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# Effect of pressure on sterically congested cyanoalkylation reactions of alcohols

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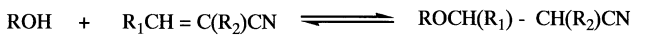
**Abstract**—The pressure effect on the phosphine-catalyzed nucleophilic addition of alcohols to unsaturated nitriles is examined. As a general result, pressure promotes these reactions. Their sensitivity to pressure increases with increasing steric congestion of either the alcohol or the nitrile. Activation volumes are found to be very negative pointing not only to a late transition state, but essentially to a considerable electrostriction contribution depending on steric hindrance to ionization. This means that pressures favors formation of the carbanion and attack of the nitrile. The results highlight the synthetic utility of high pressure to remove steric inhibition. 

## 1. Introduction

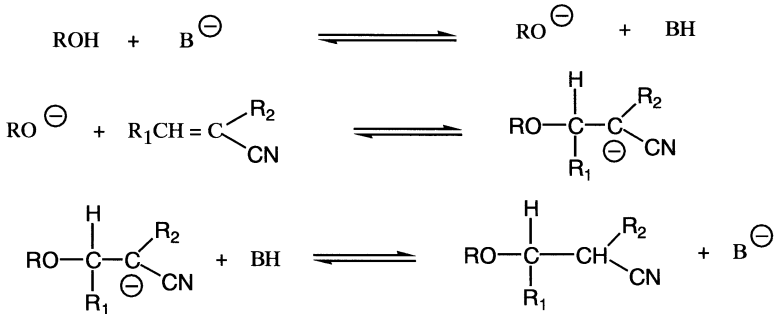
The process traditionally known as cyanoethylation involves cyanoethylating agents such as acrylonitrile.[1] Cyanoethylation of monohydric alcohols with acrylonitrile is an old reaction already studied in the 1920s.[2] A comprehensive review appeared a long time ago.[3] In spite of its ancientness the reaction deserves a wide and real interest for the synthesis of number of compounds e.g. drug intermediates. The general equation can be written as (Eq. (1)):




(1)

The reaction is apparently a Michael type nucleophilic addition and occurs only in presence of a base via the intermediate alkoxy anion. The base must be strong and consists usually of aqueous solutions of alkali hydroxides, alkoxides, tetraalkyl ammonium hydroxides. New heterogeneous basic catalysts have been recently proposed to improve the catalytic activity in the cyanoethylation of alcohols by acrylonitrile.[4] However, alkyl substituted acrylic nitriles react with alcohols less easily. The two methyl substituted unsaturated nitriles, methacrylonitrile and crotononitrile, require much longer reaction times than acrylonitrile in their reaction with methanol.[3]

Some time ago we investigated the pressure effect in some nucleophilic additions such as Michael and Henry reactions and found that they are fairly promoted by pressure.[5] We felt of interest to examine the high pressure synthesis of hindered cyanoethers which can be forbiddingly difficult




**Scheme 1.**

*Keywords*: high pressure kinetics; steric hindrance; nucleophilic addition; cyanoether synthesis.

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**Table 1.** Effect of the base on cyanoalkylation of 1-propanol by methacrylonitrile

| Base[a] | Yield (%) | |
|---|---|---|
| | 0.1 MPa | 300 MPa |
| Aqueous NaOH[b] | 2 | No run |
| Aqueous $Bu_4NF{\cdot}3H_2O$[b] | 0 | No run |
| DABCO | 0 | 0 |
| DMAP | 0 | 1 |
| DBU | 0 | No run |
| Tetramethylguanidine | 0 | 3 |
| Tri-*n*-butylphosphine | 18 | 67 |
| Tri-*n*-butylphosphine[b] | 2 | No run |
| Phosphazene[c] | 48 | 99 |

Nitrile (1.8 mmol), propanol (13.3 mmol), *T* (323 K), *t* (4 h).
[a] Base (0.18 mmol). DABCO (diazabicyclo[2.2.2]octane), DMA (4-dimethylaminopyridine), DBU (1,8-diazabicyclo[5.4.0]undec-7-ene).
[b] Water (28 mmol) is added. No agitation is provided.
[c] Phosphazene base $P_4$-*t*Bu (from Fluka).

or impossible to synthesize under ordinary conditions. A previous note reported the considerable yield improvements by application of high pressure.[6]

## 2. Results

The study was made essentially with methacrylonitrile and crotononitrile. The nitriles are two isomers only differing by the position of the methyl group at the α or β position. The reaction sequence for a classic Michael reaction is depicted in Scheme 1. Clearly, the attack on the β position in the rate determining step, obviously, should be more difficult when $R_1 \neq H$, meaning that the addition of an alcohol would occur more easily on methacrylonitrile.

