# Nucleophilic substitution of vinylic halogens in 3-halomethacrylonitriles. Some observations on olefin stabilities

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3-Chloro- and 3-bromomethacrylonitrile (*E*- and *Z*-) have been shown to undergo nucleophilic substitution at C-3 with >95% retention of configuration. The configuration of each product has been established by the use of nuclear magnetic resonance spectroscopy. The thermodynamic position of equilibrium for each pair of *E*–*Z* isomers has been determined and the factors which affect this equilibrium are discussed. Some form of *cis* interactions, non-steric in origin, dominates in determining the equilibrium positions.

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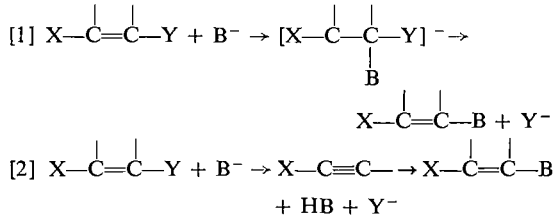
## Introduction

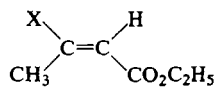
Although nucleophilic reactions in activated ethylenic systems have been studied mechanistically in great detail (1–11), few quantitative measurements of the thermodynamic stability of the various reaction products appear to have been made. In the present work the *E* and *Z* isomers (highest priority groups *cis* for *Z* and *trans* for *E* (12)) of 3-bromo- and 3-chloromethacrylonitrile have been synthesized and their reactions with nucleophiles investigated. Both the mechanism of reaction and the stability of the products have been determined.

As a general rule, simple vinylic halides are unreactive, compared to their saturated counterparts, towards nucleophilic attack. When the carbon atom β to the site of substitution bears an electron-withdrawing group, however, e.g. CN (7), $CO_2C_2H_5$ (4, 6, 10), $COCH_3$ (13–15), $SO_2Ph$ (2, 9), F (16), or *p*-nitrophenyl (1, 17), replacement of the vinylic halogen by nucleophiles readily occurs. This replacement usually follows one of two pathways, although others are possible (8, 10, 18), either "direct substitution", eq. [1] or "elimination-addition", eq. [2]. The former

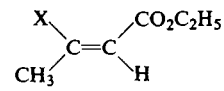


mechanism appears to be the preferred path in the reaction of activated substrates with polarizable, weakly basic nucleophiles (1–11); the latter mechanism is mainly encountered when the nucleophile is an alkoxide ion, particularly when the leaving groups are *trans* orientated (2, 3, 10). Usually direct substitution occurs with retention of configuration although cases are known in which only the thermodynamically stable product has been isolated (2, 5, 7, 17).

Less quantitative information is available on the thermodynamic stability of the various reaction products. It does appear, however, that electronic factors play an important part in determining the relative stability of the *E* and *Z* isomers formed in these reactions. Thus it has been found qualitatively that the β-substituted crotonates (**1**, X = Cl, $N(C_2H_5)_2$, PhS, mesitylthio, $C_2H_5O$) are all more stable in the *E* configuration (4, 10, 19–21), despite the varying steric requirements of the group X. When X is



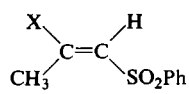
**1** (*E*)



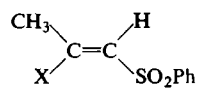
**1** (*Z*)

alkylamino, however, the *Z* isomer is the more stable due to internal hydrogen bonding between the amino proton and the carboethoxy group (20, 22). Methyl crotonate itself exists approximately 82% in the *E* form (*trans*) between 200 and 500° (23).

Similar results have been obtained by Stirling (24) with the corresponding sulfones (**2**). When X = $OCH_3$ or $(PhCH_2)_2N$ the sulfone **2** exists



**2** (*E*)



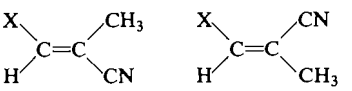
**2** (*Z*)

100% in the *E* form whereas when X = $PhCH_2NH$ approximately 34% of the *Z* form is

present at equilibrium. The reduction in the equilibrium amount of *Z* isomer in the sulfone **2** (X = $PhCH_2NH$) compared with the crotonate **1** (X = RNH) probably reflects a combination of increased steric hindrance and weaker hydrogen bonding in the sulfone.

