Heavy Atom Kinetic Isotope Effects in HCN Elimination from Some Tricyanides in Methanol [1]

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Tricyanides, Heavy Atom Kinetic Isotope Effects

Rates of HCN elimination from polycyanides N,N-dimethyl-4-(1,2,2-tricyanooethyl)-
aniline (1), 9-cyano-9-dicyanomethyl fluorene (2), 1,1-diphenyl-1,2,2-tricyanoethane (3),
and 2-phenyl-1,1,2-tricyanopropane (4) have been studied in methanol. Elimination from 1
occurs via (E1cB) mechanism. On the other hand olefin formation from 2-4 has been
shown to occur via (E1b) anion pathway. Heavy atom kinetic isotope effects indicated that
product stability is not the sole factor controlling the transition state geometries. Values
of k12/k14 were found to be in the order 2 > 3 > 4 > 1 which implied transition states with
more carbanion-like structure in the opposite direction. Solvent isotope effects and
enthalpies of activation were also determined and discussed in terms of transition states
geometries.

Introduction

In general β-elimination reactions involve the removal of HX molecule from two adjacent atoms
with the development of a multiple bond. This process could be catalyzed either by acids or
bases [2]. Our main concern is to investigate the elimination reactions leading to olefin formation in
neutral media e.g., methanol, viz.,

\[
\begin{array}{c}
\text{R}^1 \text{C} = \text{C} - \text{X} \\
\text{R}^2 \\
\text{R}^3 \\
\text{R}^4 \\
+ \text{B} \\
\end{array}
\]

\[
\begin{array}{c}
\text{R}^1 \\
\text{C} = \text{C} - \text{R}^3 \\
\text{R}^2 \\
\text{R}^4 \\
+ \text{BH}^+ \\
\text{X}^- \\
\end{array}
\]

\[\text{(B = Base)}\]

Ingold was the first to realize that three mecha-
nistic classes are possible, E1cB, E2 and E1 path-
ways [3]. The E2 mechanism is one where cleavage
of Cβ-H and Cα-X occur simultaneously; with the
development of sp² bonding between Cβ-Cα and
formation of H-·B bonding. On the other hand,
E1cB and E1 mechanisms necessitate the rupture
of the Cβ-H and Cα-X bonds respectively prior to
the development of unsaturation i.e., a step wise
fashion [3]. However, Ingold et al., have recognized
that in an E2 transition state, different degrees of
bond rupture and formation are possible [4]. Thus,

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reaction coordinate. Thus, the net effect of a substituent on a transition state (with a negative force constant) is obviously opposite to that on the stable reactant molecules (with a positive force constant). Applying this principle to elimination reactions, Steffa and Thornton adopted a new technique, namely; measuring $k_{OH}/k_{OH}$ for elimination from some 'onium compounds [10]. The data obtained from these measurements coupled with the previous knowledge of primary kinetic isotope effects allowed the deduction of transition state structures with reasonable success [10].

Cockerill’s studies of isotope effects on elimination from 2-arylethylmethylisulphonium bromides when reacted with sodium hydroxide in water with different proportions of added dimethyl sulfoxide [11] were found to support Thornton’s rule [9]. Nonetheless, numerous workers [12] did not agree with Thornton’s speculations, mainly due to the disregard of the symmetrical vibrational, i.e., perpendicular effect to the reaction coordinate [9]. Recently, Thornton revised his theory [13], taking into account the substituent perpendicular effect, by using the More O’Ferrall diagrams [14]. To make things worse, Bell [15] and Blackwell et al. [16] argued persuasively for the contribution of tunneling effects in the proton transfer step of elimination reactions. The magnitude of tunneling decreases with larger values of $k_{H}/k_{D}$ obtained for elimination from some 4-substituted phynylethyl chlorides in $t$-BuOH/$t$-BuOK [16].

