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# ESTERIFICATION KINETICS AND MECHANISM OF STEREOISOMERS OF SUBSTITUTED 4-HYDROXYPIPERIDINES AND CYCLOHEXANOLS†

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**Abstract**—Esterification rates of stereoisomeric substituted 4-hydroxypiperidines and cyclohexanols (in the presence of N-methylpiperidine) with benzoyl chloride in tetrachloroethylene at 25° are found to indicate intramolecular catalysis and intermolecular acylation, respectively. Isomers of 4-hydroxyperidines with an axial hydroxyl group undergo acylation four times as fast as their 4-equatorial hydroxyl epimers accounted for by higher stability of the resulting intermediate complex.

Acylation of stereoisomers of substituted 4-hydroxypiperidines is an important step in the synthesis of new anaesthetics and analgetics whose activity exceeds that of natural alkaloids such as cocaine and morphine. It is therefore of importance to elucidate the mechanism of this type of reaction to assist directed syntheses of promising new drugs. The attempted elucidation[1-5] of the relationship between structure and reactivity of stereoisomers of some 4-hydroxypiperidines and their analogues in acylation reactions gives rather ambiguous results.[1,3,6] The esterification kinetics of such compounds is exemplified solely by the reaction of stereoisomers of 3-substituted 1-methyl-2,6-diphenyl-4-hydroxypiperidine with acetic anhydride in pyridine,[6] but is thus insufficient to describe the process.

This work is concerned first with the effect of the presence of nitrogen atom in the cycle on the esterification rate of cyclic alcohols and, secondly, with the dependence of the reactivity of stereoisomers of substituted cyclohexanols and 4-hydroxypiperidines on their spatial structure when acylated with benzoyl chloride in tetrachloroethylene at 25°.

## RESULTS AND DISCUSSION

A study is made of cis- and trans-isomers of 1,3-dimethyl-4-hydroxypiperidine **1**, **2**,[7] 3-methyl-1-tert-butyl-4-hydroxypiperidine **3**, **4**,[8] 4-tert-butylcyclohexanol **5**, **6** and cyclohexanol **7**. The presence of the tert-butyl group in **3–6** is a factor ensuring their conformational homogeneity. The spatial structure of compounds **1–4** is determined[8,9] by means of NMR spectra.

To study the effect of the presence of a nitrogen atom in the ring on the reactivity of the hydroxyl group of cyclic alcohols the esterification rate of cyclohexanol **7** and that of the stereoisomer of piperidinol **1** with an equatorial hydroxyl group are compared. In the absence of catalysts, no reaction of **7** with benzoyl chloride in tetrachloroethylene ($C_0^{alc.} = 0{\cdot}16$ M, $C_0^{RCOCl} = 0{\cdot}1$ M) is observed for 5 hr at 25°, which corresponds to $k = 10^{-6}\ M^{-1}\ sec^{-1}$ as compared with $k = 8 \times 10^{-3}\ M^{-1}\ sec^{-1}$ for compound **1** with the same spatial orientation of the OH-group (Table 1). Increased rate by four orders on passing from cycloalkanol **7** to its heterocyclic analogue **1** cannot be accounted for by the inductive effect of the nitrogen atom and shows convincingly that in this case the determining factor is nucleophilic catalysis by nitrogen atom, as is also the case on esterification of aliphatic amino-alcohols.[10]

The possibility of such catalysis has been postulated before.[3-5] No proof was presented however, and it was uncertain whether catalysis was intra- or intermolecularly. Second order constants $\bar{K}_2$, calculated for esterification of compound **1** and its isomer **3** remain constant both in the course of experiments and on varying initial concentrations. It might therefore be considered as proved that the reaction is first order in each component. This fact points in turn to intramolecular catalysis. Had it been intermolecular, the reaction would have been of second order for piperidinol and of overall third order.

To obtain further substantiation of the intramolecular nature of the catalysis, and to compare its performance with that of intermolecular catalysis, cyclohexanol **7** and stereoisomers of 4-tert-butylcyclohexanols **5**, **6** were esterified with benzoyl chloride in tetrachloroethylene at 25° in the presence of 1-methylpiperidine. The study showed this reaction to be of the third order (of first order for acid chloride, alcohol, and amine) with third order rate constants $\bar{K}_3$ being rather similar for compounds **5** and **7** and amounting to $\sim 4 \times 10^{-3}\ M^{-2}\ sec^{-1}$ (Table 2).