## Mechanistic Studies

Since the 3-halogenomethacrylonitriles do not possess an α hydrogen, they cannot undergo nucleophilic substitution by a simple elimination–addition process. Our observations, that 3-bromomethacrylonitrile (**3**, *E*- and *Z*-, X = Br) gives substitution with sodium methoxide, sodium thioethoxide, and dimethylamine and that 3-chloromethacrylonitrile (**3**, *E*- and *Z*-, X = Cl) gives substitution with diethylamine, indicate that substitution can in all of these cases take place without the requirement of elimination.

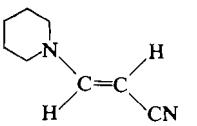


**3** (*E*) **3** (*Z*)

In all cases reaction occurred with greater than 95% retention of configuration at C-3, as determined by vapor phase chromatography (v.p.c.) or nuclear magnetic resonance (n.m.r.) spectral analysis, despite the fact that the product is thermodynamically less stable than its isomer in many cases. Where v.p.c. analysis was employed, it was shown that the respective *E* and *Z* isomers did not interconvert under the conditions used. No products resulting from α elimination were detected (8, 18).

The above results are consistent with the direct substitution (addition–elimination) mechanism, eq. [1], proposed by Miller and Yonan (1) and modified by Jones *et al.* (4), in which the attacking nucleophile is assumed to approach at right angles to the plane of the double bond.

The path requiring the least energy is a 60° rotation to place the halogen parallel to the orbital carrying the electron pair followed by *trans* elimination of halide. This path, eq. [3], requires a minimum of eclipsing (H against CN or $CH_3$) and leads to a product of retained configuration, as observed. It also permits the formation of some product of the opposite configuration as is frequently observed. Scotti and Frazza (7) have proposed a similar mechanism to account for the retention of configuration observed in the reaction of 3-chloroacrylonitrile with ethoxide or *p*-toluene sulfide ion. With piperidine, however, only one product was isolated, starting from either chloronitrile, to which they assigned the *trans* structure (**4**). Furthermore, kinetic evidence was obtained which indicated that both chloronitriles were



**4**

reacting by the same mechanism (addition–elimination). The reason for this lack of stereospecificity is not clear, especially as in the present work both 3-chloro- and 3-bromomethacrylonitrile (*E*- and *Z*-) react stereospecifically with diethylamine and dimethylamine respectively, in spite of the ease of isomerization of the products. Pattenden and Walker (11) have observed a similar lack of stereospecificity in the reactions of trisubstituted phosphines with 3-halogenoacrylic acid derivatives, which they attribute to steric crowding in the the transition state.

In the present work, since the mechanism of reaction is based only on product distribution, it was necessary to assign the correct stereochemistry to each pair of *E*–*Z* isomers. This has been achieved by n.m.r. spectroscopy; in all cases the isomer with the more deshielded olefinic proton has been assigned the *E* configuration (Table 1) in which the olefinic hydrogen and the cyano group are *cis* orientated (25–27). In addition, the configurations of the isomeric chloromethacrylonitriles have already been determined by chemical means (28).

3-Methoxymethacrylonitrile-*E* has been prepared previously by Lichty (29) by treatment of

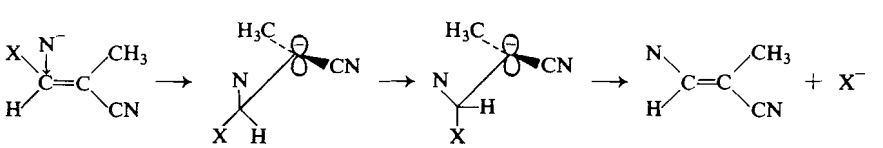
[3] 

TABLE 1

Chemical shifts and coupling constants for the 3-substituted methacrylonitriles (**3**)

| R | *E* isomer* | | | | *Z* isomer* | | | |
|---|---|---|---|---|---|---|---|---|
| | $\tau_R$ | $\tau_{CH_3}$ | $\tau_H$ | *J*(Hz) | $\tau_R$ | $\tau_{CH_3}$ | $\tau_H$ | *J*(Hz) |
| Br | — | 7.99d | 2.84q | 1.5 | — | 7.98d | 3.13q | 1.5 |
| Cl | — | 7.98d | 3.09q | 1.5 | — | 7.96d | 3.31q | 2.0 |
| $CH_3O$ | 6.20s | 8.27d | 3.29q | 1.5 | 6.21s | 8.24d | 3.39q | 1.5 |
| $CH_3CH_2S$ | 8.65t | | | 1.5 | 8.64t | | | |
| | 7.18q | 8.17d | 3.03q | 7.0 | 7.18q | 8.04d | 3.28q | 7.0 |
| $(CH_3)_2N$ | 7.04s | 8.07s | 3.61s | — | 6.98s | 8.21s | 3.77s | — |
| $(CH_3CH_2)_2N$ | 8.85t | | | | 8.82t | | | |
| | 6.69q | 8.12s | 3.59s | 7.0 | 6.69q | 8.21s | 3.80s | 7.0 |

*s, singlet; d, doublet; t, triplet; q, quartet.

