Constituent Analysis of the Interaction of Solvents with the Leaving Group Anions for S_N1–$E1$ Reactions. Thermodynamic Evidence for the Nature of the Conjugate Base of *p*-Nitrophenylhydrazonomalononitrile

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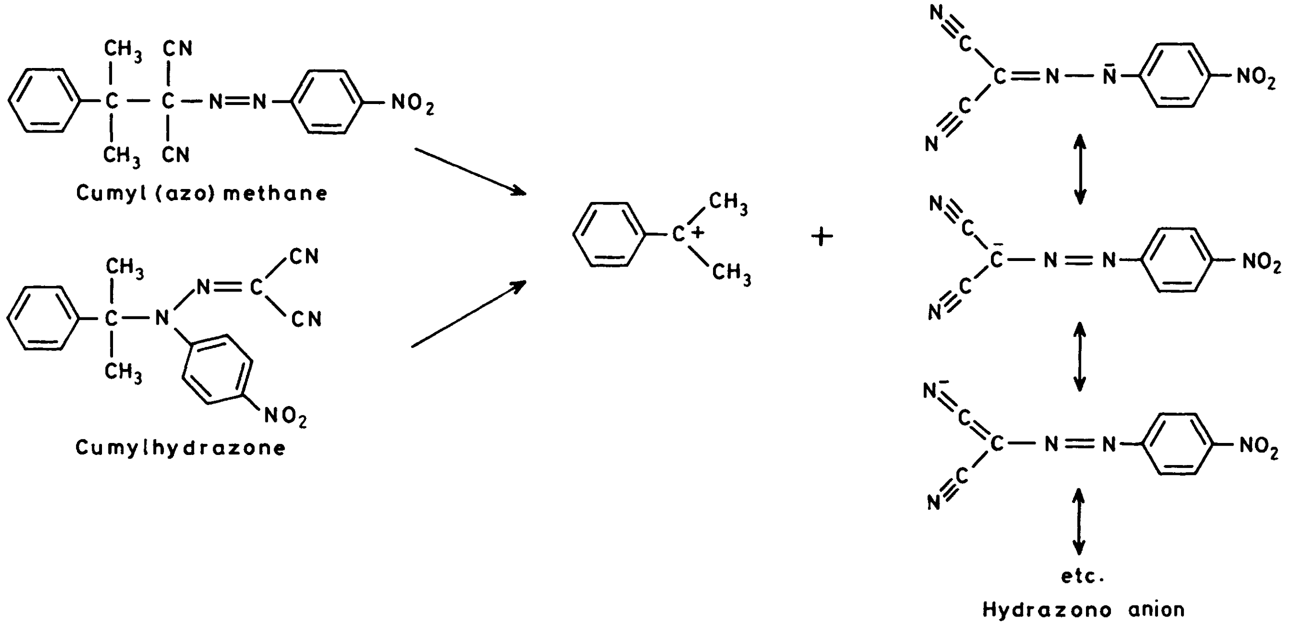
Enthalpies of solution in dimethyl sulphoxide and in methanol for the tetraethylammonium salt of the conjugate base of *p*-nitrophenylhydrazonomalononitrile were measured and compared with those of tetraethylammonium chloride. The former salt is more stable in the strongly dipolar aprotic solvent dimethyl sulphoxide than in the protic solvent methanol, whereas the latter is more stable in methanol because of hydrogen bonding of the solvent with chloride ion. Single ion enthalpies of transfer were determined in acetonitrile–methanol mixtures for the hydrazono anion as well as for tosylate ion and were dissected into constituent terms; a 'more physical' and a 'specific' interaction, solvation being due to hydrogen bonding. The hydrazono anion resembles $BBu^n{}_4{}^-$ and $ClO_4{}^-$ in that the contribution from the latter term is negligible. On the other hand, tosylate ion is susceptible to hydrogen bonding as is halide ion. The result is consistent with the kinetic behaviour of the leaving group anions for S_N1–$E1$ reactions.

S_N1–$E1$ Reactions of uncharged substrates are greatly influenced by the nature of the solvent.[1,2] Halides and sulphonates are generally used for kinetic studies, and substrates of both kinds possess reliable scales of 'solvent ionizing power' for a large number of protic and aprotic solvents. These scales are based on the rate of heterolytic decomposition of t-butyl chloride,[3–5] and *p*-methoxyneophyl tosylate,[6] respectively, and give a good correlation with each other.