In order to shed more light on this ever increasingingly controversial subject, a study of heavy atom kinetic isotope effects of $H^{14}CN$ elimination from some tricyano compounds in neutral media were carried out where;

$$X = R^1 = R^2 = NC^-; \text{ and } R^2 = H,$$

$$R^4 = 4-(CH_2)_3N-C_6H_{14}, N,N\text{-dimethyl}-4-(1,2,2-$$

$$\text{tricyanoethyl})\text{-aniline (1)};$$

$$R^2 + R^4 = \text{fluorenyl group, 9-cyano-9-dicyano-}$$

$$\text{methyl fluorene (2);}$$

$$R^3 = R^4 = C_6H_{15}, 1,1\text{-diphenyl-1,2,2-}$$

$$\text{tricyanoethane (3); and}$$

$$R^2 = CH_2, \text{ and } R^4 = C_6H_{13}, 2\text{-phenyl-1,1,2-}$$

$$\text{tricyanopropane (4).}$$

The advantages of this system are:

a) It is a straight forward E1 cB reaction due to the high acidity of $C_5\text{--H}$ proton and the very slow ejection of the poor leaving cyano group. Thus, ambiguities in explaining low values of primary kinetic isotope effects, $k_{H}/k_{D}$, are eliminated. According to Westheimer [13, 18, 19] a low $k_{H}/k_{D}$ may indicate either a more or less than half transfer of $C_5$ proton to the base. This necessitates additional knowledge of other parameters such as $q$ values [19] or solvent isotope effects [10], to reveal the extent of proton transfer.

b) The facile preparation of the radioactive label and deuterated analogues of 1-4.

**Experimental**

**Materials**

Tricyano compounds used in this study have been prepared according to the standard method i.e., in two steps:

a) Condensation of the given aldehyde or ketone with malonitrile to give the 2,2-dicyanoethylene derivatives.

b) The addition of sodium cyanide to the dicyanoolefin followed by acidification to yield the corresponding tricyano compound.

For compounds 1, 2 and 3 m.p. were 138–139 °C, 152–153 °C and 134–135 °C (Lit. [20] 138–139 °C, Lit. [21] 151.5–153 °C and Lit. [22] 135 °C respectively). Compound 3 was crystallized from toluene-cyclohexane, 50% mixture, and had m.p. 153–155 °C.

$C_{17}H_{11}N_3$

- **Found** C 79.25 H 4.34 N 16.31,
- **Calcd** C 79.36 H 4.31 N 16.33.

The $C_5^{14}CN$ materials ($1^{14}C)\text{--}(4^{14}C)$, were prepared similarly, using $K^{14}CN$. The $C_5^{14}D$ analogues, ($1^{14}D)\text{--}(4^{14}D)$, were prepared by rapid crystallization of the protiated substrates 1–4 from methan-[2H$_j$]-ol. NMR showed deuterium incorporation at $C_5 > 95\%$.

**Solvents**

Fisher spectro grade methanol and methan-[2H$_j$]-ol (Merck, Sharp and Dohme) were doubly distilled after purification according to method described by Vogel [23a]. Methanol prepared according to this procedure showed less than $10^{-6}$ basic or acidic impurities as measured by conductivity and potentiometric titration (c.f. methanol prepared according to Ritchie [23b]). However, different batches of methanol purified by either procedures gave 10–15% changes in specific rate coefficients. A large preparation was used for all compounds. All other reagents/solvents were purified commercial products. The water used was conductivity water.

**Quantitative estimation of products under kinetic conditions**

Compound 1 (0.2 g; ~0.009 mole) was dissolved in methanol (100 ml) and kept at 30 °C for four days.
On cooling, deep orange crystals had precipitated and were collected by filtration. The precipitates had an m.p. identical to that of 4-dimethyl-aminobenzal-malonitrile. The yield obtained from several experiments was 36-40\%. The filtrate was freeze-dried, and the residue was shown to be the starting material \(1\) plus a trace of the ethylene. The same procedure was applied to compounds 2-4, the corresponding ethylene was isolated almost quantitatively with 95-98\% yield after 10-15 days storage in methanol at 30 °C.