### 2.1. Selection of the base

In the preliminary stage we were seeking an appropriate base for our purpose. The traditional bases employed in cyanoethylation—aqueous alkali hydroxides or tetraalkylammonium salts—are not suitable (Table 1). In addition, as they lead to heterogeneization of the reaction medium, they require stirring which cannot be achieved in our high pressure device. Organic bases such as tertiary amines are ineffective as is also the case of weak (DMAP) or even strong bases (DABCO, DBU, guanidine). In the runs carried out with the above bases high pressure (300 MPa) does not significantly enhance the reactivity. Good results, however, were obtained with phosphorous bases (phosphines and phosphazenes).[7] Phosphazenes are extremely strong bases, one of the strongest being phosphazene Base $P_4$-*t*Bu:[8] a 48% yield of cyanopropylether is produced at ambient pressure whereas the reaction is quantitative at 300 MPa. Tri-*n*-butylphosphine though much less basic is revealed as a convenient catalyst leading to 18 and 67% yields, respectively. The availability and cheapness of the phosphine prompted us to use it as the base in most reactions examined in this paper.

**Table 2.** Cyanoalkylation of linear primary alcohols (Eq. (1)). Effect of pressure

| R | $R_1$ | $R_2$ | Time (h) | Yields (%) | |
|---|---|---|---|---|---|
| | | | | 0.1 MPa | 300 MPa |
| $CH_3$ | H | $CH_3$ | 2 | 62 | 100 |
| $CH_3$ | $CH_3$ | H | 2 | 80 | 100 |
| $C_2H_5$ | H | $CH_3$ | 3.5 | 33 | 78 |
| $C_2H_5$ | $CH_3$ | H | 3.5 | 32 | 99 |
| $C_3H_7$ | H | H | 2 | 34 | 100 |
| $C_3H_7$ | H | $CH_3$ | 4 | 18 | 67 |
| $C_3H_7$ | $CH_3$ | H | 4 | 5 | 94 |
| $C_4H_9$ | H | $CH_3$ | 4 | 10 | 57 |
| $C_4H_9$ | $CH_3$ | H | 4 | 2 | 95 |
| $C_5H_{11}$ | H | $CH_3$ | 4 | 7 | 68 |
| $C_5H_{11}$ | $CH_3$ | H | 4 | 2 | 85 |
| $C_7H_{15}$ | H | $CH_3$ | 4 | 0 | 23 |
| $C_7H_{15}$ | $CH_3$ | H | 4 | 0 | 33 |

Nitrile (1.8 mmol), solvent (ROH), tri-*n*-butylphosphine (0.18 mmol), *T* (323 K).

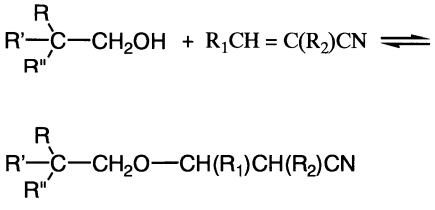
The reactions presented throughout were found not reversible under our conditions. This was checked for some cyanoalkylethers which were exposed to the same conditions as for the forward reactions (temperature, concentration of phosphine, time) or worked up upon addition of aqueous chlorhydric acid. The cyanoalkylethers were recovered unchanged in the same amount as initial.

### 2.2. Addition of primary linear alcohols

In a second step, we investigated the pressure effect in the cyanoalkylation of linear primary alcohols by both unsaturated nitriles (Table 2). The results show that in agreement with Ref. 3, crotononitrile reacts easier than methacrylonitrile in the cyanoalkylation of methanol. In the case of ethanol, reactions yields are similar. However, with increasing chain length of the alcohol, the addition reaction becomes more sluggish and it does not proceed with 1-heptanol. The reactivity of alcohols with crotononitrile is significantly depressed, in larger extent than in the reactions involving methacrylonitrile.

Considering the pressure effect, the reaction becomes gradually more pressure sensitive independently of the structure of the nitrile when the chain of the alcohol is made longer. Another item worth noting in Table 2 includes the fact that it becomes clear that at 300 MPa crotononitrile reactions are more accelerated than the corresponding methacrylonitrile reactions. This is a contrasting though highly interesting result since the reaction center in crotononitrile is much less accessible.

