Kinetics and Product Orientation in Oxidation of Aldehyde 2,4-Disubstituted Phenylhydrazones by Lead Tetra-acetate; Hydrazone Azo Tautomers

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Oxidation of aliphatic aldehyde phenylhydrazones containing *ortho*-substituents (NO_2, Br, or Me) in the *N*-phenyl ring with lead tetra-acetate gives significant yields of α-unsubstituted azo-acetates which are azo tautomers of hydrazones. With aromatic aldehyde derivatives the product-orienting influence of the ortho-substituent in the *N*-phenyl ring was negated or reduced by the aromatic methine substituent. Kinetic measurements were made on series of aliphatic aldehyde 2,4-dinitrophenylhydrazones and 2-bromo-4-nitrophenylhydrazones. Strong steric effects (δ 0.83) for methine substituents were detected for the 2,4-dinitrophenylhydrazone series. The relative influences of the 2-NO_2 and 2-Br substituents on the rates were examined. The 2-NO_2 group had an exceptionally large rate-retarding effect. The mechanism of the reaction is discussed.

ALDEHYDE 2,4-dinitrophenylhydrazones (DNPHs) are relatively unreactive towards electrophilic attack. With bromine as electrophile first-order reactions were observed in which the rates were governed by slow *syn–anti* isomerisation in the hydrazones.[1] These hydrazones are also relatively unreactive towards lead tetra-acetate (LTA) in synthetic reactions, but not inert.[2] This unreactivity with LTA has been ascribed [3a] to steric shielding of the amino site by the *ortho*-substituent rather than to stereoisomerism, and it has been suggested as possible evidence for initial electrophilic attack at the amino site of the hydrazone chain. However, in the absence of a full understanding of the apparent unreactivity of DNPHs in synthetic reactions, the initial site of LTA attack on hydrazones is still uncertain.[4] This is also the case with oxidations by LTA of related heteroallylic systems,[5] including enamines,[6] enols,[7] α-CH ketones,[7] and oximes.[4] The usual site for electrophilic attack on hydrazones is the methine carbon atom.[8]

The purpose of the present work was (i) to investigate the apparent unreactivity of the DNPH system towards LTA and the relative influences of individual NO_2 groups and geometrical isomerism in the hydrazones, and (ii) to attempt to establish the initial site of attack on the hydrazone chain. There are six possible sites of attack: the methine carbon, the imino nitrogen and the amino nitrogen atom, each in either the *E*- or the *Z*-isomer. Our approach to this second objective was to measure steric substituent effects at the methine carbon atom and at the *ortho*-position of the *N*-phenyl ring. Because of experimental difficulties and because of ambiguities arising from the proximity of the sites and the large bulk of the reagent this objective was achieved only partially, and we feel that it may not be possible to obtain a direct unequivocal resolution of this problem from a kinetic approach. Nevertheless the present kinetic study advances the problem from the realm of intuition where it resides at present.[4] We have previously attempted to solve this question directly by isolation of metallic hydrazone intermediates from oxidations with LTA and with mercury(II) acetate.[9]

RESULTS AND DISCUSSION

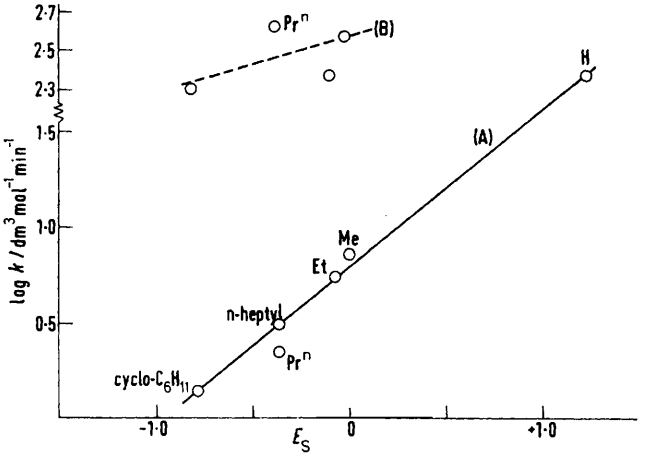
(i) *Kinetic Studies.*—The Table shows the rate constants for a series of aldehyde 2,4-disubstituted hydrazones. The rates were measured by following the disappearance of the hydrazone u.v. absorption at the wavelengths shown. LTA shows a u.v. maximum at 220—250 nm, which tails off up to 350 nm.[10,11] With one exception (No. 1 in the Table) all the rates were measured at wavelengths above 350 nm, and under the conditions used no difficulties were encountered nor were the results impaired owing to LTA absorption or to photolysis (Experimental section). Our present data are consistent with the data previously reported for ketone nitrophenylhydrazones (Nos. 7, 16, and 17 in the Table).