**Kinetic procedures**

Solutions of 1-4 in dry methanol (10\(^{-4}\) mol \(1^{-1}\)) were prepared daily. Samples of these solutions were transferred at recorded time intervals to 5 mm silica housing of a Beckman DB spectrophotometer. Absorbance readings were taken at the \(\lambda_{\text{max}}\) of the product, see Table I. The reactions of 1-4 or (1-D)-(4-D) in methanol-\(2\text{H}_2\)-ol or methanol were similarly studied. Care was taken to minimize solvent evaporation. Rate coefficients, enthalpies of activation and isotope effects are assembled in Table I. Rates under nitrogen atmosphere were similar to those carried out under air within experimental uncertainty. Error in specific rate coefficients is in the range of ±1%.

For \(^{14}\text{C}\)-isotope effect measurements, simultaneous optical absorption experiments were performed on the solution to determine the precentage of the reaction at any given time. Four ml aliquots of \(10^{-4}\text{mol}/l^{-1}\) solution of the labeled reactant in methanol were transferred to a scintillation vial containing 0.5 ml methanolic hydrogen chloride (2 g HCl gas in 100 ml methanol) and the reaction was terminated. The hydrogen cyanide and the solvent containing HCl were removed by freeze-drying. Five ml of dry methanol and 10 ml of toluene solution of 2,5-diphenyloxazole (0.5\% W/W) was added to the residue. The radioactivity of the unreacted starting material was counted using a Beckman LS-133 liquid scintillator. Blank experiments using K\(^{14}\text{CN}\) showed that hydrogen cyanide removal was >95\% by this technique. Measurements of \(^{14}\text{C}\)-isotope effects were made in the range of 0-20\% reaction to minimize any complications which may arise from the addition of hydrogen cyanide to the product ethylene at higher percentage reaction. The kinetic isotope effect was calculated from the equation [24],

\[
k_{12}/k_{14} = 1 + \log (N/No)/\log (1-f)
\]

where: \(N\) is the radioactivity of the recovered unreacted substrate,

\(No\) is the initial radioactivity, and

\(f\) is the fraction of the material reacted.

Reproducibility of \(^{14}\text{C}\)-isotope effects of the four studied tricyanides (1)-(4) was excellent.

**Results and Discussion**

**Deductions from Kinetic behaviour**

**Elimination from tricyano compounds (2)-(4):** Hydrogen cyanide elimination from these compounds proceeded almost quantitatively to give the corresponding olefin in methanol and followed zero-order kinetics up to 70\% product formation. From this point deviation towards higher order kinetics was observed. Zero-order specific rate constants \(k_n\) were determined from plots of product concentration, \([C]\), against time, \(t\), Fig. 1. This situation is similar to hydrogen cyanide elimination from other

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<td>(k_{1}^{\text{H}})</td>
<td>61.9</td>
<td>97.7</td>
<td>140</td>
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<tr>
<td>(k_{1}^{\text{D}})</td>
<td>32.5</td>
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<td>92.2</td>
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<td>(k_{2}^{\text{D}})</td>
<td>2.8</td>
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<tr>
<td>(k_{1}^{\text{H}}/k_{1}^{\text{D}})</td>
<td>1.04 ± 0.01</td>
<td></td>
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<tr>
<td>(E/k_{JM}^{-1})</td>
<td>59 ± 4</td>
<td>125 ± 9</td>
<td>109 ± 6</td>
</tr>
<tr>
<td>(\Delta S)</td>
<td>33.6</td>
<td>16</td>
<td>3.5</td>
</tr>
<tr>
<td>(\lambda_{\text{max}})</td>
<td>431</td>
<td>346</td>
<td>318</td>
</tr>
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\(^{a}\) Values of first-order rate constant \(\times 10^{5} \text{min}^{-1}\), first-order rate coefficient for 2-4 were obtained by devising the corresponding zero-order values by the concentration of the polycyanide. \(k_{1}^{\text{H}}\) for HCN elimination from 1 represents the first term of equation (9).

\(^{b}\) \(k_{1}^{\text{H}}\) is the rate coefficient \(\times 10^{7} \text{mol}^{-1} \text{min}^{-1}\) for CN- addition to the olefinic product i.e., the second term of equation (9). Error in specific rate constants is ±1\%.
Fig. 1. Typical zero-order plots for HCN elimination from 2 in methanol at a) 35 °C, b) 30 °C and c) 25 °C.

