

## Stereoelectronic Suppression and a Remarkably Low Effective Concentration for a Cyclization to a Benzo-fused Five-membered Ring

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The cyclization of *o*-chloromethylbenzylamine to dihydroisoindole has an effective concentration of 8.3 M (in CD<sub>3</sub>OD at 21 °C); this very low value for a cyclization to a benzo-fused five-membered ring is ascribed to lessened conjugation in the transition state as compared to that of the model reaction, and is relevant to both the synthesis of rings and the application of effective concentrations in obtaining evidence of mechanism.

Cyclizations to form five-membered rings fused to an aromatic nucleus are notable for their extreme ease. Taking the kinetic effective concentration<sup>†</sup> as a convenient index of cyclization facility, we find that some of the largest effective concentrations in Kirby's compilation<sup>1</sup> belong to this class of reaction which shows a typical range of  $C_{\text{eff}}$  values of 10<sup>5</sup>–10<sup>9</sup> M.<sup>‡</sup>

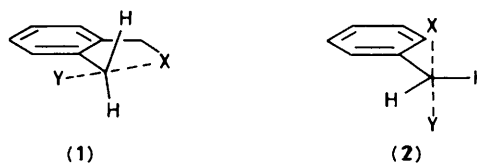
As we have noted elsewhere,<sup>2</sup> one example of this class,

<sup>†</sup> The effective concentration for a cyclization, as determined by kinetic measurements, is given by  $C_{\text{eff}} = k_1/k_2$ , where  $k_1$  is the first-order rate constant for the cyclization and  $k_2$  the second-order rate constant for a suitable bimolecular model reaction.<sup>1</sup>

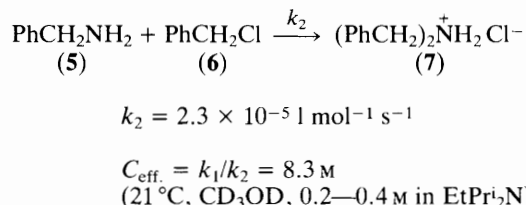
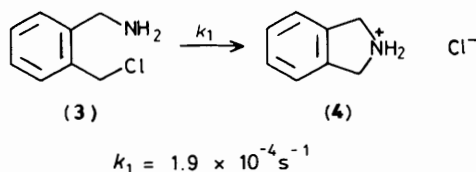
<sup>‡</sup> Of 15 examples of such cyclizations,<sup>1</sup> 13 fall in the range  $>7 \times 10^4$ –10<sup>9</sup>; this includes all of the reactions listed (a) with effective concentrations based on actual rate ratios, and (b) having starting materials lacking further substitution on the benzene ring. One of the two exceptions, the value of 960 for the acid-catalysed cyclization of *o*-mercaptomethylbenzoic acid, is clearly too low because it was estimated using the rate of the corresponding reaction of acetic rather than benzoic acid as the model; the correction factor of about 290 (see ref. 1, Table B2, footnote a) brings it into the typical range. The remaining exception is discussed in the final paragraph of the text.

namely cyclization *via* a transition state like that in (1), is expected to be atypical. Our reasoning was based on two points: (i) we had found<sup>2</sup> that a ring opening *via* (1) took place 8000 times more slowly than the analogous reaction *via* (2), and (ii) the chief feature held to be responsible for the reactivity difference, *i.e.* diminished conjugation at the reacting centre in (1) relative to (2), was common to both ring closure and opening.

Accordingly we have looked at the rates of the cyclization of *o*-chloromethylbenzylamine (3)<sup>§</sup> to dihydroisoindole hydrochloride (4) and of an analogous bimolecular process (5) + (6) → (7).

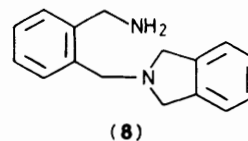


<sup>§</sup> Prepared *in situ* from *o*-chloromethylbenzylammonium chloride<sup>3</sup> and di-isopropylethylamine.



The effective concentration for the cyclization was found to be 8.3 M, more than four orders of magnitude less than the lower end of the typical range cited above. Evidently the entropic advantage of a five-membered cyclization is almost entirely lost because the required geometry leads to suppression of the conjugative stabilization in the transition state. In full accord with the idea that benzylic conjugation in the transition state is indeed an important factor in the comparatively high reactivity of benzyl chloride (6), we found that the reaction of 1-chlorobutane with benzylamine under the same conditions was more than 300 times slower than that of (6).

This result has implications in synthesis since it emphasises the need for care to avoid side reactions, even in a class of reactions in which this is not usually necessary. An initial concentration of (3) of 0.5 M, for example, gave a roughly 2 : 1 yield of (4) and a by-product assigned structure (8), the product of reaction of dihydroisoindole with unchanged (3). An initial concentration of (3) of 0.01 M, however, led to (4) in good yield with <1% of the by-product.



Finally, the present study displays the value of effective concentrations in drawing attention to, and providing information on, such elusive mechanistic features as stereoelectronic effects. The anomalous  $C_{\text{eff.}}$  value mentioned in footnote‡ provides an example. For the cyclization of *o*-bromoacetylphenoxide anion  $C_{\text{eff.}}$  is reported<sup>4</sup> to be 390. This reaction is a nucleophilic displacement at a carbon  $\alpha$  to a carbonyl group and is subject to a stereoelectronic effect closely related to that in the benzylic  $S_N2$  process.<sup>5</sup> In the present context it appears highly likely that the relatively low  $C_{\text{eff.}}$  is at least partly due to the effect of the diminished (or negligible) conjugation in the cyclization relative to that in the model reaction.

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