The esterification rate constants of piperidinols and cyclohexanols pertaining to reactions of different order, their relationship accounts for the concentration that can be identified with the so-called "effective catalyst concentration". This means that at such a catalyst concentration esterification of piperidinols would proceed under ideal intermolecular catalysis (of pseudozero order for catalyst) at the same rate as does the experimentally observed intramolecular catalysis. In our case this value is ~2 mol/l whereas the true concentration of catalytic centres on piperidinol esterification ($C_0^{am.alc}$) amounts to 0·01–0·05 mol/l (Table 1). The electronic and steric properties of compounds **1** and **7** as well as of **1** and 1-methylpiperidine are rather similar. It might therefore be suggested that the different reactivity of piperidine and cyclohexane alcohols is due to these compounds undergoing esterification by different mechanisms. Our data show that esterification of cyclohexanols **5–7** is effected in the presence of N-methylpiperidine by intermolecular catalysis, whereas acylation of piperidinols **1** and **2**

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Table 1. Kinetics of acylation of stereoisomers of 1-alkyl-3-methyl-4-hydroxypiperidines **1–4** with benzoyl chloride (tetrachloroethylene, 25°)

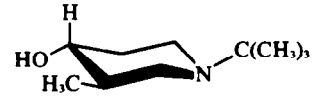
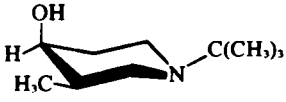
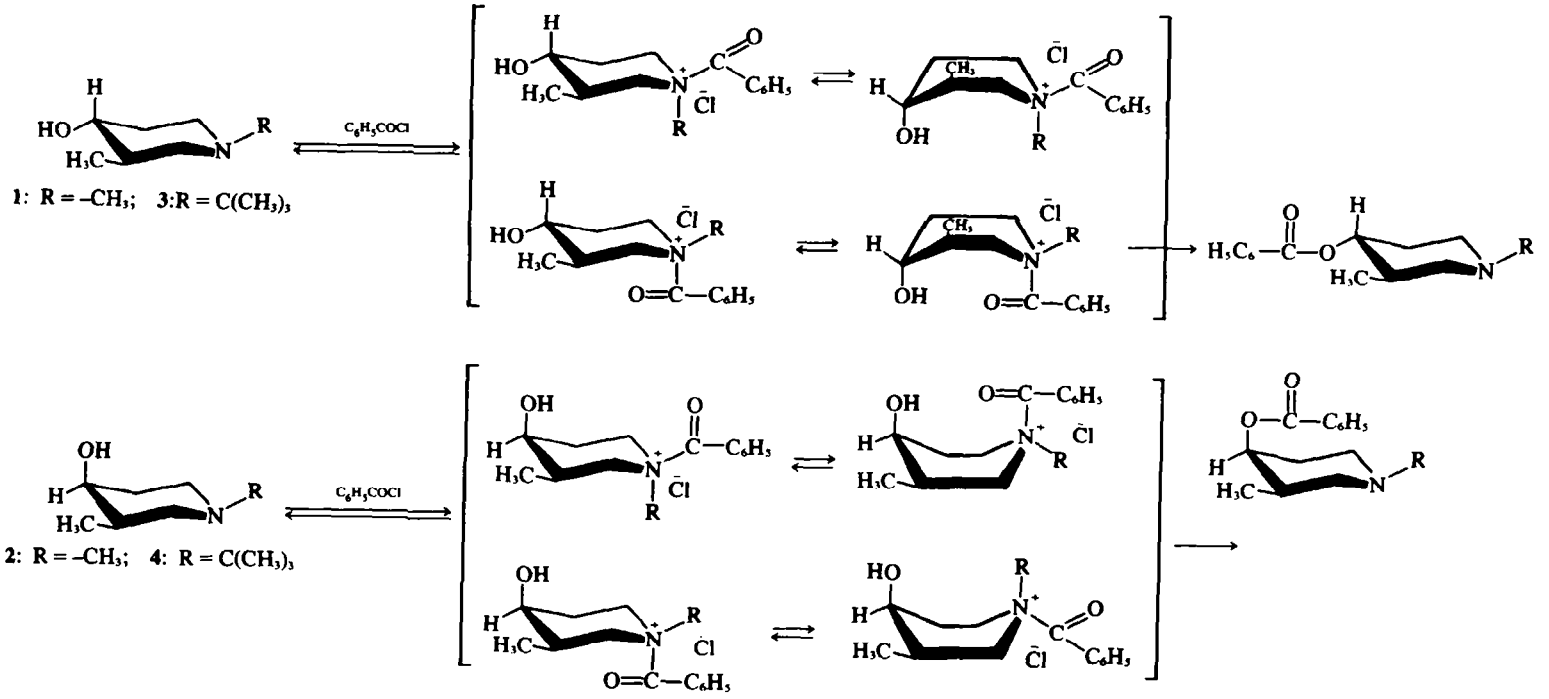
| | Compound | Initial concentration $C_0^{RCOCl}$ | Initial concentration $C_0^{am.alc}$ | Rate constant $k \times 10^3\ M^{-1}\ sec^{-1}$ |
|---|---|---|---|---|
| 1 |  | 0·005–0·01 | 0·01–0·016 | 8 ± 2 |
| 2 |  | 0·005–0·01 | 0·009–0·049 | 30 ± 4 |
| 3 |  | 0·17–0·29 | 0·23–0·41 | 0·024 ± 0·006 |
| 4 |  | 0·15–0·2 | 0·22–0·24 | 0·08 ± 0·03 |

