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TRANSFORMATION OF COMPOUNDS CONTAINING C-N BONDS ON HETEROGENEOUS CATALYSTS-7.[x] THE STEREOCHEMISTRY OF THE DEHYDROGENATION OF 2-ALKYL-3-DIMETHYLAMINO-1-PHENYLPROPAN-1-OLS

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Abstract - Evidence supporting a mechanism involving a sterically hindered transition state was found in the dehydrogenation of erythro-2-alkyl-3-dimethylamino-1-phenylpropan-1-ols by using a linear free energy relationship with Charton's steric constants.

Introduction

The kinetics and selectivity of heterogeneous catalytic reactions are determined by many factors. In particular cases, however, steric interactions exert the most important effects on the course of the reaction. The presence of the catalyst influences the stereochemistry of the reaction proceeding on the surface.

In these transformations strong steric interactions may arise between the substituents of the reacting molecule, and between a substituent and the surface. The transformation may proceed if the reacting molecule has enough energy to overcome the free energy barrier due to these repulsions. The bulkier the substituent, the greater the hindrance is expected to be as compared to the case when the substituent is only a hydrogen atom. The quantitative verification of such hindrance lends support to the proposed structure of the adsorbed species on the surface.

On the basis of similar principles, Taft introduced the use of a linear free energy relationship (LFER) to characterize steric interactions.[1] These parameters were determined experimentally and were criticized for relating not only to the space-filling properties, but also to electronic factors.[2] Nevertheless, they are in good correlation (r= 0.978, n= 104) with Charton's steric constants,[3] which are calculated on the basis of the van der Waals radii of the substituent groups.

In an earlier paper, significant differences in reactivity were observed in the copper-catalysed transformations of certain 1,3-amino alcohols with alkyl substituents in positions 2 into ketones containing identical numbers of carbon atoms (Fig. 1).[4] The sequential transformation of these amino alcohols involves

(i) dehydrogenation of the hydroxy group,

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(ii) the elimination of dimethylamine from the amino ketone intermediate, leading to the formation of an unsaturated ketone,

(iii) hydrogenation of the unsaturated ketone to give the product ketone.

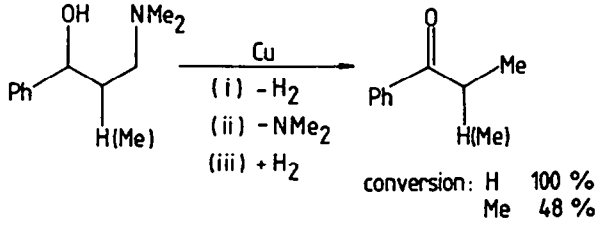


Fig. 1. Transformation of 1,3-amino alcohols to ketones on copper.

The differences in reactivity of the unsubstituted and methyl-substituted molecules were assumed to be related to steric hindrance of the formation of the adsorbed species to be dehydrogenated.

This paper reports an attempt to use the LFER approach with Charton's constants to establish the stereochemistry of the adsorbed intermediate in the dehydrogenation of certain amino alcohols.

Results and discussion

In the experiments, the consumption of the starting amino alcohols was measured. The use of excess diethylamine reagent in the reaction mixture ensured stable catalytic activity and selective reaction conditions for ketone formation by the complete suppression of a possible side-reaction, the acid-catalysed dehydration of amino alcohols.

Since the elimination of dimethylamine from the amino ketone intermediate (step (ii) in Fig. 1) at high temperature is fast and can be regarded as irreversible, the kinetics of the consumption of the amino alcohol is determined by the rates of adsorption and dehydrogenation, both of which are expected to follow first-order kinetics. However, only a small kinetic isotope effect ($X_H/X_D \sim 1.2$) was observed in the dehydrogenation of a model compound, 1-phenylpropan-1-ol-[1-^{2}H]. Therefore, it is more likely that a monomolecular reaction step preceding the rupture of the C(1)-H bond, e.g. adsorption, is the rate-limiting step. Literature data support this conclusion.[5] Thus, the kinetics is expected to fit the Basset-Habgood equation:[6]

$$Kk = -\frac{F}{273\ R\ W} \ln(1-x)$$

where K is the equilibrium constant of adsorption, k is the first-order rate constant of dehydrogenation, F is the flow rate of the carrier gas (ml min^{-1}), W is the weight of cata-

lyst (g), x is the fractional conversion, and R = 8.3 J mol^{-1} K^{-1}. This equation was used to determine the rate of dehydrogenation of amino alcohols.

On the other hand, the formation of the sterically crowded species (Fig. 2), regardless of the fine details of the mechanism, seems to be necessary, i.e. this is the adsorbed form of the product. A linear free energy plot with steric parameters could prove the proposed structure of the intermediate. The use of the pulse method for such purposes has been recommended[7] because of its simple operation.