2-cyano-1,2-dichloropropane with methanolic sodium hydroxide. The stereochemistry of the product was not given but a boiling point comparison with the isomers we have prepared shows it to most closely compare with the *E* isomer. The above experiment was repeated under milder conditions and was shown to give the *Z* isomer as the major (82%) product, and thus Lichty's preparation undoubtedly gave the product as the equilibrated mixture which contains 78% of the *E* form.

## Equilibration Studies

The positions of equilibrium for the 3-substituted methacrylonitriles, **3**, prepared in this study, are presented in Table 2. It is of interest to consider the factors that determine the position of this equilibrium. Although steric factors have traditionally been emphasized, in recent years the observation that a number of *cis*-1,2-disubstituted olefins are more stable than their *trans* isomers suggests an important stabilization due to

TABLE 2

Equilibration results for the 3-substituted methacrylonitriles (**3**), $XCH{=}C(CH_3)(CN)$

| X | % *E* isomer at equilibrium | Method of equilibration* | % *E* predicted from Table 3 |
|---|---|---|---|
| Cl | 60† | *1* | 58 |
| Br | 60† | *1* | |
| $CH_3O$ | 78† | *1* | |
| $C_2H_5S$ | 68† | *2a* | |
| $(CH_3)_2N$ | 13‡ | *2b* | |
| $(CH_3CH_2)_2N$ | 13‡ | *2b* | |
| $CH_3$ | 20† | *3* | 18 |

*1) Bromine in sunlight at about 30°; *2a*) thermally in sealed tubes at 210°; *2b*) equilibration occurred on v.p.c. columns at 210°; *3*) trace of sodium methoxide in methanol at 25°.
†The v.p.c. analysis.
‡The n.m.r. analysis.

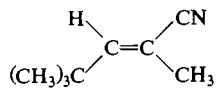
TABLE 3

Position of equilibrium for *cis–trans*-1,2-disubstituted ethylenes

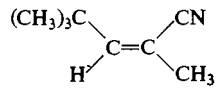
| Substituents | % *cis* | Temperature |
|---|---|---|
| Cl, $CH_3$ | 75.5 (30, 31) | 30° |
| Br, $CH_3$ | 68 (33) | 0–100° |
| Cl, CN | 69 (30) | 30° |
| $CH_3$, CN | 57 (30), 58 (34) | 80°, 400° |
| $CH_3$, $CH_3$ | 23 (35) | |

a van der Waals or electrostatic attraction between many groups. This attractive interaction is illustrated by the percent *cis* isomer at equilibrium as given in Table 3 for compounds related to those of the present study.

For the methacrylonitriles the relative steric requirements of the methyl and the nitrile groups can be evaluated in 3-*t*-butylacrylonitrile (36) where steric factors will clearly be dominant. Equilibration of **5** at 30° with bromine and sunlight gives 8% of the *E* form. Thus as expected from other studies the methyl has a larger steric requirement than the nitrile group.




**5** (*E*)




**5** (*Z*)

The data in Table 2 indicate that only in the 3-dimethylamino and possibly in the 3-methyl compounds are the steric factors dominant in determining equilibrium positions. The dimethyl amino group, in order to provide conjugation with the nitrile group, would become planar and thereby introduce a steric requirement of an order equivalent to a *t*-butyl group. The equilibrium positions for the other compounds in Table 2 show effects similar to those which con-

tribute to the favored *cis* orientations noted in Table 3.

In the range of compounds where steric effects are not dominant we might expect the equilibrium position for a trisubstituted olefin to be equal to that predicted by an additive contribution of the vicinal pairs.[1] It is interesting therefore that the data of Table 3 can be used to predict two of the observed equilibria in Table 2 to within the combined experimental error of the measurements. On the other hand, data from Table 3 predicts the equilibrium position for 2-bromo-2-butene to be 88% *trans*, a value which is close to, but outside, the experimental error for the observed value of 83% (37, 38). It seems, however, that it would be desirable to further evaluate additivity in these systems. It may, for example, be advantageous to only use data at infinite dilution in a common solvent at a common temperature.