(a) *Methine carbon atom.* The reactions were all second order and the rates were dependent on the concentration of LTA, thus eliminating isomerism in the hydrazones as being of significance. The DNPH series (Nos. 1—6 in the Table) showed strong steric effects for methine substituents. A plot of log *k* against Taft E_S values was linear (*r* 0.992, *s* 0.08) [Figure, line (A)] and gave a high δ value of +0.83 for the reaction. For bromination [1] of aliphatic aldehyde DNPHs the steric susceptibility factor (δ) was 0.49, the rate-determining step being *syn–anti* isomerisation in the hydrazone, in which the reagent was not involved. The high δ value and the second-order kinetics now observed for the LTA reaction are consistent with involvement of both reactants in the rate-determining step. The similarity of the

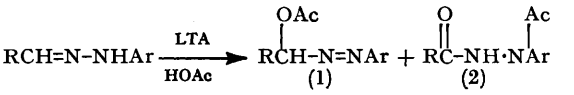
[1] A. F. Hegarty and F. L. Scott, *J. Org. Chem.* 1968, **33** 753.
[2] R. N. Butler and W. B. King, *J.C.S. Perkin I*, 1975, 61.
[3] (*a*) W. A. F. Gladstone, J. B. Aylward, and R. O. C. Norman, *J. Chem. Soc.* (*C*), 1969, 2587; (*b*) M. J. Harrison, R. O. C. Norman, and W. A. F. Gladstone, *J. Chem. Soc.* (*C*), 1967, 735.
[4] R. N. Butler, T. A. F. O'Mahony, and F. L. Scott, *Chem. Rev.*, 1973, **73**, 93.
[5] R. N. Butler, *Chem. and Ind.*, 1976, 499.
[6] R. B. Boar, J. F. McGhie, M. Robinson, and D. H. R. Barton, *J.C.S. Perkin I*, 1975, 1242.
[7] R. M. Moriarty, 'Selective Organic Transformations,' ed. B. S. Thygarajan, Wiley, New York, 1972, vol. 2, pp. 183—237.
[8] J. Buckingham, *Quart. Rev.*, 1969, **23**, 37; P. Bouchet, J. Elguero, and R. Jacquier, *Bull, Soc. chim. France*, 1967, 4716.
[9] R. N. Butler and W. B. King, *J.C.S. Perkin I*, 1976, 986.
[10] V. Franzen and R. Edens, *Angew. Chem.*, 1961, **73**, 579.
[11] K. Heusler and H. Loeliger, *Helv. Chim. Acta*, 1969, **52**, 1495.

kinetic pattern for all the hydrazones to the formaldehyde case (No. 1 in the Table) where *syn–anti* isomerisation cannot occur further confirms this. There was much less, if any, steric effect with the corresponding 2-bromo-4-nitrophenylhydrazones (BNPHs) [Table, Nos. 9—12, δ 0.2—0.4 for a poor linear correlation; Figure, line (B)]. The two 4-nitrophenylhydrazones (Nos. 14 and 15) also showed little steric effect at the methine carbon atom, giving a small change in rate for a change in the E_s value of the methine substituent of 0.07 to 0.79.

