The Stereochemistry of Alkylation of α-Aminonitrile Anions by Chiral 1-Methylheptyl Halides

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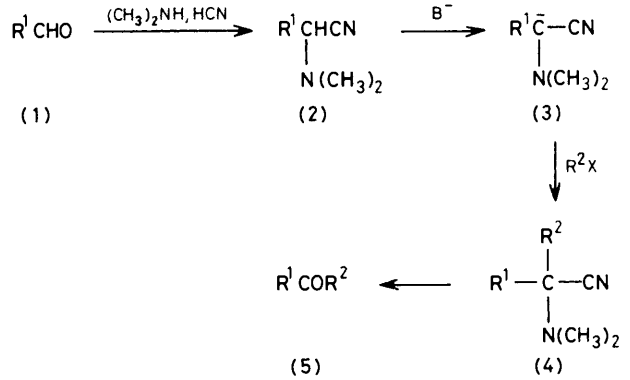
The alkylation of the α-dimethylaminophenylacetonitrile with chiral 1-methylheptyl halides in liquid ammonia involves a partial inversion of the configuration. The accompanying racemization is dependent on the basic reagent and is the consequence of partial racemization of the alkylating agent and of the participation of an electron transfer process in the alkylation.

α-Aminonitriles react with a great variety of nucleophiles and electrophiles [1] and are useful synthons in alkaloid synthesis.[2] The reaction with electrophiles was studied by Hauser *et al.*[3] who transformed the α-dimethylaminophenylacetonitrile (2; R^1 = Ph) into the carbanion (3) and alkylated it with various alkyl halides (Scheme 1).

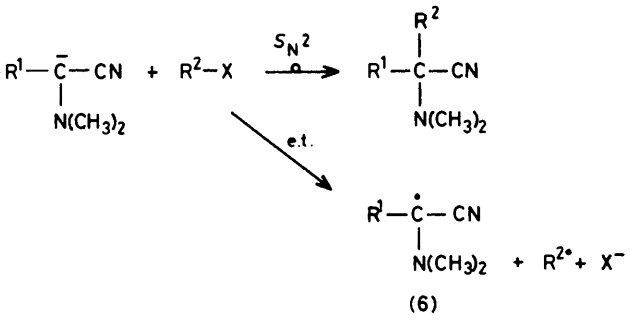
A large number of studies have been performed with several types of anion (3): [4] aromatic derivatives have been widely used in benzoin condensations [5] and in deuteriation.[6] Aliphatic aminonitriles can be alkylated according to Scheme 1 either by a modification of the original procedure [7] or in a more efficient way by the choice of an appropriately substituted amino-group and experimental conditions.[8]

The starting aminonitrile (2) is easily obtainable from the aldehyde (1) and the aminonitrile (4), resulting from the alkylation, is smoothly transformed by hydrolysis into the ketone (5). So the reactions depicted in Scheme 1 demonstrate that the carbanion (3) is related to the acyl anion $R-\bar{C}=O$.[4]



Scheme 1

Despite the great utility of this reaction, stereochemical information on its mechanism is lacking. As well as the widely accepted S_N2 substitution mechanism for alkylation of carbanion (3) we must also consider an electron transfer (e.t.) process.[9] This would involve the stable radical (6) and may become competitive with the S_N2 process (Scheme 2). This competition has been demonstrated by a stereochemical study of the alkylation of aromatic radical anions using chiral 1-methylheptyl halides [10] and the same method can be used to detect radical intermediates in this alkylation. A racemized product is obtained by the e.t. path of Scheme 2, or by a more complicated process involving the transformation of the alkyl halide into a radical intermediate.

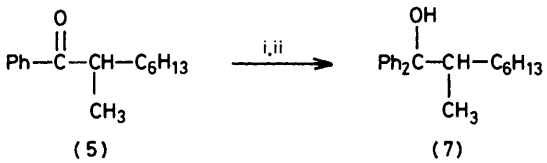


Scheme 2

Results

In order to obtain the required stereochemical information, aminonitrile anion (3; R^1 = Ph) was generated using potassium amide ($B^- = NH_2^-$) or potassium t-butoxide ($B^- = Bu^tO^-$) as base in liquid ammonia under various experimental conditions and alkylated with 1-methylheptyl halides of known optical purities. This reaction runs smoothly with the iodide, is slower with the bromide, and gives only traces of products with the chloride even after several hours (see Table). The resulting aminonitrile (4; R^2 = 1-methylheptyl) is hydrolysed by a silver nitrate solution in D_2O–THF–diethyl ether mixture. We prefer this method to the simpler one using silica gel as hydrolysing agent [8] because the lack of incorporation of deuterium in ketone (5) allowed us to preclude the possibility that the racemization occurred *via* enamine formation (*cf.* ref. 3) or by enolization.

