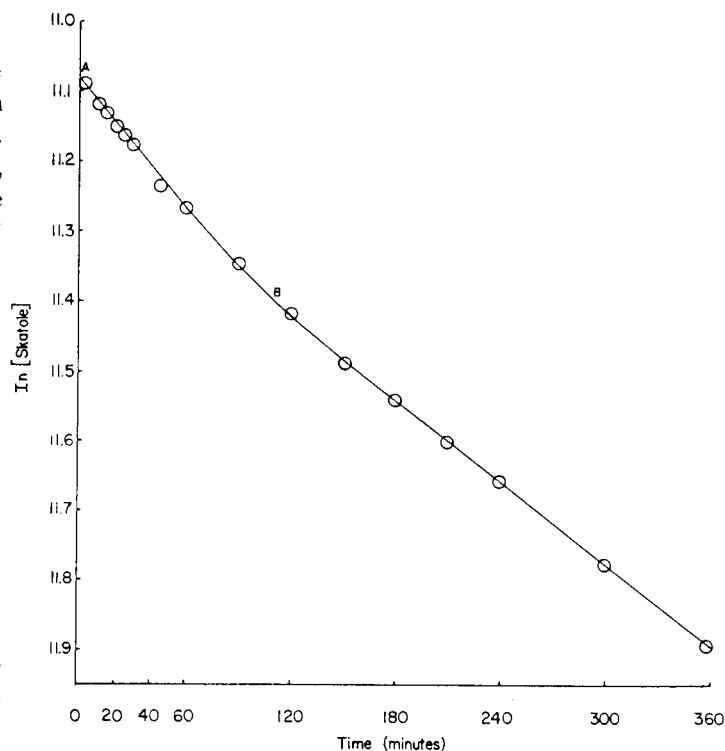


Figure 1. Successive pseudo first-order absorption and polymerization rate curves for skatole at 51°, with the reaction rate curve extrapolated to zero time. Correction of the absorption curve for the polymerization effect would give an almost vertical line, indicating rapid equilibration of monomer between solution and resin.
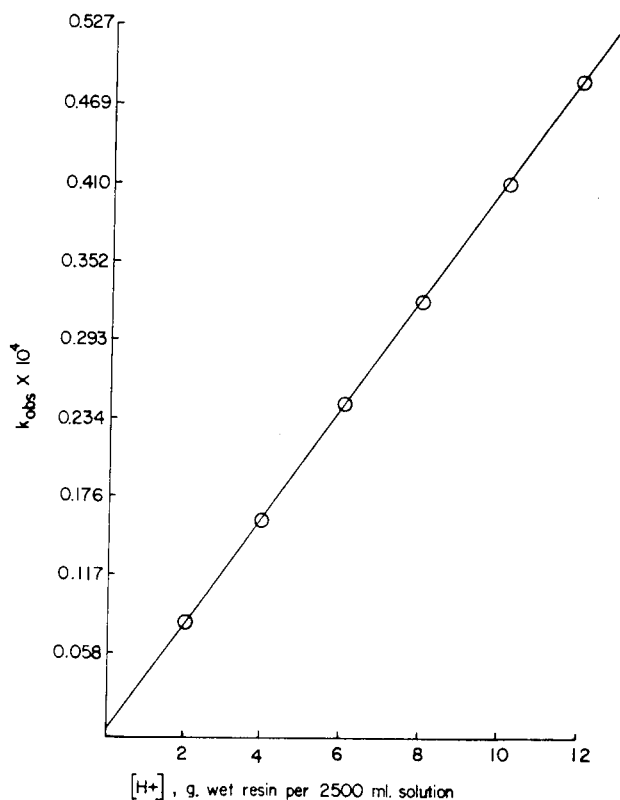
Figure 2. Resin mass effect on polymerization rate; correlation coefficient between measured points and the line is 0.996.

Table I

Rate Constants at Various Temperatures for Indole and Skatole

| Temperature, °C | Skatole (k x $10^4$) | Indole (d x $10^4$) |
|---|---|---|
| 30 | 0.225 | 0.288 |
| 40 | 0.322 | 0.353 |
| 50 | 0.410 | 0.393 |
| 60 | 0.506 | 0.508 |
| 70 | 0.713 | 0.551 |

Table II

Comparative Thermodynamic Activation Parameters for the Skatole and Indole Polymerizations with Evaluated Confidence Limits

| | | |
|---|---|---|
| Energy of activation, kcal/mole | 5.67 ± 0.28 | 3.42 ± 0.14 |
| Entropy, e. u. | -62.9 ± 3.1 | -69.9 ± 2.8 |
| Enthalpy, kcal/mole | 5.03 ± 0.25 | 2.78 ± 0.11 |
| Gibbs free energy, kcal/mole | 25.4 ± 1.0 | 25.4 ± 1.0 |

EXPERIMENTAL

Apparatus.