### 2.3. Addition of branched linear alcohols




(2)

Informed by the results listed in Table 2, we were expecting that increasing bulkiness of the alkyl rest of the alcohol (in the case of branched primary alcohols) would induce low or

**Table 3.** Cyanoalkylation of branched primary alcohols (Eq. (2)). Effect of pressure

| Entry | R | R′ | R″ | $R_1$ | $R_2$ | Time (h) | Yields (%) | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | 0.1 MPa | 300 MPa |
| 1 | $CH_3$ | $CH_3$ | H | H | $CH_3$ | 8 | 22 | 70 |
| 2 | $CH_3$ | $CH_3$ | H | $CH_3$ | H | 8 | 4 | 81 |
| 3 | $CH_3$ | $CH_3$ | H | $C_2H_5$ | H | 8 | 0 | 61 |
| 4 | $C_2H_5$ | $CH_3$ | H | H | $CH_3$ | 22 | 38 | 79 |
| 5 | $C_2H_5$ | $CH_3$ | H | $CH_3$ | H | 22 | 11 | 95[a] |
| 6 | $C_2H_5$ | $CH_3$ | H | $C_2H_5$ | H | 24 | 0 | 80 |
| 7 | $CH_3$ | $CH_3$ | $CH_3$ | H | $CH_3$ | 24 | 13 | 84 |
| 8 | $CH_3$ | $CH_3$ | $CH_3$ | $CH_3$ | H | 24 | 1 | 92[a] |
| 9 | $CH_3$ | $CH_3$ | $CH_3$ | $C_2H_5$ | H | 8 | 0 | 40 |
| 10 | Cyclohexyl | | H | H | $CH_3$ | 24 | 43 | 56 |
| 11 | Cyclohexyl | | H | $CH_3$ | H | 24 | 2 | 58[a] |

Nitrile (1.8 mmol), solvent (ROH), tri-*n*-butylphosphine (0.18 mmol), *T* (323 K).
[a] The Baylis–Hillman dimer of crotononitrile is also formed.[8]

no reactivity at ambient pressure and, on the other hand, an interesting pressure effect. We examined the cyanoalkylation of isobutanol (entries 1–3), 2-methyl-1-butanol (entries 4–6), neopentanol (entries 7–9), cyclohexylmethanol (entries 10, 11) with methacrylonitrile, crotononitrile and *cis*-2-pentenenitrile (Table 3). Clearly, the results of Table 3 are completely in agreement with our expectations and observations detailed in the preceeding paragraph. We take note of the following features:

Placing bulky substituents on the β-center of the acrylic nitrile create steric inhibition and cause considerable rate penalty at ambient pressure. In fact, such encumbered nitriles exhibit only marginal activity (entries 2, 5, 11) or are fully refractory to addition (entries 3, 6, 8, 9). On the other hand, methacrylonitrile shows some reactivity in these reactions (entries 1, 4, 10) even with the crowded neopentanol (entry 7).

Pressure has a beneficial effect in all reactions. The most significant observation is that application of pressure seemingly removes steric restrictions. However, the pressure dependence varies with the type of nitrile involved. Reactions of methacrylonitrile are fairly sensitive. The yields at 300 MPa are increased by a factor varying from 1.5 to 7 depending on the bulky nature of R, R′, R″. The corresponding additions involving methyl and ethyl β-substituted acrylic nitriles are revealed as highly pressure dependent reactions. With increasing steric complexity nearly quantitative yields are obtained (entries 5, 8). Some reactions occur only under 300 MPa pressure (entries 3, 6, 8, 9).

At last, with the less reactive bulky alcohols, the Baylis–Hillman dimer of crotononitrile was also formed as described in one of our former papers.[9] The occurrence of this reaction largely depends on the feasibility of the corresponding cyanoalkylation. For example, the dimerization extent at 300 MPa is respectively 4% in entries 5 and 8, up to 29% on entry 11.