(b) N-*Phenyl* ortho-*substituent*. The unreactivity of the 2,4-dinitrophenylhydrazone system is due to the 2-NO_2 group, which showed an exceptionally large rate-retarding effect. (*cf.* Nos. 3, 14, and 18 in the Table). A much smaller rate-retarding effect was observed with a 2-Br group * (Nos. 1—6 *vs.* 9—12). The unreactivity of the DNPH series resulting from the 2-NO_2 group is unlikely to be due solely to a steric effect. Previously, it has been shown [13] that such hydrazones display a special stabilization of the ground state involving resonance electron depletion at the amino nitrogen atom and also an intramolecular hydrogen bond. The consequent reduction in the nucleophilicity of the hydrazone chain and the increased activation energy due to the loss of the special ground state stabilization, which would occur in the transition state for a direct attack at the amino nitrogen atom, probably results in much reduced reactivity for the hydrazone chain. This could also favour an approach by the electrophile away from the *ortho*-substituent above the plane of molecule *via* the imino π-cloud, *e.g.* as in formula (3), or possibly initially at the imino lone pair. The stronger steric effects at the methine carbon for the DNPH series favour an initial approach near to this site, but unfortunately do not unequivocally prove it since a direct attack at the amino nitrogen might also give a steric effect at the methine carbon because of



Taft plot of log k against steric substituent constant, E_s; (A) aldehyde 2,4-dinitrophenylhydrazones; (B), aldehyde 2-bromo-4-nitrophenylhydrazones



No.	Hydrazone R	Hydrazone Ar	Yield of (1) (%)	Yield of (2) (%)	k / dm³ mol⁻¹ min⁻¹	λ / nm
1	H	2,4-$(NO_2)_2C_6H_3$	90 [a]	3.5	58.4 (1.24) [c]	344
2	Me		85 [a]	5	7.02 (0.0) [c]	352
3	Et		75 [a]	14	5.46 (−0.07) [c]	355
4	Prⁿ		66 [a]	19	2.18 (−0.36) [c]	353
5	n-Heptyl		59 [a]	29	3.07 (−0.36) [c]	355
6	Cyclohexyl				1.41 (−0.79) [c]	354
7	Acetone DNPH				0.61 [d]	359
8	Ph	2,4-$(NO_2)_2C_6H_3$	<1 [a]	40		
9	Me	2-Br-4-NO_2·C_6H_3	28—33 [b]	55—66 [b]	380 [e]	368
10	Et		32—38 [b]	51—58 [b]	231	370
11	Prⁿ				433	370
12	Cyclohexyl				204	371
13	Me	4-NO_2·C_6H_4	<1 [a]	70		
14	Et		<1 [a]	61	3 080 [f]	375
15	Cyclohexyl				2 800 [f]	375
16	Benzophenone 4-NPH [h]				52.5 [g]	
17	Fluorenone 4-NPH [h]				3.20 [g]	
18	Et	2-NO_2·C_6H_4	76 [a]	10	65.5	420
19	Ph		<1 [a]	48		
20	Ph	2-MeC_6H_4	28—31 [b]	47—50 [b]		
21	*p*-ClC_6H_4		25—31 [b]	60—68 [b]		

[a] From ref. 2. [b] Structures were established from elemental analyses and i.r., u.v., ^1H and ^{13}C n.m.r. spectra. [c] Parentheses contain E_s values from R. W. Taft, 'Steric Effects in Organic Chemistry,' ed. M. S. Newman, Wiley, New York, 1956, p. 598. [d] Lit.[12] value, 0.51 (Experimental section). [e] Error ±12%. [f] Measured by stopped-flow technique. [g] From ref. 3b. [h] 4-NPH = 4-nitrophenylhydrazone.

* Iffland *et al.* [12] reported that the reaction of LTA with acetone 2-nitrophenylhydrazone in methylene chloride was slower than that of acetone 2-bromophenylhydrazone (which could not be measured).

[12] D. C. Iffland, L. Salisbury, and W. R. Schafer, *J. Amer. Chem. Soc.*, 1961, **83**, 747.