A three-liter jar with a sealed top fitted for stirring and sampling was used as the reaction vessel for the experiments upon which the tabulated kinetic parameters depend. Stirring was maintained as constant as possible at high speed. A Haake, Type NBS, constant temperature bath was used to control the temperature to within 0.1°. Quantitative analyses were done with a Beckman DB prism spectrophotometer. For collecting fractions separated by column chromatography, a Buchler fraction collector was used.

Chemicals.

Medium porosity Amberlite IR-120 and Dowex-50 X 8 cation exchange resins were used. To remove resin compounds that would be extracted during the kinetic runs and absorb light of the analytical wavelengths, thus causing error in analyses, the regenerated resins were continuously extracted with water a minimum of twelve hours in a Soxhlet extractor.

Kinetic Studies.

Rates of polymerization of indole and skatole were measured at ten degree intervals from 30 to 70°. The reaction mixture initially contained 2450 ml. of 1% ethanol and 10.00 g. of wet resin (46.70% water for Amberlite IR-120). After equilibrating this mixture 30-40 minutes at the chosen temperature, 50 ml. of 100 ppm monomer in 1% ethanol was added and the reaction was begun. Samples were taken periodically and analyzed. Each run lasted 3-4 hours. After each run the apparatus was cleaned with 95% ethanol.

Some variations of the basic procedure were used to study such variables as the amount of catalyst.

No evidence of oligomers in the aqueous solution during the reaction could be found by extraction and thin-layer chromatography, hence monomer in the solution was measured directly by uv spectrophotometry. The difference between the starting concentration and the amount found at any sampling time represented the combined amount of monomer and polymer in the resin. Initially, uv measurements were made by the empirical ratio method at 221 and 280 nm for skatole, but single wavelength measurements were found to give comparable results. Thereafter, skatole was measured at 221 nm and indole at 215 nm by ordinary spectrophotometry. Molar absorptivities were 2.62 x $10^4$ and 3.25 x $10^4$, with blanks of -0.0066 and +0.0134 a.u.

Results and Discussion.

Kinetics.

Batch and column absorption of indole and skatole from solution indicated that two successive pseudo first-order reactions occurred (Figure 1). These could be separated into extraction by the resin, which varied with stirring and reaction conditions, and polymerization within the resin matrix, which showed good reproducibility. By making the stirring more efficient, the extraction part of the curve was made fast enough to be almost undetectable.

The first part (AB of Figure 1) of the curve results from development of the equilibrium $M_s \leftrightarrows M_r$, distribution of monomer between solution and resin. The distribution coefficient for the extraction is

$$D = [M_r] / [M_s] \text{ or } [M_r] = D [M_s].$$

Kinetics of a first-order reaction within the resin is given by

$$\frac{d\ [M_r]}{[M_r]} = \frac{d\ (D\ [M_s])}{D\ [M_s]} = -k_1 dt$$

which integrates to

$$\ln\ ([M_s]_2\ /\ [M_s]_1) = -k_1 t_2 + k_1 t_1$$

when the distribution coefficient becomes constant, that is, a partition coefficient, $K_d$, as equilibrium between phases is established. As reaction in the resin proceeds beyond this point, monomer from the solution phase replaces polymerized monomer in the resin at the rate necessary to maintain the monomer partition coefficient. If no reaction occurs in the resin, as observed with 2-methylindole, ln ( $[M_s]_2\ /\ [M_s]_1$ ) = 0, since $[M_s]_2 = [M_s]_1$.

Table I gives the rate constants for the chemical reactions of indole and skatole, calculated from the second part of curves such as in Figure 1 and the first-order equation

$$\ln A = -kt + \ln A_0$$

Linear addition polymerization to form long chains is indicated, because it is pseudo first-order and can be acid catalyzed. Activation parameters given in Table II were calculated using fundamental equations of kinetics (16). Confidence limits are derived from correlation coefficients, coefficients of variation, and duplications of rate constants between Rush and Brown. 2-Methylindole is absorbed by resin, but shows no reaction step analogous to skatole and indole. If no chemical reaction occurred on the resin, skatole and indole concentrations with respect to time would become constant as does 2-methylindole concentration.