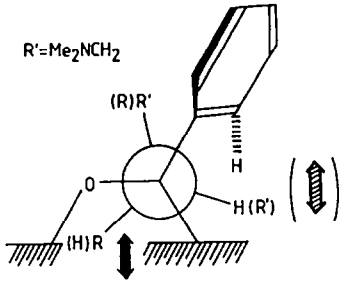
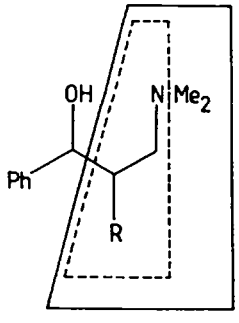


Fig. 2. Surface complex in dehydrogenation of the hydroxy group of 2-alkyl-3-dimethylamino-1-phenylpropan-1-ols on copper. Groups and arrow in parentheses represent a different conformation and steric interactions between the substituents in this conformation, respectively.

Unfortunately, as far as we are aware, the steric constants of the groups concerned (see Formula, the part in the full box) are not available in the literature. However, careful comparisons of the Charton's constants of homologous series convincingly demonstrate that atoms within a distance of three bonds from the reaction centre determine the values of these constants (compare the trends of constants of alkyl groups in Table 1 arranged in different series). Further, the covalent radii of an sp^3 hybridized carbon (77 pm) and a nitrogen atom (70 pm), and the lengths of the carbon-carbon (154 pm) and the carbon-nitrogen (147 pm) single bonds are only slightly different. Similarly, the bond angles are very close (e.g. $\overset{C}{H}\!\!\smile\!\!H$ = 109.5° ± 1°, $\overset{N}{H}\!\!\smile\!\!H$ = 105.8° ± 1° in methylamine).



R= H 1
Me 2
Et 3
1Pr 4
2 Pr 5

Formula

Table 1. Steric parameters of several alkyl groups[8]

methyl	ethyl	1-propyl	1-butyl	1-pentyl
0.52	0.56	0.68	0.68	0.68
		2-methyl-	3-methyl-	4-methyl-
2-propyl		1-propyl	1-butyl	1-pentyl
0.76		0.98	0.68	0.68
		2-methyl-	3-methyl-	
2-hexyl		1-butyl	1-butyl	1-pentyl
1.07		1.00	0.68	0.68

The above figures clearly indicate that the bonding geometries of carbon and nitrogen are very similar. Additionally, the Me_2N group is rather far from the reaction centre. These considerations led us to the approximation of replacing of the Me_2N group with a Me group in our calculations. As a result, the use of the steric constants of the model substituent groups corresponding to those indicated in the small box in the Formula was considered satisfactory.

The model substituents, the corresponding steric parameters and the experimentally determined reactivity values are given in Table 2. Testing of LFER requires only the use of relative reactivity values. For this reason, and because of the difficulties in determining the equilibrium constant of adsorption (K), only the products Kk were calculated from the experimentally determined conversion values (x) by the Basset-Habgood equation.

Table 2. Steric parameters and experimental results measured in the transformation of 2-alkyl-3-dimethylamino-1-phenylpropan-1-ols

compound	1	2	3	4	5
model substituent derived by substituting Me for Me_2N	propyl	2-butyl	3-pentyl	3-hexyl	2-methyl-3-pentyl
steric constant ($\underline{v}$)	0.68	1.02	1.51	1.51	2.11
Kk	7.5	3.2	1.2	1.1	0.4
log Kk/K_ok_o*	0.0	-0.37	-0.80	-0.83	-1.27

*K_ok_o = 7.5, i.e. the value for the unsubstituted compound 1.

The correlation between the steric parameters ($\underline{v}$) and the relative reactivities (log Kk/K_ok_o) is depicted in Fig. 3. The result of the least square fit gives the following equation,

$$\log \frac{Kk}{K_ok_o} = -0.89\underline{v} + 0.56$$

where the values of K_0k_0 and Kk are those for the unsubstituted and substituted molecules, respectively, while v is the steric constant.

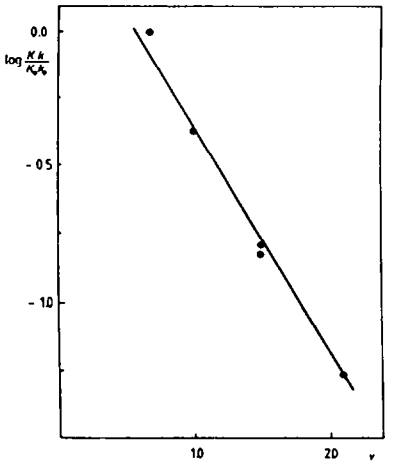


Fig. 3. Variation in log Kk/K_0k_0 as a function of steric parameter v.