Heterolytic cleavage of these substrates proceeds much more rapidly in the protic solvent methanol than in the dipolar aprotic solvent dimethyl sulphoxide (DMSO), though the dielectric constant and dipole moment of methanol (ε 32.6, μ 1.69) are smaller than those of DMSO (ε 48.9, μ 4.3) and furthermore it is well known that cation-solvating ability is much greater in DMSO than in methanol. The factor determining this order of solvent ionizing power is stabilization due to hydrogen bonding of methanol with leaving group anions, so that the solvent effect demonstrated through free energy changes should be expressed at least in the form of a linear combination of two factors, the hydrogen bonding interaction and others. Charge dispersal of ionic species reduces contributions of both factors; the strength of hydrogen bonding is extremely sensitive to negative charge dispersal.[7,8] If the extent of negative charge dispersal overwhelms that of positive charge dispersal, the order of 'solvent ionizing power' would be inverted between methanol and DMSO.



Scheme.

Table 1. Enthalpy of solution in DMSO and in MeOH at 25 °C (kJ mol^{-1})

	Cumyl(azo)methane	Cumylhydrazone	$Et_4N^+(NC)_2C{=}N{-}\bar{N}{-}C_6H_4NO_2\text{-}p$	$Et_4N^+Cl^-$
DMSO	26.1	23.1	31.25	11.8
MeOH	27.4	28.95	37.7	3.90[a]

[a] Ref. 8.

Table 2. Enthalpy of solution in acetonitrile–methanol at 25 °C (kJ mol^{-1})

x_{MeOH}	$Et_4N^+(NC)_2C{=}N{-}\bar{N}{-}C_6H_4NO_2\text{-}p$	$Me_4N^+TsO^-$
0	28.4	20.5
0.10	27.7	9.35
0.25	27.9	7.95
0.50	29.9	10.6
0.75	32.7	14.9
0.90	34.8	
1.0	37.7	22.95

x_{MeOH} = mole fraction of methanol.

Recently some arylazomalononitrile derivatives were found to undergo facile carbon–carbon bond heterolysis.[9,10] The first example of a reaction showing the inverted order of 'solvent ionizing power' was shown by this kind of compound. (*p*-Nitrophenyl)azo-t-cumylmalononitrile [termed here cumyl(azo)methane] was able to serve as a substrate to generate t-cumyl cation, a typical carbocation in S_N1–$E1$ reactions, and kinetic studies revealed that the reaction proceeds much more rapidly in DMSO than in methanol, contrary to the decomposition of t-cumyl chloride.[11] The leaving group anion is the conjugate base of *p*-nitrophenylhydrazonomalononitrile (termed here hydrazono anion), and is expected from its resonance forms to behave as an extensively charge-delocalized anion. *N*-(t-Cumyl)(*p*-nitrophenyl)hydrazonomalononitrile (termed here cumylhydrazone) undergoes carbon–nitrogen bond heterolysis to give the same ions as the isomer, cumyl(azo)methane, and exhibits a similar trend of 'solvent ionizing power'.

It is therefore quite intriguing to examine the thermodynamic behaviour of hydrazono anion in solution through enthalpy of solution measurements. We first discuss the interaction of the above two solvents with hydrazono anion as a leaving group anion on the basis of enthalpies of solution of cumyl(azo)methane, cumylhydrazone, and the tetraethylammonium salt of hydrazono anion together with kinetic data previously reported,[11] and then analyse the single ion enthalpy of transfer in acetonitrile–methanol for hydrazono anion as well as for tosylate ion by means of the recently developed dissection method to compare with the results previously obtained for other anions.[7,8]

Experimental

Materials.—Tetramethylammonium tosylate was obtained as follows. A methanol solution of tetramethylammonium hydroxide was prepared under effective stirring by mixing a freshly precipitated silver oxide (1.2 equiv.) with finely granulated tetramethylammonium iodide (1.0 equiv.) in methanol. After insoluble components were removed by filtration, the solution was carefully neutralized with toluene-*p*-sulphonic acid, and then the mixture was evaporated to dryness. The residue was dissolved in acetonitrile and the resulting solution was dehydrated with calcium hydride. Evaporation of the solvent gave *tetramethylammonium tosylate* which was recrystallized three times from acetonitrile to give crystals (Found: C, 53.7; H, 7.8; N, 5.65; S, 13.1. $C_{11}H_{19}NO_3S$ requires C, 53.85; H, 7.8; N, 5.7; S, 13.1%).