[13] Z. Rappoport and T. Sheradsky, *J. Chem. Soc.* (*B*), 1968, 277; G. L. Karabatsos, F. M. Vane, R. A. Taller, and N. Hsi, *J. Amer. Chem. Soc.*, 1964, **86**, 3351.

the size of the reagent.† However, the differences in the methine steric effects for the DNPH series and the BNPH and 4-nitrophenyl series certainly suggest mechanistic differences.

We were not able to measure a steric δ value for a series of 2-substituted 4-nitrophenylhydrazones or 2-substituted phenylhydrazones owing to difficulties (Experimental Section) in obtaining suitable derivatives. Only recently [14] has an effective route to the 2-bromo-4-nitrophenyl derivatives been developed. However, a steric susceptibility factor for the *ortho*-position can be calculated from the two pairs of compounds (Nos. 14 and 10 and Nos. 15 and 12) (Table) by using the expression $\log k - \rho^* \sigma^* = \delta E_s$. This expression gives δ 0.58 for each pair (by using the reported [3b] ρ value, −1.95, and σ* and E_s values from footnote *c* in the Table). These data, when combined with the data of line (B) in the Figure and Nos. 14 and 15 (in the table) provide a limited ‡ comparison of steric effects at both ends of the hydrazone chain. While *ortho*-substituents in the *N*-phenyl ring may exhibit relatively strong steric effects even for direct attack at the methine carbon atom,[15] such steric effects could not be expected to be greater than those of substituents directly bonded to the methine carbon atom itself, and these data, although limited, tend to favour a direct approach to the amino nitrogen atom for these *p*-nitrophenylhydrazones without an *o*-nitro-substituent.

The special effect of the *ortho*-NO_2 group in the DNPH series may be due either to resonance electron depletion at the amino nitrogen (enhanced by the 4-NO_2 group) or to hydrogen bonding with the amino H–N, or indeed to a combination of both factors. The present data do not allow a distinction of the relative importance of these factors. However, the large difference between the *ortho*- and *para*-NO_2 groups of mononitrophenylhydrazones (Nos. 18 and 14 in the Table) may imply at least a significant contribution from the hydrogen-bonding effect.

† Molecular models were used to estimate the steric effects which might be expected at the methine carbon for an attack at the amino nitrogen atom. These models suggested that a direct attack at the amino nitrogen of the *E*-isomer should produce only small steric effects from substituents (*trans*) at the methine carbon atom whereas an attack at the amino nitrogen of the *Z*-isomer should produce strong steric effects. However, that such an attack at the crowded side of the isomer disfavoured on steric grounds is the main mode of reaction is intuitively unlikely and it is not consistent with (i) the results for bromination (ref. 1), where the *Z*-isomer was indeed the reactive form but was attacked at the methine carbon from the uncrowded side; (ii) the general second-order kinetic pattern which was retained for rates varying over three orders of magnitude (for a slow attack on the *Z*-isomer, *k* should be less than the rate of *syn–anti* isomerisation); (iii) the comparison with the BNPHs where similar methine steric effects were not observed but which should be no different to the DNPH series if the preferred attack were at the amino nitrogen of the *Z*-isomer in both cases, and (iv) the much increased steric effects at the methine carbon of ketone derivatives in comparison with aldehyde derivatives (No. 2 *vs.* 7 and 14—17 in the Table). The methine substituent of the aldehyde hydrazone *Z*-isomer bears the same spatial relationship to the amino nitrogen as does the corresponding ketone hydrazone; hence, for example, if the NH of the *Z*-isomer were the site of attack, there should be effectively no difference between Nos. 2 and 7 (Table) for second-order kinetics. For these reasons we believe that the attack is occurring on the *E*-isomer.

