

## Tritium Exchange in Specifically Labelled Xylenols, Indanols and Tetrahydronaphthols and Their Methyl Ethers \*

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The first-order rate constants for the detritiation of specifically labelled 3,4-dimethylphenol, 5-indanol, 6-tetralol, and their methyl ethers in anhydrous trifluoroacetic acid at 20.0° have been determined. The data indicate that the substituents in the ar- $\beta$  position of the bicyclic compounds strongly influence the directing effect of the annulated rings. This effect is greatest in the tetralin series.

The electrophilic substitution of the two benzocycloalkanes indane and tetralin has been studied ever since Mills and Nixon<sup>1</sup> reported that 5-indanol was substituted preferentially at the 6-position (ar- $\beta$  position), and 6-tetralol at the 5-position (ar- $\alpha$  position) of the molecule. This effect was later referred to as the "Mills-Nixon effect".

Many investigations of the electrophilic substitution of indane and tetralin have been performed, using the unsubstituted hydrocarbons. In these compounds, the reactivity differences between the ar- $\alpha$  and the ar- $\beta$  positions are very minor or not observable.<sup>2,3</sup> Thus, Vaughan *et al.*<sup>4</sup> have studied the bromination and nitration of *o*-xylene, indane, and tetralin, and they did not observe the reaction specificity described by Mills and Nixon.<sup>1</sup> Kinetic determinations of the detritiation of the same compounds, carried out by Vaughan and Wright,<sup>5</sup> showed the same general reaction pattern. However, Bassindale *et al.*<sup>6</sup> found that the rate of protodesilylation at the various aromatic positions in trimethylsilyl derivatives of *o*-xylene, indane, and tetralin were in the same order as could be predicted according to the work by Mills and Nixon. This may indicate that the degree of reaction specificity depended on the reaction studied. It is conceivable that the specificity observed is due to the annulated rings,<sup>7</sup> which exert directing effect in the aromatic part of the molecules.

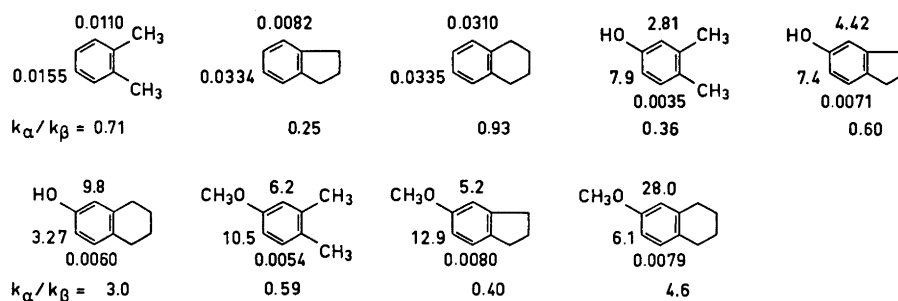
Substitution reactions<sup>1,4,7</sup> in compounds with an ar- $\beta$  substituent (*e.g.* OH) indicate that the reaction specificity is more pronounced in these structures

\* The directing effect of annulated rings in aromatic systems. VII. Part. VI, Ref. 11.

than in the unsubstituted analogs. This would suggest that the ar- $\beta$  substituent could enhance the directing effect of the annulated ring. The purpose of the present work was to further investigate these indications.

## RESULTS AND DISCUSSION

Vaughan and Wright<sup>5</sup> determined the rate of detritiation of specifically labelled *o*-xylene, indane, and tetralin in trifluoroacetic acid. They found higher reactivity in the ar- $\beta$  positions of all the three structures studied (Scheme 1). In analogous experiments, using specifically labelled ar- $\beta$  substituted *o*-xylene, indane, and tetralin, we have now been able to demonstrate a significant difference in the directing effect of a five- and a six-membered annulated ring.



Scheme 1. Values of  $k \times 10^3$  ( $\text{sec}^{-1}$ ) for detritiation of ar- $\beta$  hydroxy and methoxy substituted *o*-xylene, indane, and tetralin in anhydrous trifluoroacetic acid at 20.0° and of the parent hydrocarbons at 70°. The values for the hydrocarbons were determined by Vaughan and Wright,<sup>5</sup> and are included here for comparison.