Cumyl(azo)methane and cumylhydrazone were prepared as reported previously.[11] The preparation of the hydrazono anion Et_4N^+ salt will be reported elsewhere.[12] DMSO was distilled twice under reduced pressure after storage over calcium hydride overnight. Other materials were prepared and purified as described previously.[7,8]

Heat of Solution Measurements.—Heat of solution was measured with Tokyo Riko twin isoperibol calorimeter (TIC-2D) at 25.0 ± 0.05 °C. The final ranges of concentration are 0.5—1.0 × 10^{-2} mol dm^{-3}. Experimental errors were estimated to be ±2% from duplicate or triplicate runs.[7,8]

Results

Enthalpies of solution in DMSO and in methanol for uncharged substrates, cumyl(azo)methane, and cumylhydrazone, as well as for the tetraethylammonium salts of hydrazono anion and chloride ion are given in Table 1. Enthalpies of solution in acetonitrile–methanol for the tetraethylammonium salt of hydrazono anion and tetramethylammonium tosylate are summarized in Table 2.

Discussion

As already mentioned, one of the most remarkable features of the heterolytic decomposition of cumyl(azo)methane as well as for cumylhydrazone is that the reaction proceeds faster in the dipolar aprotic solvent DMSO than in the protic solvent methanol, in contrast to the case of t-cumyl chloride; the relative ease of heterolytic cleavage is completely inverted on going from cumyl(azo)methane to t-cumyl chloride [k_{DMSO}/k_{MeOH} is 12.1 for cumyl(azo)methane and 1.12 × 10^{-2} for t-cumyl chloride, see Table 3].[11]

Since transfer enthalpies for cumyl(azo)methane and cumylhydrazone are available together with the relevant activation enthalpies (Tables 1 and 3), the transfer enthalpy for the activated complex can be derived through the thermodynamic cycle [equation (1) where AC and S denote activated complex and substrate, respectively].

$$\Delta H^{\ddagger}_{\mathrm{MeOH}} - \Delta H^{\ddagger}_{\mathrm{DMSO}} = \Delta H_t^{\mathrm{DMSO \rightarrow MeOH}}(\mathrm{AC}) - \Delta H_t^{\mathrm{DMSO \rightarrow MeOH}}(\mathrm{S}) \quad (1)$$

The thermodynamic behaviour of the hydrazono anion Et_4N^+ salt in solution is assumed to simulate the solvation pattern of the activated complex for the heterolytic reaction to generate the same hydrazono anion, if the transition state is located far along the reaction co-ordinate as has been inferred for the heterolysis of t-butyl chloride.[13,14] The endothermicity observed for the three transfer enthalpies, $\Delta H_t^{\mathrm{DMSO \rightarrow MeOH}}$ for the hydrazono anion salt (6.45 kJ mol^{-1}), and for the activated complexes from cumyl(azo)methane (13.4 kJ mol^{-1}) and from cumylhydrazone (8.75 kJ mol^{-1}) strongly supports the internal consistency of the series of measurements as well as the validity of the above assumption.

Table 3. Rate constants and activation enthalpies (at 31 °C)

	Cumyl(azo)methane			Cumylhydrazone			t-Cumyl chloride
	$10^5 k$ / s^{-1}	$\Delta H^{\ddagger}$ / kJ mol^{-1}	$\Delta H_t^{DMSO\rightarrow MeOH}$ (AC) / kJ mol^{-1}	$10^5 k$ / s^{-1}	$\Delta H^{\ddagger}$ / kJ mol^{-1}	$\Delta H_t^{DMSO\rightarrow MeOH}$ (AC) / kJ mol^{-1}	$10^5 k$ / s^{-1}
DMSO	32.3[a]	90.0[a]	0	8.66[b]	107.1[a]	0	8.30[c]
MeOH	2.67[a]	102.1[a]	13.4	2.53[b]	110.0[a]	8.75	742[d]

[a] Value determined in deuteriated solvents.[11] [b] Value determined in deuteriated solvents at 60.0 °C.[11] [c] Ref. 22. [d] Ref. 23.

