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MECHANISM OF THE OXIDATION OF ALCOHOLS BY 2,2,6,6-TETRAMETHYLPIPERIDINE NITROSONIUM CATION

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Abstract: Simple Hammett studies, hydrogen isotope effects, and attempted preparation of proposed transient intermediates are used to probe the mechanism of oxidation of alcohols by 2,2,6,6-tetramethylpiperidine nitrosonium ion.

The oxidation of alcohols to aldehydes and ketones with 2,2,6,6-tetramethylpiperidine nitrosonium cation (1)[1] has been developed as a synthesis method by several groups,[2-5] but little is known about the mechanism. As outlined in Scheme 1, a number of pathways can be written for key steps: (a) simple electron abstraction/proton loss from the alcohol to give the hydroxyl radical and the familiar nitroxyl 3; (b) direct hydride abstraction by 1 to give an oxonium ion and hydroxylamine 2; (c) formation of a reactive adduct (4) by nucleophilic addition to the nitrogen atom of 1; and (d) formation of a similar adduct (5) by addition to the oxygen atom of 1. The intermediates 4 and 5 might undergo elimination via proton abstraction involving internal and external base. In this paper we report preliminary studies which support an intermediate such as 4.

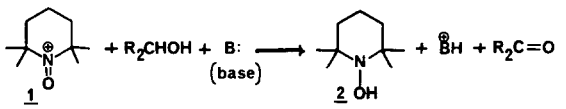
In a simple Hammett study by competition within pairs of para substituted benzyl alcohols,[6] only small rate differences were observed. With p-$NO_2C_6H_4CH_2OH$ assigned a relative rate of 1.0, the rate for p-$CH_3C_6H_4CH_2OH$ is 2.2 while that for p-$MeOC_6H_4CH_2OH$ is 2.1. Similarily, direct monitoring of the reaction progress (glpc analysis of aliquots) shows that reaction of 1-(p-nitrophenyl) ethyl alcohol is slower by a factor of about 5 compared to 1-(p-tolyl)ethyl alcohol. These data suggest the development of only slight positive charge at the benzylic carbon in the rate determining step and are inconsistent with a simple hydride abstraction mechanism (path b in Scheme 1). Also inconsistent with hydride abstraction is the lack of reactivity of nitrosonium ion 1 toward triphenylmethane and toward simple ethers. There is a strong selectivity for primary over secondary alcohols.[5a,7] Chrysanthemyl alcohol (a cyclopropyl carbinol) is oxidized to the aldehyde under the usual conditions[5a] without rearrangement, again inconsistent with long-lived carbocations or radicals centered at the hydroxyl-bearing carbon.

The general oxidation process shows a significant primary hydrogen isotope effect, in both intramolecular and intermolecular competition. The intermolecular isotope effects were measured by product analysis after allowing a pair of labeled and unlabeled alcohols to be

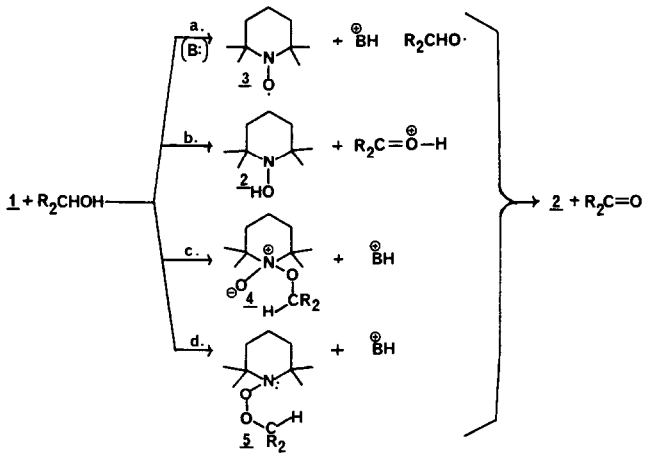
oxidized with a limiting amount of 1, typically 0.5 mol-equiv.[8] The results are displayed in Table 1, entries 1-3. In the case of the secondary aliphatic alcohol (entry 3), reaction rates for labeled and unlabeled samples were also measured, at two concentrations for each.[9] The ratio k_H/k_D obtained as the ratio of reaction half-lives was 1.8, in good agreement with the product analysis in the competition study (entry 3). These data are consistent with several interpretations, including (a) equilibrium formation of 4 or 5 followed by elimination at a comparable rate, to form 2 and $R_2C{=}O$, and (b) a cyclic elimination process[10] from 4 or 5 (figure 1) as rate-determining step. Intramolecular hydrogen isotope effects were measured for both primary benzylic (entry 4) and primary aliphatic (entry 5) alcohols.[11] Each substrate was oxidized to complete conversion and the resulting aldehydes were analyzed by ^1H NMR. The isotope effects were nearly identical, and slightly greater than those measured in the intermolecular competition. The product-determining step shows a kinetic isotope effect of about 2.1, consistent with the cyclic eliminations shown in Figure 1.[10] By intermolecular and by intramolecular competition, and with varied structural types, the isotope effects are remarkably similar. In these and related studies, the reaction rates are approximately independent of the nature of the base (2,6-lutidine, sodium acetate suspension) and the concentration of base. The simplest consistent mechanism is the rapid formation of 4 (or 5) followed by internal elimination as the rate-determining step.