Polycyano-compounds carried out in aprotic solvents as chloroform in the presence of nitrogen bases [25a]. The extent of zero-order reaction was directly proportional to the concentration of the nitrogen base used [25a].

Interestingly, reactions of 2 carried out in the presence of increasing concentrations of triethylamine at constant concentrations of triethylamine hydrochloride showed linear plots of log k, against log [Base] with positive slopes. A similar trend was also observed when methoxide ions were used as a base [25b]. Specific rate coefficients increased steadily then reached a plateau with increasing NEt₃: NEt₃HCl ionic strength at a constant pH, which implies a general base-catalysis [25b]. Closely related results were reported earlier by Patai et al. [25c].

One can account for the zero-order kinetic behaviour of the present situation by assuming the formation of a substantial concentration of the conjugate base, viz.,

\[
\text{RCN}^- \xrightarrow{k_2 \text{slow}} \text{RCN} \quad \text{(3)}
\]

\[
dR/dt = k_2 [\text{RCN}^-] \quad \text{(4)}
\]

\[
K_e = k_1/k_2 = [\text{RCN}^-]/[HRCN] \quad \text{(5)}
\]

Substituting [RCN⁻] in equation (4),

\[
dR/dt = k_2 k_1 [\text{HRCN}] [\text{MeOH}] / [\text{MeOH}] [\text{HRCN}] \quad \text{(6)}
\]

Assuming a substantial ionization of the substrate, HRCN, in the solvent methanol (say > 90%) the effective concentration of HRCN would tend to have a very small value and can be neglected. Accordingly, reaction rate would be independent of [HRCN] and equation (6) can be arranged to give:

\[
dR/dt = (k_1 k_2 [\text{MeOH}]) / (k_{-1} [\text{MeOH}_2]) = k_H \quad \text{(7)}
\]

However, departure from zero-order linearity at later stages of the reaction may be due to increased concentration of hydrogen cyanide which shifts the equilibrium to the left resulting in an apparent deviation to higher order within the run. Substantial, i.e., non-steady state formation of carbanion followed by the slow ejection of the leaving cyanogroup can be regarded as (E₃) anion mechanism as denoted by Bordwell [5]. Elimination in methanol-[²H₃]-ol, which is regarded as a stronger base than methanol [26], showed that zero-order reactions of 2-4 or (2-D)-(4-D) could be followed up to 85% reaction. This is in agreement with Rappoport's observations that increasing base concentration would increase the range of zero-order kinetics [25a].

The reasonably high acidity of these substrates, (2)-(4), is manifested in:

a) The spontaneous exchange of C–H as shown by NMR, when a drop of a methan-[²H₃]-ol is added to the solutions of these substrates in CDCl₃. This phenomenon has been taken advantage of in preparing the deuterated analogues by rapid crystallization of the protiated substrates from methan-[²H₃]-ol.

b) Cross-over experiments showed very close solvent kinetic isotope effects, Table I.
c) The high values of $\Delta S$ in Table I, point to a very slow ejection of $C_\beta-CN$, from the substantially formed conjugate base. Thus, Breslow's assumption that hydrogen denterium exchange at $C_\beta$ is not necessarily indicative of elimination via carbanion intermediates [27], does not manifest itself in our study.

Other workers have studied elimination reactions from derivatives of fluorene. Their studies showed that elimination did proceed via carbanion intermediates. Streitwiser et al., studied elimination of hydrogen floride from 9-trifluoromethylfluorene in methanolic sodium methoxide solutions and showed the intermediacy of the delocalized 9-trifluoromethylfluorenyl anion [28]. In this reaction proton loss occurs from the ring and not from the exocyclic carbon atom [28], as it is also the case in elimination of water from 9-fluorenylmethanol [14, 29]. In this latter reaction, the stabilization of the carbanion by delocalization of the charge around the fluorenyl group, led to a reaction via E1cB mechanism in aqueous or methanolic solutions.

