Neighboring Group Participation in Proton Transfers[1]

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Abstract: The predominant term in the base-catalyzed iodination of 4-nitrovaleric acid is first order in the carboxylate ion and zero order in bases and iodine; it is attributed almost wholly to proton abstraction by the neighboring carboxylate ion. Even with added pyridine only the first-order term is important. Neither 3-nitropropionate nor 6-nitrohexanoate ions iodinate as rapidly, and other intermolecular catalysis terms contribute importantly. The racemization of optically active 4-nitrovaleric acid in water or in aqueous *tert*-butyl alcohol follows a similar rate law. In water with less than an equivalent amount of strong base and in aqueous *tert*-butyl alcohol with added pyridine the rates of iodination and the rates of racemization are the same, but in aqueous *tert*-butyl alcohol with less than 1 equiv of added sodium hydroxide the racemization is slower than the iodination. The discrepancy is discussed but not satisfactorily explained. The racemization is connected with the formation in the absence of halogen of levulinate ion, and the mechanism of this unusual Nef reaction is discussed.

The acidic proton in a nitroalkane is susceptible to attack by various bases. We shall be concerned here with the importance of attack by neighboring basic sites in the same molecule, such that the transition state is describable as a cyclic species with a hydrogen bond. Bell and Fluendy[3] studied the halogenation of some keto acids, and believed that neighboring group participation was most favorable with a six-membered (including the proton) ring transition state. Most of the present work concerns 4-nitrovaleric acid; the corresponding carboxylate ion can form such a cyclic transition state.

The observed[4] general base catalysis in halogenation of nitro compounds in the case of a nitro acid leads to a number of possible terms, since reaction of all bases with either the acid or the carboxylate is possible. Under the conditions of our experiments only three terms are expected when the acid is partially neutralized by a strong base, *i.e.*, an expression of the form of eq 1. In this the first term has solvent as the

$$-\mathrm{d}(\mathrm{I_2})/\mathrm{d}t = k_a(\mathrm{RCO_2H}) + k_b(\mathrm{RCO_2H})(\mathrm{RCO_2^-}) + k_c(\mathrm{RCO_2^-}) \quad (1)$$

base and un-ionized acid as the proton source, the second uses the external carboxylate ion as the base, but the third is composite. It includes the intramolecular carboxylate ion participation, the attack of solvent as a base on carboxylate, and the attack of lyate ion on the un-ionized acid.

In the presence of a weak base, B, the concentration of carboxylate is low and is measured by an equilibrium constant $K = (\mathrm{RCO_2^-})(\mathrm{BH^+})/(\mathrm{RCO_2H})(\mathrm{B})$, and the expected rate expression becomes eq 2, with

$$-\mathrm{d}(\mathrm{I_2})/\mathrm{d}t = k_a(\mathrm{RCO_2H}) + k_cK^{1/2}(\mathrm{B})^{1/2}(\mathrm{RCO_2H})^{1/2} + k_d(\mathrm{RCO_2H})(\mathrm{B}) \quad (2)$$

k_a and k_c having the same values as in eq 1.

Results

When a less than equivalent amount of sodium hydroxide is added to 4-nitrovaleric acid and the rate of iodination is measured by the procedure used earlier,[5] eq 1 is indeed followed with the rate constants given in Table I, which also shows the results on three other acids, 4-nitro-3-methylvaleric acid, 3-nitropropionic acid, and 6-nitrohexanoic acid. The blank spaces under k_b for the valeric acid derivatives do not mean that the value is zero, but only that this term was not detected. Since only low concentrations of carboxylate were used, the bimolecular term would have contributed very little.

In the aqueous *tert*-butyl alcohol solvent with added pyridine, eq 2 was followed except that the k_d term was undetected. The value of k_c from Table I could be used requiring a value of the equilibrium constant $K = 1 \times 10^{-2}$. In this medium 4-nitrovaleric-*4-d* acid was also iodinated, and the value of k_c was $38 \pm 3 \times 10^{-6}$, corresponding to $k_c^H/k_c^D = 5.5 \pm 0.5$. The experiment did not yield a useful value of k_a^D.

The racemization of optically active 4-nitrovaleric acid was followed under the same conditions. Table II shows the observed first-order rate constants in water with less than 1 equiv of sodium hydroxide and in aqueous *tert*-butyl alcohol with pyridine with the rate constants calculated from iodination rates using eq 1 and 2 and the rate constants and the equilibrium constant previously determined. It is seen that the racemization and iodination are closely related.