**Table 4.** Cyanoalkylation of secondary and tertiary alcohols (Eq. (3)). Effect of pressure

| Entry | R | R′ | R″ | $R_1$ | $R_2$ | Time (h) | Base | Yields (%) | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | 0.1 MPa | 300 MPa |
| 12 | $CH_3$ | $CH_3$ | H | H | H | 24 | DMAP | 0 | 81 |
| 13 | $CH_3$ | $CH_3$ | H | H | H | 24 | $P(C_4H_9)_3$ | 90 | 100 |
| 14 | $CH_3$ | $CH_3$ | H | H | $CH_3$ | 24 | DMAP | 0 | 0 |
| 15 | $CH_3$ | $CH_3$ | H | H | $CH_3$ | 20 | $P(C_4H_9)_3$ | 3 | 56 |
| 16 | $CH_3$ | $CH_3$ | H | H | $CH_3$ | 20 | Phosphazene | 78 | 98 |
| 17 | $CH_3$ | $CH_3$ | H | $CH_3$ | H | 24 | DMAP | 0 | 0 |
| 18 | $CH_3$ | $CH_3$ | H | $CH_3$ | H | 20 | $P(C_4H_9)_3$ | 0 | 65[a] |
| 19 | $CH_3$ | $CH_3$ | H | $C_2H_5$ | H | 20 | $P(C_4H_9)_3$ | 0 | 22 |
| 20 | $C_2H_5$ | $CH_3$ | H | H | $CH_3$ | 20 | $P(C_4H_9)_3$ | 2 | 35 |
| 21 | $C_2H_5$ | $CH_3$ | H | $CH_3$ | H | 20 | $P(C_4H_9)_3$ | 0 | 38[a] |
| 22 | $iC_3H_7$ | $iC_3H_7$ | H | H | $CH_3$ | 24 | $P(C_4H_9)_3$ | 0 | 2 |
| 23 | $iC_3H_7$ | $iC_3H_7$ | H | $CH_3$ | H | 22 | $P(C_4H_9)_3$ | 0 | 15[a] |
| 24 | $iC_3H_7$ | $iC_3H_7$ | H | $CH_3$ | H | 22 | Phosphazene | 0 | 27[a] |
| 25 | $C_6H_5$ | $CH_3$ | H | H | $CH_3$ | 24 | $P(C_4H_9)_3$ | 16 | 47 |
| 26 | $C_6H_5$ | $CH_3$ | H | $CH_3$ | H | 24 | $P(C_4H_9)_3$ | 7 | 54[a] |
| 27 | Cyclohexyl | | H | $CH_3$ | H | 24 | $P(C_4H_9)_3$ | 0 | 24[a] |
| 28 | Cyclohexyl | | H | $CH_3$ | H | 24 | Phosphazene | 0 | Complex mixture |
| 29 | $CH_3$ | $CH_3$ | $CH_3$ | H | H | 24 | $P(C_4H_9)_3$ | 0 | 10 |
| 30 | $CH_3$ | $CH_3$ | $CH_3$ | H | H | 24 | Phosphazene | 0 | 15 |
| 31 | $C_2H_5$ | $CH_3$ | $CH_3$ | H | H | 24 | $P(C_4H_9)_3$ | 0 | 0 |

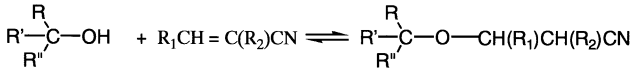
Nitrile (1.8 mmol), solvent (ROH), tri-*n*-butylphosphine (0.18 mmol), *T* (323 K).
[a] The Baylis–Hillman dimer of crotononitrile is also formed.

**Table 5.** Addition of allylcyanide to alcohols (standard conditions)

| Nitrile | Alcohol | Yields (%) | |
|---|---|---|---|
| | | 0.1 MPa | 300 MPa |
| Allyl cyanide | Ethanol | 40 (4 h) | 100 (4 h) |
| Crotononitrile | Ethanol | 32 (3.5 h) | 99 (3.5 h) |
| Allyl cyanide | Propanol | 26 (6 h) | 100 (6 h) |
| Crotononitrile | Propanol | 5 (4 h) | 94 (4 h) |
| Allyl cyanide | Isopropanol | 4 (6 h) | 80 (6 h) |
| Crotononitrile | Isopropanol | 4 (8 h) | 81 (8 h) |

## 2.4. Addition of secondary and tertiary alcohols (Table 4, Eq. (3))

A cursory examination of Table 4 indicates that secondary and tertiary alcohols behave like primary alcohols in their addition to acrylic nitriles. Most of the reactions listed do not proceed at all at ambient pressure. Again, the crotononitrile dimer is produced when hindered alcohols are involved as reactants (13% in entry 18, 18% in entry 21). With highly hindered alcohols the dimer is the major product (45% in entry 24).



(3)

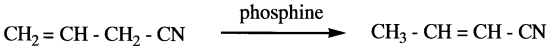
Among the three bases used in the runs, the strong basic phosphazene leads to increased yields (about twice the yields obtained when tributylphosphine serves as base). Electrostriction is addressed with entry 12. Isopropanol does not add to acrylonitrile in the presence of DMAP at ambient pressure (no formation of the isopropoxy anion) whereas the reaction proceeds to 81% at 300 MPa. However, DMAP as catalyst is unable to promote any reaction with substituted acrylic nitriles even at 300 MPa (entries 14, 17).