Elimination from 1: The results of the reaction of 1 in anhydrous methanol, in which an equilibrium is reached after ca. 40% reaction, are similar to those obtained by Rapoport et al., in their studies on 2-aryl-1,2,2-tricyanopropanes [22], but contrast with our earlier results for tetracyanoethanes [30]. The data imply a substantial ionization of the first step of the reaction. A slight dependance of rate coefficient on base strength is in accord with CN- elimination from carbanion as a rate-determining step. The attainment of an equilibrium also implies that the stability of the olefinic product, the transition state according to Bunnett [5]. This supports this assumption.

The vast difference in the percentage of formation of product between compound 1 and 2-4 encouraged us to examine elimination from other tricyanides. NMR showed that 1,2,2-tricyanoethylphenol, anisol and benzene underwent spontaneous $C_\beta$—H exchange when allowed to react with methan-2$^4$-ol, similar to 1-4. Surprisingly, olefin formation from these tricyanides proceeded up to 20–30% followed by build up of other compounds which were difficult to identify. Thus, results for kinetic comparison, especially $k_1^2/k_1^4$, were not reliable. This difference in product distribution, due to substitution at $C_\beta$, implies that the stability of the olefinic product, the most substituted in our case, would stabilize the transition state according to Bunnett [5]. This stability driving force, is not necessarily the sole factor controlling rates of elimination from these polycyanides, as $k_1^2/k_1^4$ shows that the release of strain on $C_\beta$ in going from 2 to 3 to 4 renders the transition state "looser" in the same direction i.e., transition state becomes more carbanion-like, Fig. 2a.

\[ \frac{d[R]}{dt} = k_2 [RCN^-] \quad \ldots \ldots \ldots \ldots \quad (4) \]
\[ \frac{d[R]}{dt} = k_2 (k_1 [HRCN] + k_2 [R][CN^-])/ \quad (k_1 [MeOH] + k_2) \quad \ldots \ldots \ldots \ldots \quad (8) \]
The observed initial first-order rate coefficient \(([R] \sim 0)\) is thus given by $k_2 k_1/(k_1 [MeOH] + k_2)$ in the absence of any reverse reaction i.e.,
\[ \frac{d[R]}{dt} = k_2^+ [HRCN] + k_2^+ [R][CN^-] \ldots (9) \]

\[ \frac{k^+_H}{k_2} = \frac{k_1}{[MeOH] + k_2} \ldots (10) \]
and
\[ \frac{k^+_R}{k_2} = \frac{k_1}{[MeOH] + k_2} \ldots (11) \]

From a comparison of the extrapolated values of product concentrations with the observed concentrations, the amount of olefin consumed by the addition of cyanide ions to the product can be calculated. Hence, the second term of equation (9) is evaluated, Table I. The estimates of $k_1/k_2$ suggest a much more rapid proton abstraction than cyanide ion loss (allowing $k_2 > k_2$) and thus an E1cB mechanism of the second type. Rapid $\beta$-hydrogen exchange with deuterated solvents supports this assumption.

The vast difference in the percentage of formation of product between compound 1 and 2-4 encouraged us to examine elimination from other tricyanides. NMR showed that 1,2,2-tricyanoethylphenol, anisol and benzene underwent spontaneous $C_\beta$—H exchange when allowed to react with methan-2$^4$-ol, similar to 1-4. Surprisingly, olefin formation from these tricyanides proceeded up to 20–30% followed by build up of other compounds which were difficult to identify. Thus, results for kinetic comparison, especially $k_1^2/k_1^4$, were not reliable. This difference in product distribution, due to substitution at $C_\beta$, implies that the stability of the olefinic product, the most substituted in our case, would stabilize the transition state according to Bunnett [5]. This stability driving force, is not necessarily the sole factor controlling rates of elimination from these polycyanides, as $k_1^2/k_1^4$ shows that the release of strain on $C_\beta$ in going from 2 to 3 to 4 renders the transition state "looser" in the same direction i.e., transition state becomes more carbanion-like.
Deductions from kinetic isotope effects