In contrast, the racemization of partially neutralized acid in aqueous *tert*-butyl alcohol is significantly slower than that calculated from the iodination rate, as shown in Figure 1. The straight line gives the rates calculated from eq 1, but established only at low values of the fraction ionized; the points show the significantly lower rate constants for racemization observed at different fractions ionized (f). The discrepancy appears to be less at high f values, but this conclusion requires a large extrapolation of the iodination data. Although the discrepancy between these two measures of ionization rate is unexpected, it is not without analogy. We find it difficult to ascribe the problem to

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[1] A grant from the Robert A. Welch Foundation supported this work and is gratefully acknowledged.

[2] Phillips Petroleum Co. Fellow, 1970–1971.

[3] R. P. Bell and M. A. D. Fluendy, *Trans. Faraday Soc.*, **59**, 1623 (1963); M. A. D. Fluendy, *ibid.*, **59**, 1681 (1963).

[4] R. P. Bell and D. M. Goodall, *Proc. Roy. Soc., Ser. A*, **294**, 273 (1966), among many.

[5] E. S. Lewis and L. H. Funderburk, *J. Amer. Chem. Soc.*, **89**, 2322 (1967).

Table I. Rate Constants[a] for the Iodination of Some Nitro Acids

Solvent	Acid	$k_a \times 10^6$ sec^{-1}	$k_b \times 10^4$ sec^{-1} M^{-1}	$k_c \times 10^6$ sec^{-1}
54% *tert*-BuOH[b]	4-Nitrovaleric	0.88 ± 0.05	...[c]	187 ± 4
H_2O	4-Nitrovaleric	1.40	...[c]	28.5
H_2O	4-Nitro-3-methylvaleric	0.81	...[c]	64.5
H_2O	3-Nitropropionic	1.28	1.16	2.75
H_2O	6-Nitrohexanoic	0.54 ± 0.1	1.14 ± 0.1	6.58 ± 0.2

[a] At 30°. [b] This is the "60% by volume" solvent of ref 5. The designation as weight per cent allows the solution to be made up at any temperature. [c] Not detected, but probably >0; see text.

Table II. Rate Constants for Racemization of 4-Nitrovaleric Acid

Base added	Concn × 10^2 M	$(RCO_2H)_t$[a] × 10^2 M	k_{obsd} × 10^5 sec^{-1}	k_{calcd}[d] × 10^5 sec^{-1}
Pyridine[b]	16.2	4.04	3.38	3.31
Pyridine[b]	10.10	8.95	1.83	1.80
Pyridine[b]	13.5	5.97	2.30	2.52
Pyridine[b]	6.73	11.90	1.38	1.26
Pyridine[b]	10.10	10.10	1.90	1.70
Pyridine[b]	4.14	14.30	0.91	0.89
Pyridine[b]	16.20	3.58	3.75	3.50
Pyridine[b]	10.10	8.95	1.88	1.80
OH^- [c]	10.9	9.37	2.80	2.85
OH^- [c]	5.9	14.9	1.26	1.28
OH^- [c]	9.09	12.3	2.18	2.25
OH^- [c]	7.50	7.62	2.70	2.81
OH^- [c]	3.30	16.5	0.67	0.71

[a] Total RCOOH + RCO_2^-. [b] Pyridine experiments in 54% *tert*-BuOH. [c] In water. [d] Calculated from iodination rates.

experimental error since there is good agreement in both the conditions of Table I, and we have further found good agreement between iodination and racemization rates for the reactions of methyl 4-nitrovalerate.

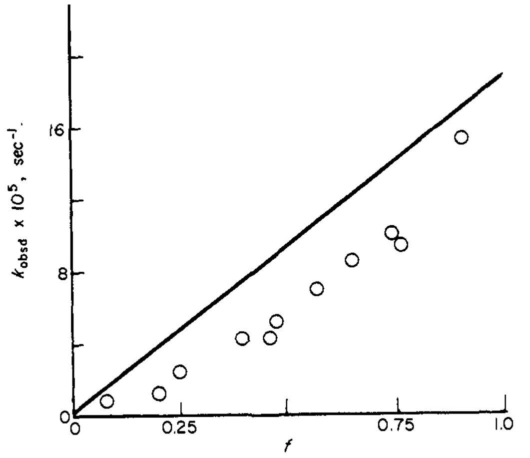

Figure 1. Comparison between observed first-order racemization constants for partially neutralized 4-nitrovaleric acid (circles) and the rate calculated from iodination rate (line) for different values of the fraction neutralized (f), in 54% *tert*-butyl alcohol.