Table 2. Acylation of stereoisomers of cyclohexanols with benzoyl chloride in the presence of 1-methylpiperidine (tetrachloroethylene, 25°)

| | Compound | Initial concentration, mol/l $C_0^{RCOCl}$ | $C_0^{alc}$ | $C_0^{amine}$ | Rate constant $k \times 10^3\ M^{-2}\ sec^{-1}$ |
|---|---|---|---|---|---|
| 5 |  | 0·05–0·1 | 0·05–0·1 | 0·12–0·22 | 4·0 ± 0·9 |
| 6 |  | 0·1–0·2 | 0·1–0·2 | 0·25–0·5 | ≤0·1 |
| 7 |  | 0·1 | 0·1 | 0·089–0·23 | 3·9 ± 0·4 |

proceeds in conformity with the mechanism of intramolecular catalysis similar to that suggested in refs. 3–5 and involving acylation by acid chlorides of the cyclic amino group to form an acylammonium salt followed by N→O acyl migration to give ester (see Scheme 1). This process appears to involve the conversion of the ring to the boat conformation, the formation of an intermediate cyclic compound (2-phenyl-2-hydroxytetrahydro-1,3-oxazine[11]) and the reconversion of the ring to the chair conformation. In the case of stereoisomers **1** and **3** it is only the axial attack of nitrogen atom by acide chloride that leads to an adduct whose conversion to the boat conformation brings together the hydroxyl and benzoyl groups thus facilitating N→O acyl migration to give the ester. On the contrary, in the case of isomers **1**, **2** and **4** such a situation arises only when the nitrogen atom is attacked by benzoyl chloride equatorially. It is known[12] that bulky reagents favour equatorial attack. Therefore stereoisomer **3**, at least with R = $CH_3$, should prove more reactive. On the other hand, with this isomer a more stable boat conformation is formed than with isomer **1** where it is additionally destabilised by the axially oriented methyl group at $C_{(3)}$. The combined effect of these factors causes the reaction rate of piperidinol **2** having an axial OH-group to exceed four times that of its isomer **1** having an equatorial hydroxyl (Table 1), that is $\bar{K}_a/\bar{K}_e = 4$, this conclusion being in accord with assumptions made in ref. 3. The ratio obtained is opposite to that usually observed in the series of stereoisomers of cyclohexanols. It is seen from Table 2 that isomer **6** having an axial hydroxyl group undergoes acylation ~40 times slower than does its isomer **5** having an equatorial hydroxyl group. This difference is usually considered as due to the axial hydroxyl group being less accessible. In compounds under study this effect is more pronounced than for example reported in Ref. 13, apparently owing to considerably greater steric hindrance of benzoyl chloride and N-methylpiperidine as compared to that of the acylating system, acetic anhydride-pyridine, used in refs. 6 and 13. An important difference in the stereospecificity of piperidinol esterification is due to the above peculiarities of the intramolecular catalytic mechanism.