The absolute configuration and the enantiomeric excess of the ketone (5) were established by two ways. (1) The first takes advantage of the optical rotation on the assumption that the reported synthesis of this ketone by alkylation of the dithian-



Scheme 3. *Reagents:* i, PhMgBr; ii, H_2O

masked benzaldehyde by 1-methylheptyl iodide [13] occurs with complete inversion of configuration. This result allows us to compare directly the stereochemical consequences of the two acyl masking methods.[1] The second method [2] involves the transformation of 1-methylheptyl phenyl ketone (5) into carbinol (7) of known configuration and optical purity [14] (Scheme 3). The two methods give consistent results (see last column of the Table), the observed difference between them resulting

Alkylation of the aminonitrile anion (3) by 1-methylheptyl anilides [a]

			Rotation and enantiomeric excess (e.e.) of the alkylating agent RX					Rotation and e.e. of products			
			Initial		Final			Ketone (5)		Carbinol (7)	
No.	Base [e]	Halide	$[\alpha]_{579}^{20}$ (°)	E.e.[b] (%)	$[\alpha]_{579}^{20}$ (°)	E.e.[b] (%)	Reaction time (h)	$[\alpha]_{579}^{20}$ (°)	E.e.[c] (%)	$[\alpha]_{579}^{20}$ (°)	E.e.[d] (%)
1	KNH_2	I	+40.0	79	+28.0	55	20	−11.2	46	−14.1	52
2	KNH_2	I	+40.0	79	+37.0	73	5	−11.7	48	−14.6	54
3	KNH_2	I	+40.0	79	+34.5	69	5	−12.8	52	−14.3	53
4	KNH_2 [f]	I	+40.0	79	+35.0	69.1	20	−15.8	64.5	−20.5	75.6
5	Bu^{t}OK [g]	I	+40.0	79	+38.0	75	1	−17.6	72	−20.3	75
6	Bu^{t}OK	I	+40.7	80.5	+39.5	78	1	−17.7	72	−20	74
7	KNH_2	Br	+35.8	85	+25.7	61	20	−12.6	51	−14.8	55
8	KNH_2	Cl	+32.7	82			20	Trace [a]			

[a] Except for the chloride, the chemical yield of these alkylations is 70—90% calculated from the starting 1-methylheptyl halides. *NN*-Dimethylbenzamide is the only by-product. Similar oxidations of aminonitrile carbanions have already been reported.[2,11b] Absolute rotations α_D^{20} of the *S*-(+)-1-methylheptyl iodide, *S*-(+)-bromide, and *S*-(+)-chloride are respectively, 64.2, 44.5, and 32.4°.[12] To these values correspond in $CHCl_3$ solution the following $[\alpha]_{579}^{20}$ values, 50.6° (*c* 6.4), 42.2 (*c* 0.8), and 39.9° (*c* 3.7). [c] The absolute rotation of the *R*-(−)-ketone (5) is $[\alpha]_{579}^{20}$ 24.5° (*c* 5, diethyl ether).[13] [d] The absolute rotation of the *R*-(−)-carbinol (7) is $[\alpha]_{579}^{20}$ 27.1° (*c* 5, benzene).[14] [e] All samples contain some iron salt if not otherwise indicated. [f] Contains *p*-dinitrobenzene. [g] Without any iron salt.

from the different correlations used for the determination of the absolute rotations.

The results in the Table demonstrate that the alkylation involves inversion of configuration accompanied by some racemization.

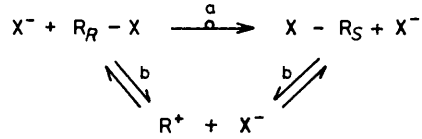
The lack of racemization of the product upon extended reaction and the identity of the optical rotation of ketone (5) recovered after incomplete or total hydrolysis (see Experimental section) confirms the optical stability of products (4) and (5) in the reaction media (liquid ammonia for the former and water for the latter).

Discussion

Racemization of the Alkylating Agent.—When potassium t-butoxide is the base and alkylation is fast,* the racemization of 1-methylheptyl iodide is relatively unimportant (Table, entries 5 and 6). But with the extended reaction time resulting from the use of potassium amide (entries 1—4) racemization increases.

The racemization of the alkyl halides probably involves a competitive S_N2 process, the Finkelstein reaction (path a in Scheme 4),[16] but we have also to consider the contribution of an S_N1 mechanism to the racemization (path b in Scheme 4). Such an S_N1 process can contribute to the racemization of the product (4) when R^+ reacts with the nucleophile (3). However, the rate of an S_N1 reaction being independent of the nucleophile, we consider that the racemization of the product by an S_N1 process cannot exceed significantly the racemization of the unreacted halide.