Extraction of oligomers from resin beads after a reaction period also indicates that polymerization of indole and
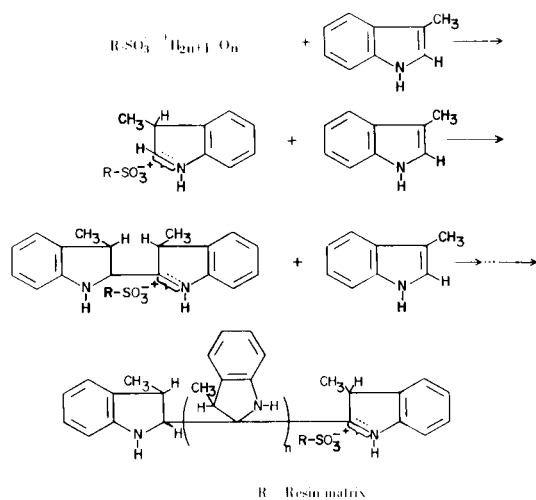
skatole occurs within the resin. That only one proton is involved in the polymerization was shown by a catalyst mass effect study. Analysis of the data, given in Figure 2, depended upon the equation

$$k_{obs} = k_0 + k_{cat}\ [catalyst]^n$$

In this equation, $k_{obs}$ is the measured rate constant for a given mass of resin, $k_0$ is the theoretical rate if no resin is present, $k_{cat}$ is the slope of the line of Figure 2 and reflects the efficiency of the catalyst, and n is the number of catalyst molecules in the reaction step (17). For skatole, least squares analysis indicated n = 1, with a coefficient of variation of 0.08% for the plotted points.

Protonation of nitrogen in nonaromatic rings of oligomers occurs. Formation of hydrochlorides reduces the solubility of skatole and indole oligomers and precipitation stops polymer growth in previously used organic solvents. The resin matrix as solvent, however, permits chains to continue to grow.

Mechanism.

The proposed mechanism for the acid-catalyzed polymerization of skatole is given in Figure 3. It is consistent with prior mechanistic studies of skatole dimer formation
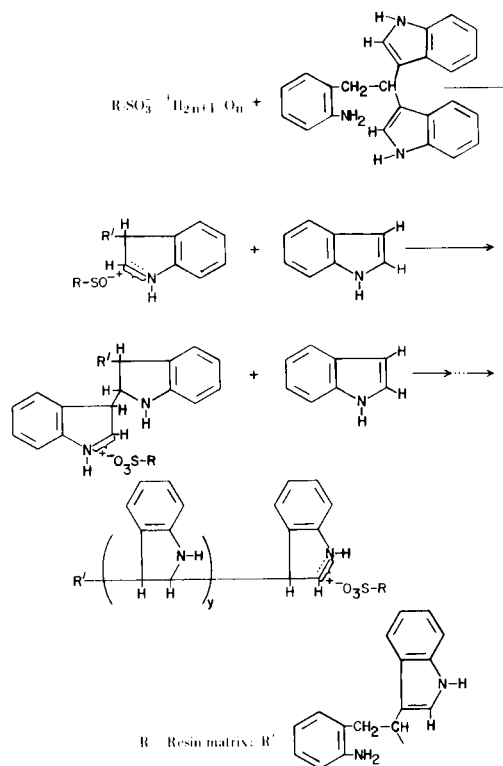


Figure 3. Proposed mechanism for the acid-catalyzed polymerization of skatole.



Figure 4. Proposed mechanism for the acid-catalyzed polymerization of indole.
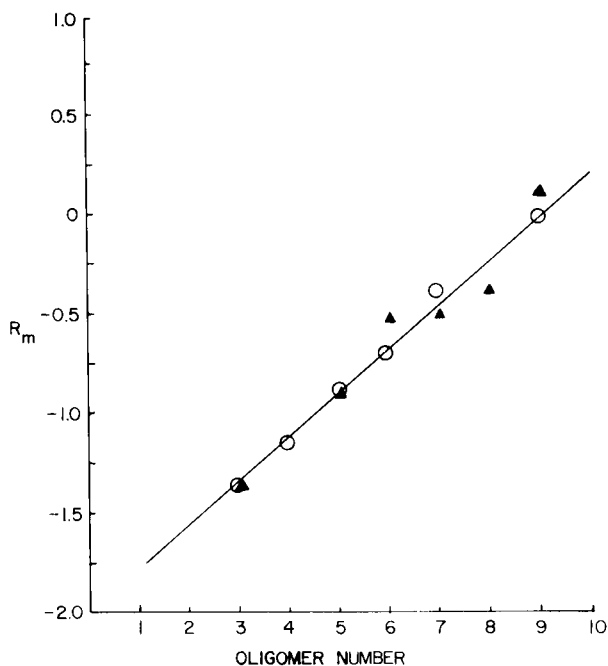
Figure 5. $R_m$ test of the homologous nature of extracted skatole (▲) and indole (o) oligomers.