Table 4. Single ion enthalpy of transfer in acetonitrile–methanol, $\Delta H_t^{AN\rightarrow MeOH}(X^-)$

x_{MeOH}	$(NC)_2C{=}N{-}\bar{N}{-}C_6H_4NO_2$-*p*	TsO^-	Cl^- [a]
0	0	0	0
0.10	−0.28	−10.25	−17.2
0.25	0.43	−11.25	−16.6
0.50	1.87	−9.55	−12.8
0.75	4.55	−5.9	−8.5
0.90	6.7		−4.85
1.0	8.3	−0.25	−2.5

[a] Ref. 8.

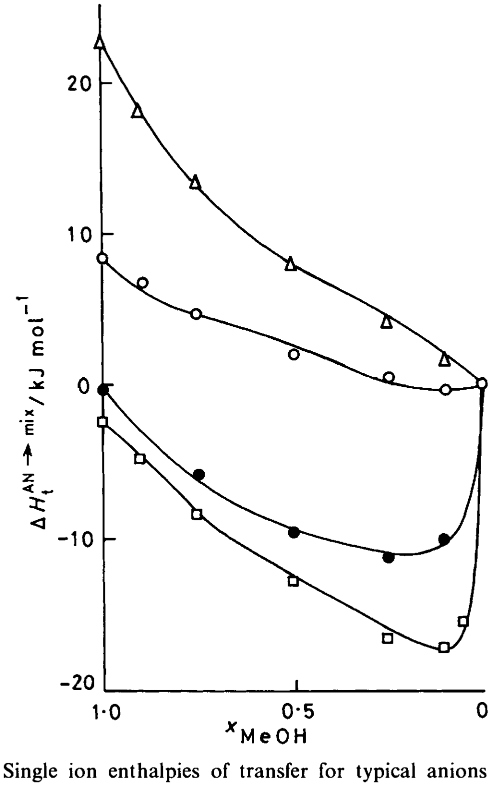


Figure. Single ion enthalpies of transfer for typical anions in AN–MeOH mixtures: △, ○, ●, □, experimental values for ClO_4^-, hydrazono anion, TsO^-, and Cl^-, respectively; ——, calculated values with use of the parameters in Table 5; for ClO_4^- and Cl^- ions, details are given in refs. 7 and 8; for hydrazono anion, these were calculated according to equation (4) with use of the value, $\Delta H_t^{AN\rightarrow mix}(BBu^n_4{}^-)$ given in ref. 7; for TsO^-, these were calculated according to equations (2) and (3)

On the other hand, the fact that the heterolysis of t-cumyl chloride is faster in methanol than in DMSO, points to more favourable solvation of the activated complex in methanol than in DMSO and consequently is consistent with the observed exothermicity of the transfer enthalpy for tetraethylammonium chloride, *i.e.*, $\Delta H_t^{DMSO\rightarrow MeOH}(Et_4N^+Cl^-) = 3.9 - 11.8 = -7.9$ kJ mol^{-1}. The endothermicity of $\Delta H_t^{DMSO\rightarrow MeOH}$ for the hydrazono anion system is reasonably assumed to imply more favourable anion solvation in the strongly dipolar aprotic solvent DMSO as well as the absence of hydrogen bonds in hydrazono anion, whereas the exothermicity of $\Delta H_t^{DMSO\rightarrow MeOH}$ for the chloride ion system would largely be attributed to the fact that chloride ion can form hydrogen bonds.

The single ion enthalpy treatment excluding the cationic species would provide more exact and detailed information on anion solvation. Based on the $Bu^n_4N^+$–$BBu^n_4{}^-$ assumption,[7,8] single ion enthalpies of transfer have been calculated for hydrazono anion and tosylate ion in acetonitrile–methanol and are compared with those for chloride ion in Table 4. The Figure shows the transfer enthalpy *versus* solvent composition profiles for these anions together with that for perchlorate ion obtained previously.[7] Evidently, anions are classified into two groups; one exhibits a steady change in transfer enthalpy, $\Delta H_t^{AN\rightarrow mix}$ with solvent composition, which implies the lack of 'specific' interaction, the solvation due to hydrogen bonding with protic solvents, *e.g.*, hydrazono anion and ClO_4^-, and the other gives a minimum in the transfer enthalpy profile at low content of methanol and seems to be stabilized through hydrogen bonding, *e.g.*, Cl^- and TsO^-. Consequently this classification is in exact harmony with that of leaving group anions or that of thermal unimolecular reactions proposed previously;[11,15] one is 'hydrogen-bond-susceptible' and the other 'hydrogen-bond–nonsusceptible', this classification being based on the relative rate of reactions in DMSO and in methanol.