Racemization of the Product.—When potassium t-butoxide is the base racemization of the product is comparable to racemization of the alkyl iodide, but when potassium amide is used, this racemization (entries 2—4) becomes much more important, and to consider only the contribution of an S_N1 racemization is no longer satisfactory.



Scheme 4

Having ascertained the enantiomeric stability of the products (4) and (5) under the reaction conditions, we have to assume that when potassium amide is used there is a peculiar mechanistic contribution to the formation of the racemized product.

Before discussing the contribution of an electron transfer process in this alkylation we have to consider two other possible routes of racemization.

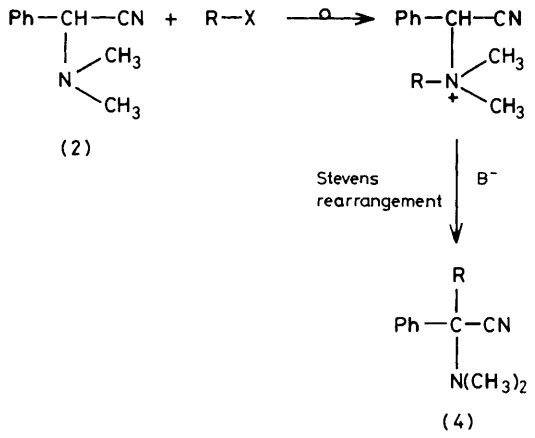
(1) The racemization is the consequence of the catalytic amount of iron salt ($FeSO_4$) used for the preparation of the potassium amide. This possibility was checked by the use of potassium t-butoxide prepared in two different ways; reaction of t-butyl alcohol either with potassium dissolved in liquid ammonia or with potassium amide previously prepared by addition of the iron salt (entries 5 and 6). Both these alkylations give the same stereochemical results and so rule out the iron salt as reponsible for racemization.

(2) When *C*-alkylation is slow enough, *N*-alkylation followed by Stevens rearrangement may occur. This rearrangement of various quaternary salts resulting from aminonitriles has already been reported [17] (Scheme 5). Since *N*-alkylation involves inversion [18] and the Stevens rearrangement retention of configuration with partial racemization,[19] this type of alkylation could well fit our stereochemical results. However the complete lack of *N*-alkylation of the aminonitrile in liquid ammonia rules out this possibility.

Let us consider finally the contribution to racemization of an electron transfer process. In favour of such a contribution is the increased inversion of configuration observed in the presence of a radical trap, *p*-dinitrobenzene (entry 4). In this case the racemization of the product does not exceed the racemization of the alkyl iodide.

This racemization process however has to be more complicated than the simple S_N2 e.t. competition depicted in Scheme 2. According to Scheme 2, the aminonitrile anion (3)

* Increased reactivity has been reported for 'complex bases' resulting from the association of alkali metal amides and alkoxides in aprotic solvents.[15] It is possible that the increased reactivity of t-butoxide is the consequence of a similar association, though such a similarity between the liquid ammonia and the aprotic solvents is unexpected.



Scheme 5

reacts either by an S_N2 or by an e.t. process, and so this competition may be expected to be independent of the base used for the generation of the anion. Our results show the contrary: the product racemization significantly exceeds the racemization of the alkylating agent with potassium amide (entries 1—3) but not with potassium t-butoxide (entries 5 and 6).

In order to take into account this role of the base, we have to consider one of the following explanations. (1) Using potassium amide instead of potassium alkoxide the slow-down of the alkylation is the consequence of the less complete ionization of aminonitrile (2); this compound can catalyse the electron transfer from the carbanion (3) to the alkyl iodide; aminonitriles [20] and nitriles [21] are indeed known to give radical-anions and to be alkylated by an electron transfer process.[21] (2) The electron transfer is not related to the carbanion (3), resulting from the aminonitrile; the actual electron source responsible of the radical path can be potassium amide. Reduction of double bonds by potassium amide in liquid ammonia has been reported.[22]

In conclusion, our stereochemical results detect an electron transfer process in the alkylation of a carbanion resulting from an α-aminonitrile by 1-methylheptyl iodide. This process is not a direct competition between S_N2 substitution and electron transfer, but involves either a catalytic electron transfer or a source of electrons which can be potassium amide.

Besides the mechanistic aspects of these results, which are not yet completely elucidated, the significant increase of inversion of configuration by the modification of the base has synthetic applications.