Scheme 1. Intramolecular catalysis esterification mechanism of isomeric 1-alkyl-3-methyl-4-hydroxypiperidines

This is substantiated by data in ref. 6 which demonstrate that under the conditions of intermolecular catalysis (acetic anhydride acylation in pyridine) the reactivity of stereoisomers in the 4-hydroxypiperidine series follows the same order as does that in substituted cyclohexanols.

To study the effect of the accessibility of the nitrogen atom on its catalytic activity the esterification rate of compounds **1** and **2** was compared with that of 1-tert-butyl-3-methyl-4-hydroxypiperidinols **3** and **4** under identical conditions. It will be seen from Table 1 that the values of $\bar{K}_2$ for **3** and **4** are ~340 times less than for **1** and **2** which is in good accord with Scheme 1, according to which a higher degree of spatial screening of the nitrogen atom in the ring should hinder the formation of acyl-ammonium salt at the first step (see also[14,15]). On the other hand it also follows from Table 1 that the regularities observed for compounds **1** and **2** are all retained by their analogues **3** and **4**. First, the reaction is of second order (of first order for each component) and hence proceeds according to intramolecular catalytic mechanism. Secondly, the esterification rate of isomer **4** having an axial OH-group is higher than that of isomer **3** having an equatorial hydroxyl.

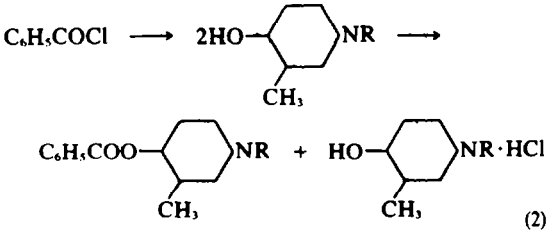
## EXPERIMENTAL

Compounds **1–7** were acylated with benzoyl chloride in tetrachloroethylene at 25° (in the case of **5–7** in the presence of 1-methylpiperidine) and the reaction rate was measured by potentiometric titration of hydrogen chloride evolved in aliquot samples diluted by acetone by 0·04–0·05 N triethylamine in toluene following the procedure described in ref. 16. The extent of conversion was corrected for the side reaction of piperidinol compounds with admixtures in tetrachloroethylene containing active chlorine as determined in controls.[16]

The second order rate constant for esterification of 1-alkyl-3-methyl-4-hydroxypiperidines **1–4** was calculated by formula (1):

$$\bar{\bar{K}} = \frac{2{\cdot}3}{t(C_0^{am.alc.} - 2C_0^{RCOCl})} \log \frac{(C_0^{am\,alc.} - 2x)C_0^{RCOCl}}{(C_0^{RCOCl} - x)C_0^{am.alc.}} \qquad (1)$$

where $C_0^{am\,alc}$ and $C_0^{RCOCl}$ are the initial concentration of amino-alcohol and acid chloride, respectively, and x is the ester concentration (equal to that of hydrogen chloride evolved) at time t. This formula was used because, due to the excess of starting piperidinol relative to the amount of ester formed, and its higher basicity,[17] it might be concluded that hydrogen chloride is quantitatively bonded to the piperidinol. Bearing in mind that piperidinol hydrochloride does not undergo esterification under the conditions of the experiment, the overall reaction equation is as follows (2):



(2)

This equation is taken account of in the stoichiometry of the reaction but does not affect its kinetics, salt formation proceeding rather quickly.

The third order rate constant for the esterification of cyclohexanols **5–7** in the presence of 1-methylpiperidine was calculated by formula (3):

$$\bar{\bar{K}} = \frac{1}{t(b-a)}\left[\frac{x}{a(a-x)} - \frac{2{\cdot}3}{(b-a)} \log \frac{(b-x)a}{(a-x)b}\right] \qquad (3)$$

where $a = C_0^{alc.} = C_0^{RCOCl}$ stands for the initial concentration of alcohol and acide chloride and $b = C_0^{am}$ is the starting concentration of 1-methylpiperidine.

The results are listed in Tables 1 and 2 with their accuracy characterized by the confidence interval calculated according to ref. 18.

The formation of esters was checked by means of IR-spectra. The frequencies of characteristic absorption bands in the reaction mixture after completion of the experiments were found to coincide with those of authentic esters.[8]

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