As successfully achieved for halide ions,[7,8] the observation of a minimum in the transfer enthalpy profile for tosylate ion enables us to dissect the transfer enthalpy into two constituent terms, 'more physical' and 'specific'. Here, the term specific refers to an interaction allowed only for protic solvents and thus corresponds to the solvation due to hydrogen bonding. The transfer enthalpy could be reproduced with the maximum deviation of ±0.4 kJ mol^{-1} by the set of equations applied to the dissection of the transfer enthalpy for halide ions, except for a slight modification. The composition dependence of a specific interaction enthalpy could be better reproduced by replacing the activity in the original formula by the mole fraction, as expressed by equations (2) and (3), where K_{se} stands for the

$$\Delta H_t^{AN\rightarrow MeOH} = \Delta H_{t,PHYS}^{AN\rightarrow MeOH} + \Delta H_{t,SI}^{AN\rightarrow MeOH} \qquad (2)$$

$$\Delta H_t^{AN\rightarrow mix} = \Delta H_{t,PHYS}^{AN\rightarrow MeOH} x_{MeOH} (1 - 1.23 x_{MeOH} x_{AN}) + \Delta H_{t,SI}^{AN\rightarrow MeOH} K_{se} x_{MeOH}/(x_{AN} + K_{se} x_{MeOH}) \qquad (3)$$

equilibrium constant for the solvent exchange process at the solvation site around the solute.[7,8] The parameters derived are 14.75 and −15.0 kJ mol^{-1} for $\Delta H_{t,PHYS}^{AN\rightarrow MeOH}$ and $\Delta H_{t,SI}^{AN\rightarrow MeOH}$, respectively, and 32.0 for K_{se} (see Figure).

With hydrazono anion, the relative value of the transfer enthalpy defined by the middle term in equation (4), according to the arguments described previously,[16] gives an almost straight line when plotted against solvent composition and can be expressed quantitatively by the right-hand side of equation (4) (see Figure). Such a curvilinear correlation has commonly

Table 5. Constituent terms of $\Delta H_t^{AN\rightarrow MeOH}$ (X^-) (kJ mol^{-1})

	$BBu^n{}_4{}^{-a}$	$(NC)_2C{=}N{-}\bar{N}{-}C_6H_4NO_2$-*p*	$ClO_4{}^{-a}$	TsO^-	I^{-a}	Br^{-a}	Cl^{-b}
$\Delta H_{t,PHYS}^{AN\rightarrow MeOH}$	−5.0	8.3	22.6	14.75	23.7	25.7	28.5
$\Delta H_{t,SI}^{AN\rightarrow MeOH}$	0	0	0	−15.0	−10.0	−20.0	−31.0

^{a} Ref. 7. ^{b} Ref. 8.

$$\delta_R\Delta H_t^{AN\rightarrow mix}\text{ (hydrazono anion)} \equiv \Delta H_t^{AN\rightarrow mix}\text{ (hydrazono anion)} - \Delta H_t^{AN\rightarrow mix}\,(BBu^n{}_4{}^-) = 13.3\,x_{MeOH} - 3.0\,x_{MeOH}x_{AN}\text{ (in kJ mol}^{-1}) \quad (4)$$

been observed for quaternary ammonium cations,[16] suggesting that the transfer enthalpy for hydrazono anion is affected mainly by the 'more physical' but not by the 'specific' interaction.

Recently, Arnett and his co-workers have reported that logarithmic equilibrium constants of the heterolytic dissociation of carbon–carbon bonds in trisubstituted cyclopropenyl-(*p*-nitrophenyl)malononitriles are inversely proportional to the dielectric constants of aprotic solvents.[17,18] This type of solvent effect, known as the Born type, could have been anticipated for reactions affected by the 'more physical' solvation, which naturally involves electrostatic and ion–dipole interactions. The present analysis for the solvation on charge delocalized anion supports this view. However, this does not exclude loose charge-transfer-type interactions, since the electron-donating or -accepting ability of solvents is apparently prone to correlate with dielectric constants or dipole moments.