## Experimental

Vapor phase chromatographic analysis and preparative separation were carried out using commercial (Varian Aerograph) 10 ft × 1/4 in. stainless steel columns containing the appropriate packing. Boiling points were determined by the microcapillary method and are uncorrected. The n.m.r. spectra were recorded on a Varian A60 instrument using 20% by volume samples in carbon tetrachloride. All new compounds gave infrared spectra consistent with their respective structures.

*3-Chloromethacrylonitrile (E- and Z-)*

The title compounds were prepared from chloroacetone cyanohydrin (28) by the method of Hurd and Rector (39). The product (70%, b.p. 54–80°/40 mm) contained 3-chloromethacrylonitrile (*E*-), (28%), 3-chloromethacrylonitrile (*Z*-) (51%), and 2-cyano-1,2-dichloropropane (21%). Separation was effected by preparative v.p.c. on a 15% QF1 – 5% carbowax 20M column at 145°.

*3-Bromomethacrylonitrile (E- and Z-)*

Bromine (80 g, 0.5 mole) in carbon tetrachloride (50 ml) was added dropwise over 3 h to methacrylonitrile (33.5 g, 0.5 mole) and the stirred solution was then left overnight at room temperature. Removal of the solvent at room temperature *in vacuo* yielded crude 2-cyano-1,2-dibromopropane (56 g, 49%). To the crude product, dissolved in *t*-butanol (50 ml), was added, with vigorous stirring, potassium hydroxide (18 g) in water (32 ml). After 21 h potassium bromide was removed by filtration and the filtrate was diluted with ether (100 ml). The aqueous layer was further extracted with ether (2 × 100 ml) and the combined ether extracts were dried over magnesium sulfate. Removal of the ether and *t*-butanol, followed by distillation at 50–70°/20 mm yielded 3-bromomethacrylonitrile (*E*:*Z* = 3:5, 25.5 g, 71%). Although thermally labile, the two isomers were readily separable by preparative v.p.c. (15% QF1 – 5% carbowax 20M) at 150° and have the following properties.

3-Bromomethacrylonitrile (*E*-); $n_D^{20}$ 1.4995.

Anal. Calcd. for $C_4H_4BrN$: C, 32.87; H, 2.74. Found: C, 33.25; H, 3.01.

3-Bromomethacrylonitrile (*Z*-); $n_D^{20}$ 1.4929.

Anal. Found: C, 32.80; H, 2.87.

If methanol was used instead of *t*-butanol in the above experiment, a small amount of 3-methoxymethacrylonitrile (*E*-) was also obtained which could not be separated from the 3-bromomethacrylonitrile (*Z*-).

*3-Methoxymethacrylonitrile (E-)*

Sodium methoxide (1 equ) in methanol was added dropwise, with stirring, to 3-bromomethacrylonitrile (*E*-) (1 equ), sodium bromide being instantly precipitated. The vigorous exothermic reaction was controlled by external cooling. On completion of the methoxide addition, the solution was stirred for 1.5 h at room temperature, then neutralized with glacial acetic acid and diluted with ether. Removal of the precipitate, followed by evaporation of the solvent under reduced pressure yielded a yellow oil which was distilled under reduced pressure. Final purification was effected by preparative v.p.c. on QF1–carbowax at 180° to give 3-methoxymethacrylonitrile (*E*-), b.p. 182–183° (lit. (29) b.p. 80–83°/27 mm), contaminated with a small amount of 3,3-dimethoxy-2-methylpropionitrile.

*3-Methoxymethacrylonitrile (Z-)*

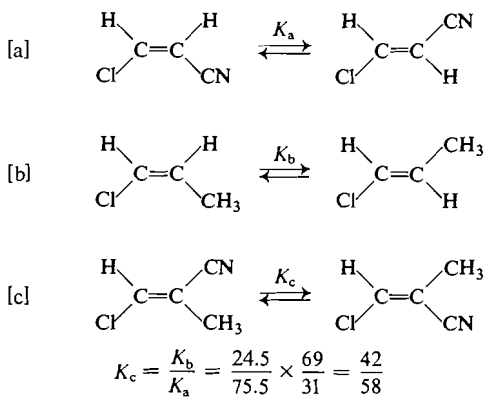
This was prepared as above from 3-bromomethacrylonitrile (*Z*-). An analytical sample had b.p. 202–203° and $n_D^{20}$ 1.4498.

Anal. Calcd. for $C_5H_7NO$: C, 61.86; H, 7.22. Found: C, 61.69; H, 7.33.