Pressure is a powerful activation mode in promoting the nucleophilic addition, particularly with acrylic nitriles in which $R_1$=$CH_3$ (entries 18, 21, 27) and $R_1$=$C_2H_5$ (entry 19). A striking example highlighting the reactivity difference between methacrylonitrile and crotononitrile under pressure is disclosed in entries 22 and 23. A 2 vs 15% yield is obtained at 300 MPa in the addition of diisopropylalcohol, a highly encumbered alcohol, to methacrylonitrile and crotononitrile respectively. This difference is noticeably enhanced under 700 MPa: the yields of cyanoethers are 4 and 54%, respectively.

Tertiary alcohols are relatively inert even under pressure. Only *tert*-butanol is able to deliver by combination with acrylonitrile the cyanoether albeit in very modest yields (entries 29, 30). It does not react with methyl substituted acrylic nitriles. *tert*-Amylalcohol is unreactive (entry 31).

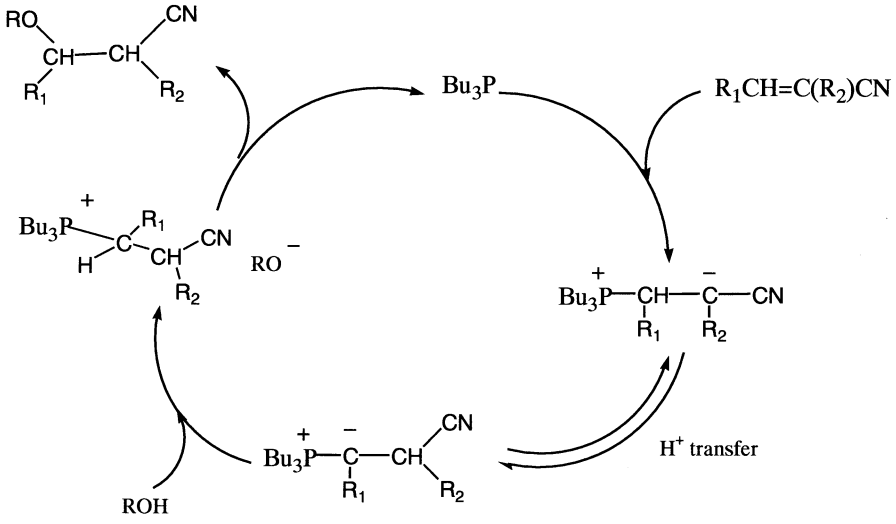
## 2.5. Addition of alcohols to allyl cyanide

In place of crotononitrile, we examined the possibility of adding its isomer, allyl cyanide, to alcohols. The allylic nitrile should not show any particular reactivity. However, we observed that it reacted with alcohols in the presence of tributylphosphine like other acrylic nitriles, apparently at the same rate as crotononitrile leading to similar yields under identical conditions. The resulting cyanoethers showed the same structures as those derived from crotononitrile (Table 5). In fact, we suspected isomerization of allyl cyanide prior to nucleophilic addition. This was verified in independent runs demonstrating that in the presence of tributyl phosphine allyl cyanide was quantitatively converted to crotononitrile (50°C, 15 h) whereas under similar conditions, crotononitrile remained unaffected.



## 2.6. Kinetic studies and interpretation

The mechanism of the phosphine-catalyzed addition is different to the mechanism outlined in Scheme 1. It can be rationalized by the proposed mechanism depicted in Scheme 2.[7,10] Pressure may affect each step. As yields are strongly dependent on steric demand both from the nitrile and the alcohol side, the rate determining step would be