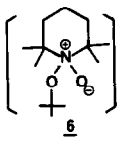
Distinguishing between path c and path d (Scheme 1) is difficult. We have not been able to detect any intermediate spectroscopically nor to obtain a fully substituted adduct (eg. 6) which presumably would be stable toward elimination. Judging from the characteristic color of solutions of 1, potassium tert-butoxide fails to react with 1 at -78°C; upon warming to 0°C, the nitroxyl 3 is detected but no other discrete product is observed. Oxidation of 7[12] with m-chloroperoxy benzoic acid, expected to proceed by N-oxidation to give 6, gave instead the nitroxyl 3 as the primary product.

overall process:

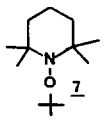


Scheme 1:





6



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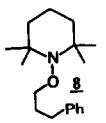

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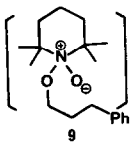

9

Carbon nucleophiles such as organo-magnesium reagents[13] and simple ketones (presumably through the enol[14] add preferentially at the oxygen of 1. The site of addition of oxygen nucleophiles has not been established directly, but the Russian group has provided evidence for the addition of hydroxide (water) at the nitrogen of 1 (adduct of type 4) through isotope exchange studies.[15] We obtained adduct 8[16] by addition of 3-phenylpropylmagnesium bromide to 1 and brought it into reaction with m-chloroperoxybenzoic acid, again with the expectation of N-oxidation to give 9. Using a deficiency of the peracid and following the reaction with 8 from -78°C to 25°C, 3-phenylpropanal was formed (90% yield) but no intermediate was detected. This observation is consistent with 4 as a viable general intermediate.

Overall, the adduct 4 is nicely supported by the data; adduct 5 cannot be ruled out. A cyclic elimination pathway (Figure 1) is proposed as the rate determining step, preceded by a fast, unfavorable equilibrium formation of 4 (or 5). The high selectivity for less crowded hydroxyl groups can also be understood based on 4 or 5. In the proper conformation for intramolecular proton-transfer (Figure 1), substituents at the carbon bearing the hydroxyl group appear from models to be interacting strongly with the equatorial methyl substituents on the piperdine ring. With a reactant-like transition state, the steric interaction would become more severe in approach to the transition states implied in Figure 1, suggesting a higher barrier as the substituents on the hydroxyl-bearing carbon are made larger.

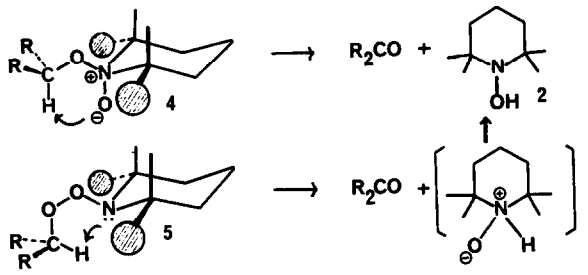

Figure 1. Cyclic elimination pathways.

Table 1. Hydrogen Isotope Effects

entry	substrate	k_H/k_D[b]
1	$p\text{-}CH_3C_6H_4CD_2OH$[a]	1.7[d,f]; 1.8[e,f]; 1.7[d,g]
2	$C_6H_5CD(CH_3)OH$[a]	1.8[d,f]
3	$C_6H_5CH_2CH_2CD(CH_3)OH$[a]	1.8[d,g]
4	$p\text{-}(tBu)C_6H_4CHDOH$[c]	2.1[h,f]
5	$C_6H_5CH_2CH_2CHDOH$[c]	2.1[i,f]

(a) Intermolecular competition, the labeled material was mixed with an equimolar amount of unlabeled compound. (b) The ratio of labeled to unlabeled aldehyde was determined by intergration of the ^1H NMR spectra. (c) Intramolecular competition. (d) The molar ratio of total alcohol to 1 is 2:1. (e) The molar ratio of total alcohol to 1 is 4:1. (f) The base is 2,6-lutidine. (g) The base is sodium acetate. (h) This is the average of three runs with values 1.9-2.3. (i) This is the average of three runs with values 2.0-2.2.

Acknowledgements. We wish to acknowledge financial support in the form of research grants from the Petroleum Research Fund (AC) and the National Institutes of Health (GM 31352).

REFERENCES

1. Atovmyan, L.O.; Golubev,V.A.; Golovina, N.I.; Klitskaya, G.A. Zh. Stukt. Khim. **1975**, 16, 92.

2. Golubec, V.A.; Rosantsev, E.G.; Neiman, M.B. Bull. Acad. Sci. USSR. **1965**, 1927-1936.

3. Cella, J.A.; Kelley, J.A.; Kenehan, E.F. J. Org. Chem. **1975**, 40, 1860-1862.

4. Ganem, B. J. Org. Chem. **1975**, 40, 1998-1999.

5. (a) Semmelhack, M.F.; Chou, C.S.; Cortes, D.A. J. Am. Chem. Soc. **1983**, 105, 4492. (b) Semmelhack, M.F.; Schmid, C.R. ibid. **1983**, 105, 6732. (c) Semmelhack, M.F.; Schmid, C.R.; Cortes, D.A.; Chou, C.S. ibid. **1984**, 106, 3374. (d) Miyazawa, T.; Endo, T.; Shiihashi, S.; Okawaka, M. J. Org. Chem. **1985**, 50, 332-1335.