(ii) *Product Studies.*—Over the full range of compounds studied there was no correlation between the rates and the product distributions. The rate-determining step is separate from the product-determining step. The main product-determining effect in the series of aliphatic hydrazones operated from the 2-position of the *N*-phenyl ring. A 2-NO_2 group strongly favoured azo-acetate (1) formation as did a 2-Br group (Nos. 9 and 10 in the Table) but to a lesser extent than an NO_2 group. The azo-acetates (1) contain an α-hydrogen atom and are stable azo tautomers of the hydrazone system. They can be expected in medium yields from the LTA–hydrazone reaction if the hydrazone substrate has an alkyl group at the methine carbon atom and an *ortho*-substituent in the *N*-phenyl ring. Increasing the complexity of the aliphatic methine substituent or changing to an aromatic group reduced the yields of azo-acetates and favoured diacylhydrazine (2) formation, which occurs *via* solvent addition to a nitrilimine intermediate (6).[3] Since the product-determining and rate-determining steps are different, and metal–hydrazone intermediates cannot be isolated, mechanistic information on the product-determining step cannot be obtained directly. The influence of substituents on the product orientation is, therefore, of considerable mechanistic importance for these reactions, and substituent influences on both kinetics and products must of necessity be combined in order to determine an overall picture of the mechanism.

The product distribution in the present reaction can only be reasonably explained § by the presence of the key intermediate (5) which enters a product-determining step (Scheme) in which the product balance is controlled by the relative effects of substituents on paths (a) and (b). In general, electron-withdrawing substituents on the *N*-phenyl ring favour path (b) by stabilising the incipient negative charge on the amino nitrogen atom. *ortho*-Substituents, however, favour path (a) owing to steric inhibition of resonance by out-of-plane rotation of the phenyl ring, a phenomenon previously observed [11] with *N*-methyl DNPHs and which should be more enhanced in an N–Pb intermediate such as (5). The large steric requirements of the 2-NO_2 group (E_s −0.75) make this more effective than a 2-Br substituent (E_s 0.0). The possibility of some weak hydrogen-bonding involving the 2-NO_2 group in the intermediate (4), which would prolong the lifetime of the species (4) thereby favouring path

‡ We have recently [9] inserted an HgOAc group at the 2-position of these hydrazone systems, and intend to explore the possibility of using this as a leaving group in further syntheses.

§ The possibilities that azo-acetates are favoured owing to blocking of acetyl migration to the amino nitrogen by *ortho*-substituents or owing to direct attack at the methine carbon followed by displacement of $Pb(OAc)_3$ by acetate are excluded by results such as Nos. 8 and 19 (Table), where the same blocking effects should be present and where a similar methine carbon attack should occur, since the NH site is equally deactivated, but where no azo-acetates were encountered.

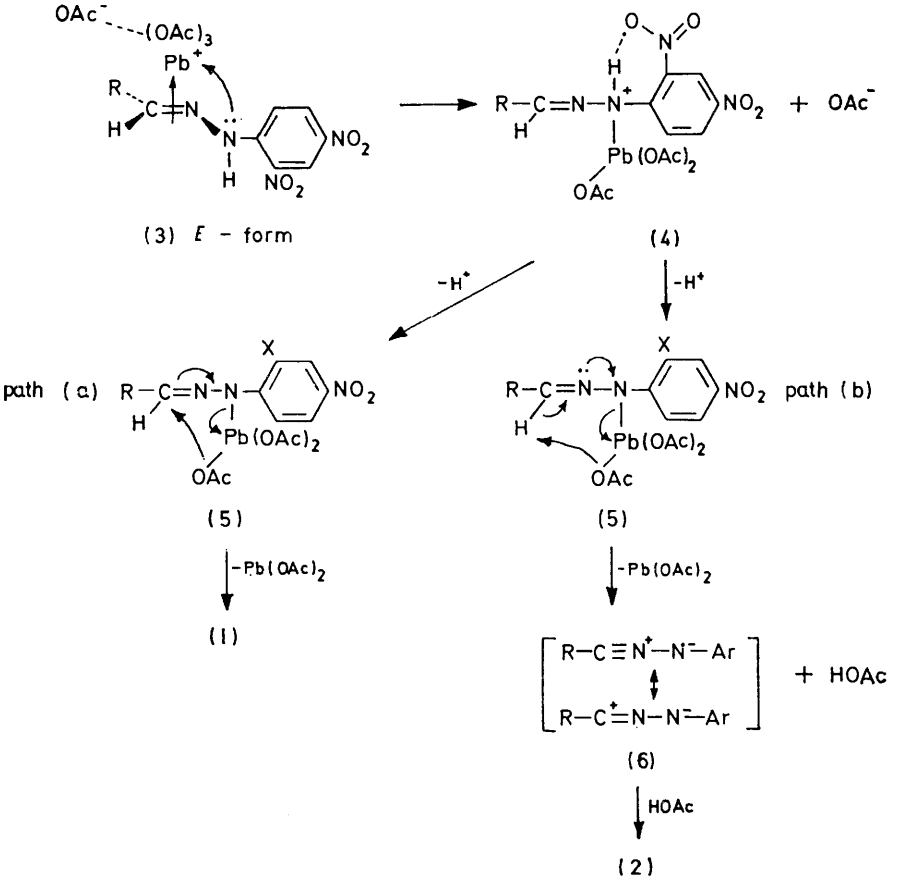
[14] J. B. Aylward, Ph.D. Thesis, National University of Ireland, 1967; J. B. Aylward and F. L. Scott, *J. Chem. Soc.* (*B*), 1969, 1080.