**Scheme 2.**

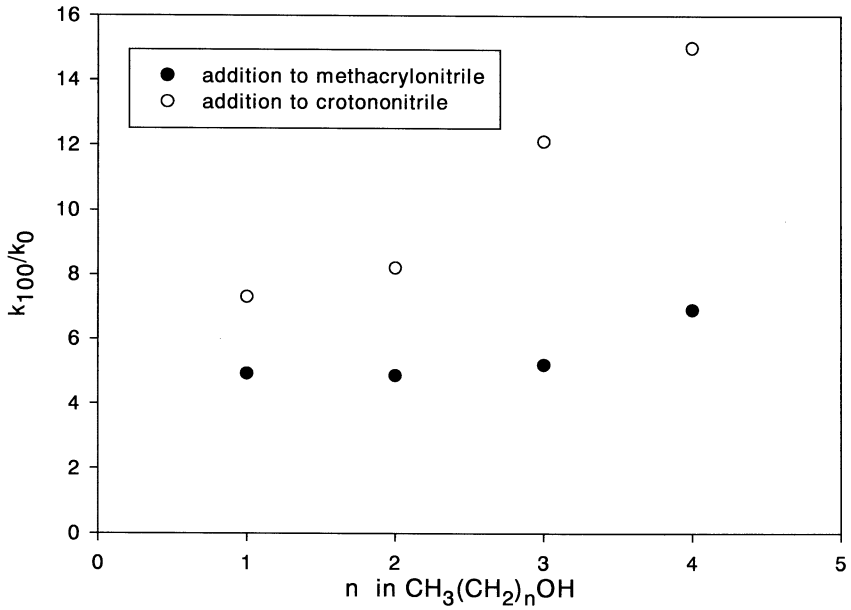



**Figure 1.** Addition of linear primary alcohols $CH_3(CH_2)_nOH$ to nitriles. Dependence of rate constant ratio on $n$ ($k_{100}$ is constant at 100 MPa and $k_0$ at 0.1 MPa, $T$ is 303 K).

deprotonation of the alcohol and addition of the alkoxy moiety on the β carbon with concomittant elimination of the phosphine.

The pressure effect on rate constants yields the volume of activation $\Delta V^{\neq}$. $\Delta V^{\neq}$ is usually a composite quantity and must be written as:[11]

$$\Delta V^{\neq} = \sum \Delta V_i^{\neq}$$

The intrinsic volume change for the associative nucleophilic addition process relates basically to the formation of the O–C bond. This geometric modification during the progression towards the transition state is characterized by a structural activation volume $\Delta V_0^{\neq}$ of about $-15$ to $-20\ cm^3\ mol^{-1}$ as it was shown in the $Bu_4NF$-catalyzed Michael addition of nitromethane to methyl vinyl ketone.[5] However, the whole body of our results is, at the evidence, not uniquely traceable to bond-making effects. In fact, a complete description of the kinetic behavior would entail an analysis of several factors. To this respect, we were prompted to determine kinetic rate constants as a function of pressure. This was done by measuring the pseudo-first-order constants $k$ in the addition of primary linear alcohols ($C_2$–$C_5$) to methacrylonitrile and crotononitrile, respectively, in the pressure range (0.1–150 MPa). Fig. 1 pictures the pressure effect on the reactivity difference between both acrylic nitriles in their addition to such alcohols. Visibly, the reactions involving crotononitrile are confirmed to be more pressure sensitive than those involving the other isomer. With lengthening of the chain of the alcohol (increasing of $n$), both reaction series become also more pressure dependent, particularly the crotononitrile reactions.

**Table 6.** Apparent resulting activation volumes for the addition of primary linear alcohols to methyl acrylic nitriles (volumes are given in $cm^3\ mol^{-1}$)

| ROH | Methacrylonitrile | | Crotononitrile | |
|---|---|---|---|---|
| | $\Delta V^{\neq}$ | $\Delta V_R$ | $\Delta V^{\neq}$ | $\Delta V_R$ |
| Ethanol | −40 | −18.5 | −52 | −15.5 |
| 1-Propanol | −40 | −16.5 | −56 | −15.5 |
| 1-Butanol | −45 | −19.0 | −68 | −17.0 |
| 1-Pentanol | −52 | nd | −75 | nd |

Estimated precision for $\Delta V^{\neq}$ (10%) (determined at $T$=303 K) and $\pm 0.5\ cm^3\ mol^{-1}$ for $\Delta V_R$ (determined at $T$=298 K).

The values of $\Delta V^{\neq}$ extracted from experimental kinetic data are listed in Table 6 which embodies also some $\Delta V_R$-values (reaction volume based on partial molar volumes cf. experimental part). These $\Delta V^{\neq}$-values are all lower than $-20\ cm^3\ mol^{-1}$ which is the typical average value for the formation of one covalent bond in a late transition state.[12] This is corroborated by the $\Delta V_R$-values which do not show very significant variations regardless of the type of either the alcohol or the nitrile. It is, therefore, necessary to consider additional volume terms in Eq. (1) especially for reactions featured by the most negative $\Delta V^{\neq}$-values. Such values refer to considerably pressure dependent reactions which, to our knowledge, have no precedence (in the Baylis–Hillman reaction $\Delta V^{\neq}$ have slightly higher values[13]). We must concede that such negative values are somewhat enigmatic, even beyond reasonable comprehension. They certainly cloud the occurrence of other phenomena which will be examined now.