The product from the iodination conditions was not readily isolable, because the iodination is reversible, but in the presence of base and either bromine or *N*-bromosuccinimide, 4-bromo-4-nitrovaleric acid was readily isolated. In the absence of halogen the 4-nitrovalerate ion is quite unstable, giving a gas (presumably nitrous oxide) and levulinate at a rate comparable to the rate of the proton transfer. 4-Nitro-3-methylvalerate also gives a keto acid readily, but 3-nitropropionate and 6-nitrohexanoate do not lose the nitro group.

Discussion

The predominance of k_c in the iodination of 4-nitrovaleric acid with base is clear from Table I. The pseudo-first-order rate constant for attack of lyate ion on the un-ionized acid can be set at below 1 × 10^{-7} sec^{-1} at the acidities used in the aqueous *tert*-butyl alcohol solvent, since that is the total rate for attack on the corresponding ester of a more basic solution containing 0.01 M sodium acetate, without any free acetic acid added.[6] The attack of solvent on the acidic proton of RCO_2^- must be slower than that of solvent on RCO_2H, with a rate constant of 9 × 10^{-7} sec^{-1}. Thus k_c must be at least 99% attributable to the intramolecular term. The predominance is still strong in water solution for 4-nitrovaleric acid, but with the acids requiring a different ring size for the neighboring group participation the rate is slower and its composition is also less clear. The presence of the bimolecular term makes the analysis a little more difficult. The result is certainly entirely consistent with the work of Bell and Fluendy,[3] in that the six-membered ring structure is favorable.

It is possible that there is some neighboring group participation even in the k_a term, since this is larger than in the iodination of 2-nitropropane, where it was undetectable in aqueous *tert*-butyl alcohol; the evidence is not compelling.

There may be some connection between the formation of levulinate and the unexpectedly low rate of racemization. The scheme of intermediates in rough outline is proposed to explain some of these features. We propose the cyclic intermediate **2** to account for the unusual[7] basic medium Nef reaction and the fact that it occurs when the ring has five members. If the racemization and the iodination go through a common intermediate, it must have the composition of **1** to account for the kinetics, and **1** must react exclusively with iodine when it is present. The slower rate of racemization of 4-nitrovalerate ion then requires **1** to return to the isomer from which it was derived faster than to the enantiomer and hence that **1** must be chiral, at least on a time scale longer than it takes to react with iodine. This chirality is not likely to result from hindered rotation about the C-3 to C-4 bond alone; in looking elsewhere we can consider as possible sources of chirality the hydrogen bond illustrated, or

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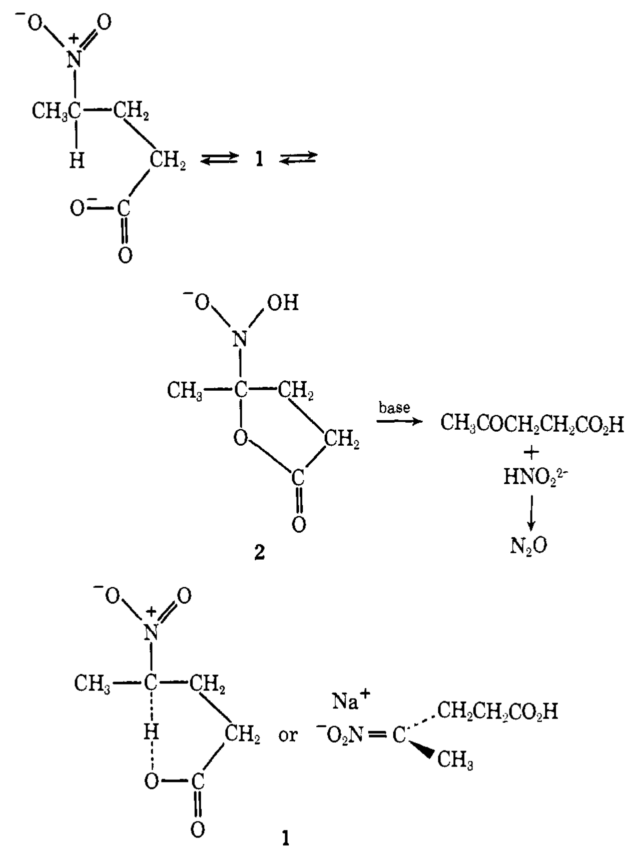
(6) H. Wilson, unpublished work.

(7) The Nef reaction normally occurs on adding strong acid to an *aci*-nitro compound. See, for example, N. Kornblum and R. A. Brown, *J. Amer. Chem. Soc.*, 87, 1742 (1965).