[15] A. F. Hegarty and F. L. Scott, *J. Org. Chem.*, 1967, **32**, 1957.

(a), may also be of importance for compounds containing a 2-NO_2 substituent. On removal of the 2-substituent path (b) becomes dominant and normal reactions are observed (13 and 14 in the Table). Aromatic methine substituents, by stabilising the carbocation end of the incipient nitrilimine, tend to mask the effects of 2-substituents in the *N*-phenyl ring and favour path (b). However, even with aromatic aldehyde derivatives, when the electron-withdrawing NO_2 group is removed from the *N*-phenyl ring and replaced by an electron-donating methyl group (steric requirements similar to that of bromine, E_s 0.0) at the 2-position, azo-acetate formation [path (a)] again becomes significant (Nos. 8 and 19—21).

EXPERIMENTAL

M.p.s were measured with an Electrothermal apparatus. I.r. spectra were measured for KBr discs or mulls with a Perkin-Elmer 377 or 457 spectrophotometer. N.m.r. spectra were measured with a JEOL JNM-MH-100 spectrometer. The nitrophenylhydrazones [16] and 2-bromo-4-nitrophenylhydrazine [14] were prepared by previously reported procedures. The *2-bromo-4-nitrophenylhydrazones* of *acetaldehyde* [m.p. 146—147° (Found: C, 37.25; H, 3.15; N, 16.6. $C_8H_8BrN_3O_2$ requires C, 37.2; H, 3.1; N, 16.3%)], *propionaldehyde* [m.p. 131—133° (Found: C, 39.5; H, 3.55; N, 15.75. $C_9H_{10}BrN_3O_2$ requires C, 39.7; H, 3.7; N, 15.45%)], *cyclohexanecarbaldehyde* [m.p. 148—149° (Found: C, 48.0; H, 5.0; N, 13.25. $C_{13}H_{16}BrN_3O_2$ requires C, 47.85; H, 4.9; N, 12.9%)], and *butyraldehyde* [m.p. 94—96° (Found: C, 42.0; H, 4.2; N, 15.05. $C_{10}H_{12}BrN_3O_2$ requires C, 41.95; H, 4.2; N, 14.7%)] were not reported previously. Benzaldehyde *o*-tolylhydrazone, m.p. 89—90° (lit.,[15] m.p. 96°) (Found: C, 79.5; H, 6.75; N, 12.95. Calc. for $C_{14}H_{14}N_2$: C, 80.0; H, 6.65; N, 13.35%), and *p-chlorobenzaldehyde o-tolylhydrazone*, m.p. 105—106° (Found: C, 68.55; H, 5.45; N, 11.65. $C_{14}H_{13}ClN_2$ requires C, 68.7; H, 5.3; N, 11.45%), were prepared by stirring cold alcoholic solutions of the aldehyde and *o*-tolylhydrazine hydrochloride. Aliphatic aldehyde *o*-tolylhydrazones, none of which have been reported previously, could not be obtained by us. When aliphatic aldehydes were treated with *o*-tolylhydrazine, in neutral, acidic, or basic solution, under either air or nitrogen, reddish brown gums were obtained in each case. When attempts were made to generate such hydrazones and treat them *in situ* with LTA, decompositions were encountered and no traces of products to be expected from LTA–hydrazone reactions were detected. Attempts to arrive at *ortho*-substituted 4-nitrophenylhydrazines by a route involving nitration of *ortho*-substituted anilines, separation of the isomers, diazotisation of the amine, and reduction of the diazonium salt proved unsuccessful owing to combinations of poor yields, difficult separations, and failures at the