6. Samples of p-methoxy-, p-nitro-, and p-methylbenzyl alcohols were allowed to complete in pairs in three separate experiments, and relative ratios of aldehydes formed after 20% completion of reaction were measured by ^{1}H NMR spectroscopy to determine relative rates. The following ratios were obtained: (a) p-MeO vs. p-NO_2 = 2.1:1.0. (b) p-MeO vs. p-Me = 1.0:1.2. (c) p-Me vs. p-NO_2 = 2.2:1.0. The three values are internally consistent, within the limits of the experiment. The standard procedure[5a] was used, with 3.0 mmol of each alcohol, 0.21-0.25 mmol of commercially available nitroxyl, **3**, and 0.2 M lithium per-chlorate in acetonitrile.

7. For examples of trityl cation as a selective oxidizing agent for alcohols via their ethers and leading references regarding other reagents with high selectivity for secondary over primary alcohols, see: (a) Jung, M.E.; Speltz, L.M. J. Am. Chem. Soc. **1976**, 98, 7882: (b) Jung, M.E.; Brown, R.W. Tetrahedron Lett. **1978**, 2771.

8. The stoichiometry for the oxidation of alcohols by nitrosonium ion **1** is two molequiv of **1** for each mol-equiv of alcohol. The initially formed hydroxylamine **2** reacts rapidly with **1** to generate two mol-equiv of nitroxyl **3** and a proton.[5a] For the measurement of kinetic isotope effects by competition, the nitrosonium ion **1** was generated in solution by electrooxidation of **3**, and then mixed with equimolar amounts on the labeled and unlabeled alcohols. The reaction was carried out in triplicate.

9. An equimolar mixture of the alcohols was oxidized under the standard conditions[5a] with preformed samples of **1**. Two reactions were studied, differing only in a dilution of 67%. In a calibration run with unlabeled material, the yield of aldehyde was shown to be 95%, at 100% conversion. Each kinetic experiment was followed to more than 60% conversion, with five aliquots being analyzed in each case. The reaction half-life ratio was calculated to be 1.75 in one case, and 1.78 in the other, with an estimated uncertainity of ±10%.

10. Hydrogen-deuterium isotope effects in the range of 2-3 are expected for rate-determining transition states with non-linear hydrogen transfer. For a theoretical discussion and some examples, see: More O'Ferrall, R. A. J. Chem. Soc. B. **1970**, 786. Primary isotope effects of 2.2 were reported for Cope-type eliminations: Kwart, H.; George, T.J.; Louks, R.; Ultee, W. J. Am. Chem. Soc. **1978**, 100, 3927.

11. Reduction of the corresponding aldehyde with lithium tetradeuterioaluminate (99%, Aldrich Chemical Co.) provided the labeled alcohols. Careful integration of the ^{1}H NMR spectra demonstrated the presence of 50±3% deuterium at the carbon bearing hydroxyl group.

12. We prepared **7** by addition of tert-butyllithium to **1**; it has been observed before: Kovtun, G.A.; Aleksandrov, A.L.; Golubev, V.A. Bull. Acad. Sci. USSR **1974**, 2197.

13. Golubev, V.A.; Kobylyanskii, E.V. Bull. Acad. Sci. USSR **1972**, 2607.

14. (a) Golubev, V.A.; Rudyk, T.S.; Sen, V.D.; Aleksandrov, A.T. Bull. Acad. Sci. USSR **1976**, 744.

15. Golubev, V.A.; Sen, V.D.; Rozantsev, E.G. Bull Acad. Sci. USSR **1980**, 1927.

16. Compound **8** showed the following analytical data. ^{1}H NMR($CDCl_3$): δ 7.2 (s,5H), 3.75 (t,2H,J=6Hz), 2.68 (t,2H,J=6Hz), 1.85 (q,2H,J=6Hz), 1.4 (s,6H), 1.12 (s,12H). Irradiation at δ 1.85 produces singlets at δ 3.75 and 2.68. ^{13}C NMR($CDCl_3$): δ 142.3(s), 128.3(d), 128.2(d), 125.6(d), 76.1(t), 59.6(s), 39.7(t), 33.0(q), 32.7(t), 30.5(t), 20.0(q), 17.2(t). IR (neat): 3060(m), 3040(m), 3000-2840(vs), 1600(m), 1540(w), 1500(m), 1470(s), 1450(s), 1375(s), 1360(s), 1135(s), 1050(s). MS: M+ at 275. **Anal** Calcd: C, 78.49; H, 10.61; N, 5.09. Found: C, 78.45; H, 10.51; N, 5.11.

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