*Reaction of 2-Cyano-1,2-dichloropropane with Methanolic Sodium Hydroxide (29)*

To a stirred solution of 2-cyano-1,2-dichloropropane (0.55 g) in methanol (1 ml) was added sodium hydroxide (0.32 g) in water (1 ml). After 1 h at room temperature the solution was extracted with ether. Analysis of this extract by v.p.c. showed, besides starting material and volatile products, 3-methoxymethacrylonitrile (*E*- and *Z*-), in the ratio 2:9.

[1]Additivity in the free energy term would appear as a product of the equilibrium constants thus for




$$K_c = \frac{K_b}{K_a} = \frac{24.5}{75.5} \times \frac{69}{31} = \frac{42}{58}$$

*3-Dimethylaminomethacrylonitrile (E- and Z-)*

3-Bromomethacrylonitrile (*E*-) (0.2 g) in ether (2 ml) was treated with dimethylamine (1 ml). The resulting solution was kept, in a screw-cap jar, overnight at room temperature then diluted with ether. After removal of the precipitated dimethylamine hydrobromide by filtration, the ether and excess dimethylamine were evaporated under reduced pressure. Analysis of the crude reaction product by n.m.r. showed that only 3-dimethylaminomethacrylonitrile (*E*-) was present. The *cis–trans* equilibration, however, occurred when an attempt was made to purify the sample by preparative v.p.c. at 210°. The resulting mixture contained both *E* and *Z* isomers in the ratio 13:87.

Anal. Calcd. for $C_5H_7NO$: C, 61.86; H, 7.22. Found: C, 61.69; H, 7.33.

Starting with 3-bromoethacrylonitrile (*Z*-) only 3-dimethylaminomethacrylonitrile (*Z*-) was present in the crude product. The same equilibrium mixture as above was, however, obtained by v.p.c. purification.

*3-Diethylaminomethacrylonitrile*

A solution of 3-chloromethacrylonitrile (*E*-) (0.88 g) in ether (6 ml) and diethylamine (6 ml) was boiled under reflux for 39 h. After dilution with ether and removal of the precipitated diethylamine hydrochloride, the solvent was removed to give a mixture of starting material and 3-diethylaminomethacrylonitrile (*E*-) in the ratio 2:3. The latter equilibrated to a mixture of *E* and *Z* forms (88% *Z*) when purified by v.p.c. on Dow Corning 550 at 210°.

The crude product obtained from the reaction of 3-chloromethacrylonitrile (*Z*-) with diethylamine contained 36% starting material and 64% 3-dimethylaminomethacrylonitrile (*Z*-). Purification by v.p.c. as above gave 3-diethylaminomethacrylonitrile (*E*- and *Z*-) in the ratio 14:86.

Anal. Calcd. for $C_8H_{14}N_2$: C, 69.56; H, 10.14. Found: C, 69.81; H, 10.34.

*3-Thioethoxymethacrylonitrile (E- and Z-)*

Treatment of 3-bromomethacrylonitrile (*E*- and *Z*-) with 1 equ of sodium thioethoxide in methanol (prepared from sodium methoxide (1 equ) and ethanethiol (1.1 equ)) yielded the corresponding 3-thioethoxy compounds. Stereospecific replacement of bromine was shown to have taken place by v.p.c. analysis on QF1–carbowax at 180°. The two isomers, isolated by preparative v.p.c., had the following physical properties.

3-Thioethoxymethacrylonitrile (*E*-): $n_D^{18}$ 1.5281, b.p. 201–202°.

Anal. Calcd. for $C_6H_9NS$: C, 56.69; H, 7.09. Found: C, 58.45; H, 7.33.

3-Thioethoxymethacrylonitrile (*Z*-): $n_D^{18.5}$ 1.5180, b.p. 216–217° (with 4% *E* present).

Anal. Found: C, 56.59; H, 7.10.

*Methods of Equilibration*

In every case, except for methyl 3-dimethylaminomethacrylate, the position of equilibrium has been determined by equilibrating each *E* and *Z* isomer separately, the following procedures being used.

*(1)* Bromine and sunlight: To a neat solution of the nitrile in a sealed or tightly-stoppered tube was added 1–2 mole % of bromine (10% solution in carbon tetrachloride). The tubes were placed in direct sunlight, samples being removed periodically for analysis.

*(2)* Thermolysis: Small samples (10–50 μl) of the nitrile were sealed in Pyrex tubes (4 mm o.d.) and placed in a furnace at 210°. Although some darkening of the samples occurred, there was no apparent decomposition. Samples were removed and analysed at fixed intervals.

*(3)* Sodium methoxide in methanol: The nitrile was treated with a trace of sodium methoxide in methanol and the mixture analyzed periodically by v.p.c.

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