(a) The transition state in these cyanoalkylations must be highly dipolar (Scheme 2) and charge pair generation should dominate so that bond making represents only a minor contribution. The pressure effect on ionogenic reactions, generally, depends largely on the medium since it is directly related to the pressure effect on its dielectric constant[14] resulting in a volume of electrostriction. Since this phenomenon can be critical to rate enhancement under pressure,[15] we examined the kinetic solvent effect (Table 7). It must be emphasized that introducing an apolar medium depressed the yields.

**Table 7.** Solvent effect in the addition of 1-propanol to crotononitrile ($T$=303 K)

| Solvent | $\delta^2$ | $10^6k$ ($s^{-1}$) | $\Delta V^{\neq}$ ($cm^3\ mol^{-1}$)[a] |
|---|---|---|---|
| Tetrahydrofuran | 83 | 0.92 | −46 |
| Dichloromethane | 104 | 1.47 | −46 |
| Acetonitrile | 141 | 4.02 | −50 |
| 1-Propanol | 142 | 18 | −56 |
| Formamide | 369 | 17 | −53 |

We checked the absence of reaction between the solvent and the acrylic nitrile (except obviously with propanol).
[a] Estimated precision (10%).

The results of Table 7 indicate a relatively moderate dependence of the rate constant on solvent polarity ($\delta^2$: cohesion energy density). The $k$-values differ by a factor of 20 from the least polar medium to formamide. However, the $\Delta V^{\neq}$-values in polar as well as in apolar media are not altered significantly (average value: $-50\ cm^3\ mol^{-1}$). The result is at variance with the usual trend e.g. a decrease of electrostrictive effects with increasing polarity of the medium.[14,15] The result contrasts with other Michael like reactions such as the addition of amines to nitriles which do not need any added base.[16] In this case, the formation of zwitterionic species is assisted by pressure producing variable $\Delta V^{\neq}$-values comparable to those shown in Table 7 ($\sim -55\ cm^3\ mol^{-1}$) in non polar media, but higher in the most polar solvents ($\sim -25\ cm^3\ mol^{-1}$).[15] We have no rational explanation for the dichotomy relative to the solvent dependence of $\Delta V^{\neq}$. An earlier paper reported the solvent effect on Michael reactions involving acrylates and aminoalcohols at ambient pressure.[17] The authors suggested that the solvent effect might be due to a change of nucleophilicity of amine and alcohols according to the solvent. Considering Scheme 2, pressure should provide strong assistance to deprotonation of the alcohol with formation of the alkoxy carbanion with subsequent addition on the β carbon. Both events should be sensitive to the bulkiness of R and the steric accessibility of the β carbon. As the yields are considerably depressed at 0.1 MPa with increasing steric congestion we are inclined to suspect steric inhibition to ionization even for polar media, which is relieved by application of pressure.

(b) The $\Delta V^{\neq}$-values illustrate what appears to be a manifestation of steric congestion. In these cyanoalkylations steric effects are manifested in the blockage to the attack of the nucleophile on the β carbon of the nitrile. More surprisingly, whereas the degree of branching and substitution of the alcohol may rationalize to some extent the yields obtained, the size of the alkyl group in primary alcohols seems also to be a critical parameter (Fig. 1 and Table 6). In fact, the kinetic effect due to steric hindrance in classic nucleophilic processes is known.[18] During the attack of the unsaturated nitrile by a nucleophile, steric effects increase around the attacked carbon atom and, whence, the steric compression of substituents in the transition state which is, therefore, destabilized. The activation energy is increased and, accordingly, the rate constant decreases.

Steric effects can be described by number of empirical LFER relations. The most known is the Taft–Hammett equation.[19] It is common practice to distinguish between the primary steric effect of a compressive group R characterizing the degree of accessibility of reaction centers due to R and the secondary steric effect involving the moderation of a polar or resonance effect by non-bonded compression.[20] Steric hindrance to ionization is often brought up to rationalize the kinetic alteration. If approach to ionic sites is hindered, solvation might suffer interference and $\Delta V^{\neq}$ is expected to depend on electrostriction. There is a known example, namely the Menshutkin reaction which is a ionogenic reaction. It was found that the reaction can be very sensitive to pressure as both electrostriction and steric effects are involved.[21]