(10-12). Water serves as co-catalyst and is protonated by the sulfonic acid groups of the resin matrix. The protonated water then reacts with skatole monomer, producing carbonium-ammonium ions fixed in the resin by ionic bonding with sulfonate anions. Neutral monomer reacts with carbonium-ammonium ions, producing dimer ions. This is essentially a 2,2' insertion of monomer between the positive end of a polymer chain and the sulfonated ion that holds the positive end fixed in the resin; its repetition causes the polymer chains to grow at the charged ends. Termination of the chains may result from deprotonation and aromatization of the heterocyclic ring, or void space of the matrix may limit polymer size.

Indole polymerization differs somewhat from that of skatole. Polymerization proceeds to the trimer stage. At this point, the carbonium-ammonium ion
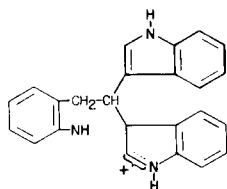


becomes the active species electrostatically held in the resin matrix by the sulfonate ion. 3,2' addition of indole then causes chain growth (Figure 4). Both indolyl groups of the trimer could be reactive during the polymerization,

causing the polymer chain to grow at both ends. The kinetic data indicate ring opening occurs a small number of times relative to monomer additions; otherwise, a linear first-order plot would not be obtained.

Except for the ring-opening step during formation of indole trimer, all indole and skatole reactions appear to be ordered ethylenic additions. Uniform addition to growing chains is necessary for polymerizations to be pseudo first-order (18). The trimer formation step does not appear to perturb the pseudo first-order kinetics of indole polymerization, thereby suggesting that a high degree of polymerization occurs in the resin beads.

The skatole reaction has a higher energy of activation than the indole reaction (Table II). This is reasonable because steric hindrance by the methyl groups leads to 2,2' bonding of skatole, which requires more energy than 3,2' bonding of indole. The enthalpies also suggest a higher energy for the skatole activated complex.

Hinman and Lang (19) determined $pK_a$'s for a number of indoles. Their data indicate that the carbonium-ammonium ion would form much more readily for the growing skatole polymer than the growing indole polymer. Since Gibbs free energy of activation is equal for the two, differences in protonation equilibria must counter steric effects as influences on the rate constants.

Structural Observations.

Aromatic primary amino groups in the poly(indole) were demonstrated with the Griess reaction (20). When sodium nitrite was added to cold 2 M hydrochloric acid containing a few resin beads partially loaded with poly-(indole), a red dye formed as the result of diazotization and coupling. Poly(skatole) did not undergo the reaction, with or without added naphthol, hence there must be no heterocyclic ring opening of skatole groups similar to that of the indole trimer.

General acid-base catalysis and ready reversibility of the polymerizations prevented isolation and complete chemical characterization of pure oligomers above the trimer. All polymeric material could be extracted from the resins with sufficiently acidic or basic solvents, such as dimethylsulfoxide and dimethylformamide, but the products depended upon the mode of extraction, as well as on the polymerization.

Extracted polymers of degree of polymerization up to 10-12 were separated by thin-layer and column chromatography. However, attempts at recovering solid compounds from eluates always ended up regenerating polymer mixtures. Plots of $R_m$, log $(\frac{1 - R_f}{R_f})$, vs. degree of polymerization (21) gave satisfactory indications that homologous series of compounds were extractable (Figure 5). The lowest oligomer of a series could be identified as a

dimer or trimer, although the individual solutes on the plates could not be extracted and structurally analyzed.

Because the compounds isolated by chromatography were colorless, acid-catalyzed polymerization must differ from photolytic and oxidative polymerizations that produce a series of products ranging over pale yellow, orange, green and black. Experiments showed, however, that photolytic and oxidative polymerizations could be drastically speeded by increasing acidity and temperature. Linear polymerization, as catalyzed by acids, may be precursor to colored polymer formation. Substituted aniline groups in the colorless polymers should make oxidative transformations of the Aniline Black type (22) possible. Using dimer hydrochloride as starting material, mixtures of oligomers of much higher degree of polymerization than previously reported were synthesized in dimethylsulfoxide. Continued heating caused these to go through color transformations from colorless to black.

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