SCHEME

[16] A. I. Vogel, 'Practical Organic Chemistry,' Longmans, London, 1962 p. 722.

diazotization stage (see footnote p. 284). Aromatic aldehyde *o*-tolylhydrazones used in the synthetic work did not prove suitable for kinetic studies.

(i) *Kinetic Measurements.*—The rates (k values ± 5%) were measured in acetic acid solution at 25.5 ± 0.5 °C by following the disappearance of the hydrazone u.v. absorption (A) at the wavelengths shown in the Table. Pseudo-unimolecular reaction conditions with a 10—50 fold excess of LTA were employed. For compounds with k (Table) <10 dm^3 mol^{-1} min^{-1}, and also for No. 10 in the Table, first-order rate constants (k_1) were obtained from plots of $\ln(A_t - A_t^{+}{}_{t}')$ against time (t).[17] For the other compounds plots of $\ln(A_t - A_\infty)$ were used. These k_1 values varied linearly with the initial concentration of LTA and the slopes of the lines thus obtained were the second-order rate constants given in the Table. This method has been used previously [3b] for measuring rates of oxidation of ketone phenylhydrazones by LTA. Our results were readily reproduced and the values quoted are the averages of at least three runs. No difficulties were encountered due to LTA absorption or decomposition. LTA in acetic acid showed effectively no absorption at the wavelengths used ($\varepsilon_{max.}$ at 350 nm varied from 0—70 on different runs; ε_λ for the hydrazones was *ca.* 20 000). For the series the infinity absorption values were generally similar and higher than the very weak absorptions due to blank LTA solutions containing the expected excess of LTA at the end of the reaction. Any possible errors due to infinity values with the slow reactions were eliminated by using the Guggenheim method.[17] The nature of the kinetic results and their comparison with other reported data [3b,12] confirm the validity of the method. Our value for acetone DNPH (No. 7, in the Table) compared favourably with the value of (0.51) previously determined [12] by the relatively crude but reliable method of weighing the quantities of lead dioxide formed from unchanged LTA by addition of water at various times. For the compounds reported (Table) there was no interference from product absorptions. However, overlapping absorptions due to gums and products proved to be a major difficulty with aromatic aldehyde derivatives and such compounds were not suitable for study by this method. All the hydrazones studied obeyed the Beer–Lambert law. A Perkin-Elmer 124 double beam u.v. spectrophotometer with constant temperature accessories was used for the measurements. For the 4-nitrophenylhydrazones (Nos. 14 and 15 in the Table), however, the rates were too great to be measured by this procedure. These rates were, therefore, measured by using an Applied Photophysics stopped-flow device. The kinetic data were recorded by using a Tektronix model 5100 storage oscilloscope. The stored traces were photographed and and plots of $\ln(A_t - A_\infty)$ *versus* t were obtained.

Details of the oxidations of the 2-bromo-4-nitrophenylhydrazones and the 2-tolylhydrazones by LTA, including spectra and structural proofs for the products, are available as Supplementary Publication No. SUP 21935 (5 pp.).*

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* For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1975, Index issue.

[17] E. A. Guggenheim, *Phil. Mag.*, 1926, **2**, 538.