Constituent terms of the transfer enthalpy for anions so far determined are compared in Table 5. 'More physical' solvation seems to be more favoured in acetonitrile than in methanol, since the transfer enthalpies, $\Delta H_{t,PHYS}^{AN\rightarrow MeOH}$ are positive for all anions, except for tetra-n-butylborate ion in which the central charge is shielded from solvent molecules by four alkyl groups sufficiently to prevent the solvation requiring some orientation of solvent molecules. The increasing endothermicity in $\Delta H_{t,PHYS}^{AN\rightarrow MeOH}$ with decreasing ionic radii, as observed for anion and quaternary ammonium ion transfers,[7,8,16] supports the view that the leading term in $\Delta H_{t,PHYS}^{AN\rightarrow MeOH}$ is an ion–dipole interaction. However, acetonitrile has the ability to stabilize anions presumably through charge-transfer-type interactions, as already suggested.[11] The large positive values of the transfer enthalpy for halide and tosylate ions may therefore reflect the electrophilic character of acetonitrile.

It is noteworthy that hydrazono anion exhibits the smallest transfer enthalpy next to that for tetra-n-butylborate ion. The result indicates that the extensive charge delocalization over the large planar molecular skeleton of hydrazono anion* not only excludes solvation due to hydrogen bonding but also reduces any other modes of solvation such as represented by the 'more physical' term. It is therefore quite reasonable that some derivatives of phenylhydrazonomalononitrile, *e.g.*, FCCP (*p*-CF_3O) and CCCP (*m*-Cl), serve as efficient uncouplers of oxidative phosphorylation in mitochondrial systems, since the anions arising from these hydrazones are expected from the above considerations to pass through the biochemical boundaries without a significant change in solvation.[19–21]

As described in the Introduction, the hydrogen-bond-susceptible nature of tosylate ion as a leaving group anion has been confirmed through kinetic analysis.[6] The significant $\Delta H_{t,SI}^{AN\rightarrow MeOH}$ values observed for tosylate ion provides thermodynamic evidence for this view.

Recently, Bentley *et al.* made a very sophisticated analysis on *m* Y_X correlations using adamantyl halides and tosylate as substrates, and invoked electrostatic and electrophilic solvation effects as the major factors of solvent effects on the rates of heterolytic decomposition for these substrates.[24,25] The decreasing trend in the slope in these correlations, Y_{Cl} (1.0) > Y_{Br} (0.96) > Y_I (0.85) > Y_{OClO_3} (0.82) > Y_{OTs} (0.80), which has been ascribed to the delocalization of anionic charge in a leaving group,[24,25] has analogy with the decreasing trend in the quantity, $\Delta H_{t,PHYS}^{AN\rightarrow MeOH}$ along the same sequence (see Table 5). The order of susceptibility to electrophilic solvation effects, OTs > Cl > Br > I,[24,25] has a conceptual as well as a thermodynamic analogy in the quantity $-\Delta H_{t,SI}^{AN\rightarrow MeOH}$, except for the slight modification introduced for the position of OTs in the series, *i.e.*, the latter quantity decreases along the sequence Cl^- > Br^- > OTs^- > I^- (see Table 5). Quite recently, very detailed analyses have been performed for the solvent effects on the heterolysis rates of adamantyl substrates, using α, β, π*, and δ_H scales.[26] The coefficients *a* which have been invoked as a measure of the effect of solvent electrophilic assistance, are likely to follow the latter sequence.[26]

The physical organic notions which have been derived for t-cumyl systems as well as for adamantyl systems on the basis of empirical and kinetic procedures, *i.e.*, hydrogen-bond-susceptible and -nonsusceptible natures, electrostatic and electrophilic solvation effects, have been obtained from thermodynamic evidence through the dissection of the transfer enthalpy into the constituent terms, 'more physical' and 'specific'. The level of sophistication would be enhanced efficiently through the co-operation of various procedures with mutually independent experimental as well as theoretical foundations.

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* The planar structure of hydrazono anion has been confirmed by *X*-ray analysis of the Et_4N^+ salt.[12]

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