The very good correlation (r= 0.996) verifies our assumptions that

(i) the course of the reaction really is influenced by steric interactions,

(ii) the model used to verify this, i.e. the choice of the kinetic equation and steric parameters, were correct,

(iii) steric repulsion does limit the rate of dehydrogenation,

(iv) the proposed structure of the surface intermediate is in accordance with the observations.

However, it remains unclear whether the steric interactions hinder the adsorption (K) or the surface reaction (k) or both. In contrast, electronic effects were expected to have little influence on the course of the reaction, and only a poor correlation was found (r= 0.921) between log Kk/K_0k_0 and Taft's inductive constant, σ^*, the uncertainty of which[2] should be borne in mind in the case of alkyl substituents. The reaction of the threo isomers of the amino alcohols may be expected to exhibit similar features. The difference as compared to Fig. 2 is merely that that the positions of the alkyl group (R) and the dimethylaminomethyl group (R') are interchanged. However, the kinetic investigation is rather difficult because of the rapid isomerization to the more stable erythro isomers.

Experimental

Materials. The five amino alcohols studied (see Formula) were synthesized by known methods.[4] The starting ketones were prepared by the reaction of benzonitrile with the appropriate alkylmagnesium bromide.[9] These ketones were converted to amino ketones by reacting them with formaldehyde and dimethylammonium chloride in ethanol or in a mixture of benzene and

nitrobenzene.[10] The Mannich bases thus prepared were reduced to amino alcohols with sodium borohydride or lithium aluminium hydride.

The erythro isomers of the amino alcohols were isolated by fractional crystallization from diethyl ether and heptane and identified via their NMR spectra.[11] The threo isomer of 2-methyl-3-dimethylamino-1-phenylpropan-1-ol was isolated and purified by chromatography on a 2x60 cm Kieselgel 40 (0.063-0.2 mm) column with a 5:1 mixture of 2-propanol and 25% ammonia solution.

1-Phenylpropan-1-ol- $[1\text{-}^2H]$ was prepared from propiophenone by reduction with lithium aluminium deuteride. The product had a better than 99% isotopic purity, as checked by NMR.

The diethylamine used as solvent for the catalytic experiments was a Carlo Erba product of analytical purity.

All the materials used in the catalytic experiments were pure, as checked by gas chromatography.

The $CuCr_2O_4$ catalyst was synthesized by standard methods.[12] Before use, it was treated in a hydrogen stream at 543 K, and then stabilized by the addition of diethylamine pulses at the selected reaction temperature.

Method. The reactions were carried out in a pulse catalytic microreactor attached to a gas chromatograph, as described earlier.[13] The reactants were dissolved in diethylamine to make a 0.10 M solution, 5 μl of which was injected into the reactor containing 3 mg of catalyst, the temperature of which was maintained at 533 K in a stream of hydrogen (40 ml min^{-1}). The effluent was analysed on a 1.2 m 15% DC-QF 1 on Chromosorb P (60-80 mesh) column at 488 K.

References

1. Taft, R.W. Jr. J. Amer. Chem. Soc. **1952**, 74, 3120-3128.
2. Unger, S.H.; Hansch, C. Prog. Phys. Org. Chem. **1976**, 12, 91-118.
3. Charton, M. J. Amer. Chem. Soc. **1969**, 91, 615-618, 619-623.
4. Molnár, Á.; Sirokmán, G.; Bartók, M. J. Mol. Catal. **1983**, 19, 25-33.
5. Patterson, W.R.; Roth, J.A.; Burwell, R.L. Jr. J. Amer. Chem. Soc. **1971**, 93, 833-838.
6. Basset D.W.; Habgood, H.W. J. Phys. Chem. **1960**, 64, 769-773.
7. Kraus, M. Adv. Catal. **1980**, 29, 151, 160.
8. a. Charton, M. J. Amer. Chem. Soc. **1975**, 97, 1552-1556.
   b. Charton, M. J. Org. Chem. **1976**, 41, 2217-2220.
9. Callen, J.E.; Dornfeld, C.A.; Coleman, G.H. Org. Synth. Coll. Vol. III, John Wiley, New York, 1955, 26-28.
10. a. Reichert, B. Die Mannich Reaction, Springer, Berlin, 1959.
    b.Tramontini, M. Synthesis **1973**, 703-775.
11. Andrisano, R.; Angiolini, L. Tetrahedron **1970**, 26, 5247-5253.
12. Lazarier, W.; Arnold, H.B. Org. Synth., Coll. Vol. II, John Wiley, New York, 1943, 142-145.
13. Notheisz, F.; Zsigmond, Á.G.; Bartók, M. React. Kinet. Catal. Lett. **1977**, 6, 481-487.