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the presence of the sodium ion in a chiral ion pair. The rather unsatisfying structure of **1** suggested is certainly not demonstrated, and indeed no peculiar feature is needed except to account for the lower rate of racemization than iodination. We presume to offer this suggestion only because of our present conviction that the rate discrepancy of Figure 1 is real and not an artifact of unknown experimental error. The intermediate **2** or an equivalent does not depend so heavily on the rate measurements. We write a base catalysis for the conversion of **2** to levulinic acid because of the upward curvature of the points in Figure 1; indeed, the points can be fitted within experimental error by adding a base catalysis term for part of the racemization, but we place little significance on this quantitative fitting. The explanation, although consistent with the observations, is unsatisfying and we are searching for a better answer.

Experimental Section

4-Nitrovaleric Acid. This was prepared by the acid hydrolysis of its methyl ester.[8] The 4-deuterio derivative was prepared over 98% deuterated by hydrolysis of the deuterated ester; the free acid could not be exchanged because of its conversion to levulinic acid. The preparation of the esters from methyl acrylate and nitroethane and the resolution *via* the quinine salt followed published procedures.[8]

3-Nitropropionic Acid. A commerical material recrystallized from chloroform, mp 63°, was used.

6-Nitrohexanoic Acid. The preparation following Sheehan and Vellturo[9] was used.

4-Nitro-3-methylvaleric Acid. A procedure following Colonge and Pouchol[10] was used.

All these substances had nmr spectra consistent with their assigned structures.

The solvent of the earlier procedure[5] was reproduced, but gravimetric preparation is more reproducible because of room temperature variation. It is 54% *tert*-butyl alcohol by weight.

Rate Measurements. Separate solutions of acid and base were brought to thermostat temperature and then mixed, and a small amount of iodine solution was added. The 10-cm spectrophotometer cell was rinsed with this solution, and then the filled cell was placed in the spectrophotometer and allowed to come to thermal equilibrium at 30.0° before recording was started. The reaction followed a zero-order course, not dependent on the time of equilibration, until nearly all the iodine was gone, but a small residual absorbance showed that there was a perceptible reverse reaction.

The procedure for racemization was similar except that the solution without iodine was placed in a 3-cm jacketed cell of a Bendix automatic polarimeter and the loss of optical rotation followed a first-order course.

In both methods the temperature reported is that measured in the cell under identical circumstances, rather than that of the thermostat.

Rate constants were fitted to an integrated rate expression by the method of least squares and converted to rate constants of eq 1 or 2 by converting the pseudo-zero- or first-order rate constants to appropriate linear expressions. The extinction coefficients of the iodine solutions required to give the rate constants were determined in separate experiments.

Products. When solutions of iodination product of 4-nitrovaleric acid were concentrated, a dark brown color, presumably iodine, appeared and only levulinic acid could be isolated. Substitution of bromine for iodine gave more tractable products; an aqueous solution of 4-nitrovaleric acid almost completely neutralized with sodium hydroxide was treated with bromine to persistence of the color. Then acidification and extraction led to a mixture of two acids; the minor one had the nmr of levulinic acid and the other had a very similar spectrum with only slightly different chemical shifts. A cleaner synthesis of this latter acid was achieved by mixing the aqueous acid with 1 equiv of *N*-bromosuccinimide and then adding less than 1 equiv of sodium hydroxide. The heterogeneous mixture became homogeneous as the reaction progressed. The resulting solution yielded after extraction the bromo nitro acid as an oil in a purer state than above, contaminated only with a little starting acid. In addition to the carboxylic proton, the nmr showed a three-proton singlet at τ 7.7, and a four-proton multiplet at τ 7.0–7.5, identical with those of the major product using bromine. Fischer esterification yielded a methyl ester with the same nmr as the bromination product of methyl 4-nitrovalerate, infrared (1560 and 1370 cm^{-1}) showing the nitro group, and a mass spectrum showing the characteristic bromine doublets and the heaviest ion corresponding to the loss of NO_2 only.

The rapid formation of levulinate in basic media could be observed by the nmr of the reacting solutions, but rates were not measured. Similar observation of 3-nitropropionic acid and 6-nitrohexanoic acid in D_2O solutions with added base showed only exchange of the protons next to the nitro with no other decomposition.

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[8] W. Thielacker and G. Wendtland, *Justus Liebigs Ann. Chem.*, **570**, 33 (1950).

[9] D. Sheehan and A. F. Vellturo, South African Patent 6,705,788 (1968).

[10] J. Colonge and J. Pouchol, *Bull. Chem. Soc. Fr.*, 569 (1962).