From the above discussion, one can represent the energy profiles for hydrogen cyanide elimination as shown in Figs. 2a and 2b. As shown in Fig. 2b, the ejection of cyano groups starts from a point very close to the bottom right corner of More O’Ferrall diagram, and take place in the transition state TS2 and not down hill as Thornton proposed for E2 transition states [13]. Consequently, the transition state will be described in this report in terms of carbanion-like or product-like. The rapid transfer of C=S-H to the solvent molecules, TS1, is not expected to exert much effect on the C=S-CN bond rupture, TS2. If there were any of this ‘flow-along effect’ [9, 10, 19] it is expected to be of almost the same magnitude in the four tricyanides provided that the acidity of C=S-H could be assumed to be the same for the tricyanides 1–4 because of the very similar environments. It could be also assumed that different substituents at Cα would not drastically affect the acidity of this hydrogen by induction. That is to say, the k12/k14 leaving group kinetic isotope effect is more or less due to the cleavage of C=S-CN in TS2 from carbanions of 1–4 and the values obtained could be compared without much concern [31].

Heavy atom kinetic isotope effect was found to increase in the direction 2 > 3 > 4 > 1, see Table I, suggesting that the TS2 becomes more carbanion-like in the opposite direction. The possible conclusions drawn from this trend are:

a) The electron repelling group (H3C)2N-C6H4- on Cα of 1 has weakened, thus shortening the Cα-CN bond in the transition state TS2, which is in agreement with Thornton’s rule [9].

b) The stability of the olefinic product, most substituted, which controlled the degree of attainment of elimination is not necessarily the only factor determining the geometry of the transition state.

The product stability expressed by λmax of the olefin on the basis of a maximum overlap between the aliphatic double bond and the aromatic ring pi-bonds leads to a bathochromic shift. One expects the reactivity to be of the order 1 > 2 > 3 > 4 which is exactly opposite to the experimental trend for compounds 2–4. It is most likely that the release of strain in compound 3 compared to 2 via the free rotation of the two phenyl groups about their bonds to Cα compared with the fixed phenyl groups of the fluorenyl ring, had resulted in more “loose TS 2” i.e., it is more carbanion-like. The same applies to 4 relative to 3. The decreased overlap between the incipient bond in TS2 and the pi-bonds of the ring in the direction 2 > 3 > 4 has been reflected on the degree of Cα-CN bond rupture and consequently on k12/k14 in the same direction. Thus, the release of strain resulted in a perpendicular contribution to the transition state geometry represented by the arrow in Fig. 2b, leading to less Cα-CN rupture in TS2 and shifting it to more carbanion-like. These results could be compared to Smith and Bourns finding in elimination from some substituted ‘onium ions’ [12]. The only disagreement with the above argument is the unexpectedly higher energy of rehybridization of 4 relative to 3. This may be due to experimental uncertainties.

The above argument received some support from cross-over experiments in protonated and deuterated methanol, Table I. According to Westheimer [18] and the detailed calculations of More O’Ferrall and Kouba [32], in proton transfer reactions, the primary kinetic isotope effect is at maximum ~7 when the proton in the transition state is half transferred to the base and approaches the value of one for more or less than half transfer to the base. Accordingly, in the present study, it would be safe to assume that the primary kinetic isotope effect approaches the value of one or very close hereto [5, 17, 33]. Thus, the values kH/kD for elimination from compounds 1–4 are primarily due to solvent effects on the slow ejection of the cyano group [17] taking into consideration, the more product-like transition states involving separation of charges are better stabilized in deuterated solvents [34]. Thus, an inverse kinetic isotope effect on the slow release of CN− is expected. Obviously, the decrease in kH/kD in the direction 1 > 4 > 3 > 2, most likely indicates that TS2 is drifting to more product-like in the same direction.

Conclusion

The data of the present study suggest that substituent effect on transition state structure is likely to agree with Thornton’s rule if proton tunneling contribution to the transition state is minimal i.e., elimination from systems with high C=S-H acidity. However, product stability as a factor
determining the reaction pathway can not be ignored. In general when proton tunneling is feasible due to either poor acidity of $C_p$-H or steric factors, an anti-Thornton behaviour prevails. In this context, Thornton's rule should be regarded as a special case.

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