Experimental

Reagents.—α-Dimethylaminophenylacetonitrile [23] and optically active 1-methylheptyl chloride,[24] bromide,[24] and iodide [25] are known reagents.

Alkylation.—$FeSO_4$ (*ca.* 20 mg) were added to distilled ammonia (150 cm³), followed by addition of clean chips of potassium metal (0.39 g), waiting after each addition until the disappearance of the blue colour. To the grey suspension of potassium amide α-dimethylaminophenylacetonitrile (2) (1.6 g) was added. The solution turned green and 5 min later, 1-methylheptyl iodide (11—12 mmol, 2.6 g) was dropped into the solution. The mixture was stirred for various times at −35 °C.

The reaction was followed by g.l.c. (1.5 m column of 5% SE 30 on Chromosorb G at 230°). A hydrolysed portion of the reaction mixture gave the following peaks (retention time in parentheses): 1-methylheptyl iodide (2 min), aminonitrile (2) (7 min), dimethylbenzamide (15 min), alkylated aminonitrile (4) (18 min). The end of the reaction was detected by the disappearance of the aminonitrile peak. After addition of diethyl ether (100 cm³), the reaction mixture was allowed to warm to room temperature. The ethereal solution was washed with water, dried, and evaporated. Three main products were separated by t.l.c. (silica gel 60 F_{254}, pentane–ethyl acetate 85 : 15), unchanged 1-methylheptyl iodide (200 mg), dimethylbenzamide (480 mg, 30%), and aminonitrile (4) (1.7 g, 70%). In several cases a small amount of 1-methylheptyl phenyl ketone (5), resulting from the partial hydrolysis of the aminonitrile (4) [8] on silica gel was also recovered.

In order to check for the eventual enolization of the ketone, or racemization of the aminonitrile, the ethereal solution was washed with D_2O without any deuterium incorporation in the recovered ketone.

We found in one experiment with 1-methylheptyl iodide ($[\alpha]_{579}^{20}$ +22°) that the recovered ketone (5) from the two hydrolysis procedures had the same rotation (hydrolysis on silica gel $[\alpha]_{579}^{20}$ −6,9°; *c* 1,7, diethyl ether and hydrolysis in D_2O $[\alpha]_{579}^{20}$ −7.09; *c* 2,8, diethyl ether).

The same procedure was used for alkylations with the other halides.

When the potassium t-butoxide was used as base it was prepared by addition of t-butyl alcohol (0.74 g, 10 mmol) dissolved in ether (1 cm³), either to potassium amide containing the iron salt or to a blue solution of potassium metal without any iron salt.

The mixture of the two diastereoisomers of aminonitrile (4) was characterized by the n.m.r. spectrum: δ 7.2 (5 H, m), 2.25 (6 H, s), 1.91 (1 H, m), 1.26 (10 H, m), 0.93 (3 H, d), and 0.86 (3 H, t). Dimethylbenzamide was identical to an authentic sample.

Attempted N-*alkylation of aminonitrile* (2). After stirring an equimolar mixture of aminonitrile (1.6 g) and 1-methylheptyl iodide (2.4 g) in liquid ammonia for 5 h both reagents were recovered unchanged.

Deuterolysis of the aminonitrile (4). Aminonitrile (4) (1.7 g, 7 mmol) was stirred for 30 min at room temperature in a solution of 0.5N-silver nitrate in D_2O (12.5 cm³), THF (25 cm³), and diethyl ether (12.5 cm³). 1-Methylheptyl phenyl ketone (5) was extracted, dried, and purified by t.l.c. with pentane–ethyl acetate (85 : 15). Any deuterium incorporation in the ketone would not be detected by mass spectrometry: the ratio of the peaks with *m/e* 134 and 135 was the same as in an undeuteriated sample. One sample of aminonitrile (4) was divided in two parts: one part was partially hydrolysed for 5 min, the other for 1 h. The samples of ketone recovered from the two experiments had the same optical rotations.

Determination of the Optical Rotations and of the Enantiomeric Excess of Reagents and Products.—Rotations were determined at 20° in a thermostatted cell (1 dm) using a Perkin-Elmer 141M polarimeter; the purities of samples were checked by g.l.c. and t.l.c. The rotations were measured in $CHCl_3$ for the 1-methylheptyl halides and in diethyl ether for the ketone (5) (as previously reported [13]). The crude ketone (5) was transformed into the carbinol (7) by a known procedure and the rotation was measured in benzene solution.[14] We also checked for the absence of special concentration effects on the measured rotations. The reported values were calculated not only from the α values reported in the Table but also from the rotations measured at several wavelengths (589, 579, and 546 nm).

Acknowledgement

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