The detritiation reactions were carried out in anhydrous trifluoroacetic acid at  $20.0 \pm 0.1^\circ$ . This reagent was chosen because it is known to have low steric requirements,<sup>5</sup> and the directing effects of the annulated rings would therefore not be masked by steric hindrance. As ar- $\beta$  substituent in the test compounds, a hydroxy or a methoxy group was chosen. We found that the methyl ethers usually had a higher rate of detritiation than the corresponding phenols, but both substituents had a similar influence on the reaction specificity. The possibility of ester formation of the phenols with trifluoroacetic acid during the exchange reaction was considered, but such esters could not be detected in the reaction mixture.

The first-order rate constants obtained are given against the appropriate positions in Scheme 1. This scheme also shows the ratio between the rate constants ( $k_\alpha/k_\beta$ ) for the positions *ortho* to the aromatic substituent.

Comparing our results with those reported by Vaughan and Wright<sup>5</sup> for the unsubstituted hydrocarbons (determined at 70°) it is apparent that the ar- $\beta$  substituent influences the directing effect of the annulated ring. In xylene itself, the reaction occurs preferably in the ar- $\beta$  position,  $k_\alpha/k_\beta = 0.71$ . This specificity is more pronounced after ar- $\beta$  substitution. Thus 3,4-dimethylphenol

has  $k_\alpha/k_\beta = 0.36$ , and for 3,4-dimethylanisol  $k_\alpha/k_\beta$  is 0.59. Similarly, the indane derivatives have a higher reaction rate in the ar- $\beta$  than in the ar- $\alpha$  positions, but here the difference is greater in the parent hydrocarbon than in the substituted analogues. The ar- $\beta$  substituent has its greatest effect in the tetralin series. Tetralin itself has a similar rate of detritiation at the ar- $\alpha$  and the ar- $\beta$  positions ( $k_\alpha/k_\beta = 0.93$ ). When this structure carries a hydroxy or a methoxy group in the ar- $\beta$  position, the relative reactivity at the adjacent ar- $\alpha$  carbon is greatly increased, the ratio  $k_\alpha/k_\beta$  being 3–5 times larger than for the hydrocarbon.

#### EXPERIMENTAL

*General comments.* Anhydrous trifluoroacetic acid was prepared by distillation of the commercial acid from sulfuric acid, as described by Eaborn and Taylor.<sup>10</sup> Toluene was distilled and dried over  $\text{Al}_2\text{O}_3$ . Preparation of the specifically labelled compounds is described in an accompanying paper.<sup>11</sup> Radioactivity was measured by liquid scintillation counting (Packard Tri-Carb Model 3375).

*Exchange-rate measurements.* These were carried out in anhydrous trifluoroacetic acid at  $20.0^\circ \pm 0.1$ . A weighed amount (20–40 mg) of the tritiated aromatic compound was dissolved in toluene (2.0 ml). Aliquots (100  $\mu\text{l}$ ) were pipetted into small test tubes of ca. 3 ml capacity (a pipette drainage time of 1  $\frac{1}{2}$  min was allowed for reproducibility) and placed in the thermostat. Trifluoroacetic acid (1.0 ml), thermostated to the same temperature, was rapidly added. After appropriate reaction times, based on the expected exchange rate at  $20^\circ$ , the mixture was neutralized by quickly immersing the test tube with its content into a small flask (250 ml), containing 15 ml of saturated  $\text{NaHCO}_3$ -solution. The solution was then transferred to a separatory funnel, the last traces being washed out with toluene, and extracted three times with toluene. The combined extract was washed with saturated  $\text{NaCl}$ -solution (10 ml) and filtered into a volumetric flask. The filter was washed with toluene (3 ml) and the volume adjusted to 25.00 ml. An aliquot of this solution was used for scintillation counting. First-order rate plots were linear over at least three half-lives when log dpm were plotted *versus* time (sec). Rate constants were determined at least in duplicate for each substance and were reproducible to within  $\pm 2\%$ . Rate constants were calculated from the equation  $k = 2.303 \times \text{slope}$  of the rate plot.

*Attempts to form phenolic esters of trifluoroacetic acid.* Indanol (100 mg) was dissolved in trifluoroacetic acid (5 ml) and left overnight at room temperature. After evaporation of the acid *in vacuo*, no ester could be detected by IR or TLC. Phenolic trifluoroacetic acid esters are known to be stable under the work-up procedures used.<sup>12</sup>

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