This is a very interesting facet of the study. It is in relation with a yet largely undeciphered phenomenon. The pressure effect on the rate of sterically hindered reactions has revealed an apparently strange aspect of piezochemistry in the sense that the volume of activation decreases (e.g. $\Delta V^{\neq}$ is more negative) with increasing steric congestion of the transition state.[22] In other words, apart from electrostatic considerations, steric hindrance would shift the transition state towards products. This could be viewed as a consequence of the Hammond postulate[23] or its corollar that for a given type of reaction, increased exothermicities imply earlier transition states or the reverse, hindered (endergonic) reactions correspond to later transition states (for a more detailed comment on energy vs volume considerations, see Ref. 21). In a comprehensive paper,[24] we proposed to take into account a steric component of $\Delta V^{\neq}$ termed $\Delta V_{\sigma}^{\neq}$ which would acknowledge the progression of the transition state along the reaction axis due to steric congestion. In the present case, steric interactions are manifested differently owing to the probable lateness of the transition state. Pressure helps the process by promoting the formation of the alkoxy carbanion (for the most hindered alcohols) and by facilitating the steric accessibility of the reaction center of the nitrile. The present results confirm the magnified pressure effect on steric hindrance to ionization and can be framed in the context of our earlier papers.[22,25,26] However, at this stage it is evident that the phenomenon requires further investigation.

## 3. Conclusion

The phosphine-catalyzed nucleophilic addition of alcohols to acrylic nitriles is a fairly pressure dependent reaction. We propose to view the accelerative effect of pressure in cyanoalkylations of alcohols as the result of

(a) geometric factors (bond formation) ($\Delta V^{\neq} \sim -15$ to $-20\ cm^3\ mol^{-1}$)
(b) electrostatic interactions. This contribution is seemingly largely dependent on the total steric constraints including steric hindrance to ionization.

Considering these effects, the reactions become highly pressure sensitive when both reactants harbour sterically compressive groups. We feel that our findings are of utmost importance for the synthesis of hindered molecules. To this respect, pressure activation appears as a highly valid tactic as we reported previously.

## 4. Experimental

Experiments were made with commercially available chemicals used as received. In a typical run, 1,2,3-trimethoxybenzene (internal standard) was weighed and placed in a flexible PTFE tube (1 mL). The tube was filled half of its volume with the considered alcohol. Tri-*n*-butylphosphine (0.18 mmol) was introduced via syringe followed by the nitrile (1.8 mmol). The volume was then completed with the alcohol. The tube was placed in the high pressure vessel and pressurized to 300 MPa for the desired time. After reaction pressure was released. Diethyl ether was added to the mixture which was washed with a 2N HCl solution, an aqueous $NaHCO_3$ solution and water (twice) successively. The organic fractions were collected and volatile compounds removed on a rotary evaporator. The residue was analyzed by $^1H$ NMR spectroscopy (Brucker AC 200) and the yield determined from the relative intensities of characteristic protons of the cyanoether vs methoxy groups of the internal standard. For analytical data, the cyanoether was purified by chromatography. We report some selected $^1H$ NMR data for unprecedented cyanoalcohols ($CDCl_3$, 200 MHz, $\delta$ ppm):

cyanoether from methacrylonitrile and neopentanol (entry 7): 3.47 (br, 2H, $OCH_2$), 3.05 (s, 2H, $OCH_2$), 2.77 (m, 1H, CHCN), 1.25 (d, 3H, $CH_3$), 0.85 (s, 9H, $CH_3$)

cyanoether from crotononitrile and neopentanol (entry 8): 3.58 (br, 1H, OCH), 2.99–3.10 (m, 2H, $OCH_2$), 2.43 (br, 2H, $CH_2CN$), 1.20 (d, 3H, $CH_3$), 0.85 (s, 9H, $CH_3$)

cyanoether from crotononitrile and isopropanol (entry 18): 3.70 (m, 1H, OCH), 3.60 (m, 1H, OCH), 2.40 (d, 2H, $CH_2CN$), 1.20 (d, 3H, $CH_3$), 1.09 (d, 6H, $CH_3$)

cyanoether from crotononitrile and 2-butanol (entry 21): 3.73 (m, 1H, OCH), 3.38 (m, 1H, OCH), 2.42 (br, 2H, $CH_2CN$), 1.38 (br, 2H, $CH_2$), 1.22 (d, 3H, $CH_3$), 1.10 (d, 3H, $CH_3$), 0.88 (t, 3H, $CH_3$).

Kinetic experiments were carried out at 303 K with 1 mmol nitrile and 0.1 mmol phosphine in 2.5 mL alcohol according to the method previously described.[15] Activation volumes were determined mathematically from the initial slope of the smoothed kinetic curve $\ln k = f(P)$. The values were compared to those calculated by means of El'yanov's procedure.[27]

Partial molar volumes serving to calculate $\Delta V_R$ were determined at 25.0°C in the given alcohol with a digital densimeter (Parr DMA 602). For full details about the determination of partial molar volumes see Ref. 28.

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