107. S_N2 Reactions with Carboxylic Esters. Selective Cleavage of Methyl Esters

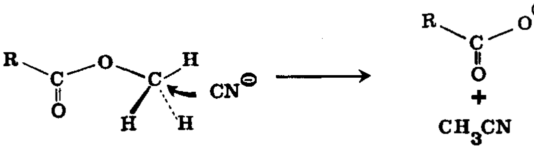
by **Paul Müller** and **Bernard Siegfried**

Département de Chimie Organique, Université de Genève,
30, quai de l'Ecole-de-Médecine, 1211 Genève 4

(14. III. 74)

Summary. Sodium cyanide in hexamethylphosphoric triamide selectively cleaves methyl esters in the presence of ethyl esters with yields of *ca.* 80%. The mechanism of the reaction has been investigated. It consists of nucleophilic displacement by cyanide of the carboxylate ion from the alcohol carbon atom ($B_{Al}2$ mechanism).

In our previous communications on nucleophilic substitutions in dipolar aprotic solvents we have reported the effects of solvent, anion and cation variation on the substitution rates of halide ions with methyl and ethyl tosylate [1]. In the combination of sodium cyanide with hexamethylphosphoric triamide (HMPT) we found a system in which bimolecular nucleophilic substitution reactions proceed at such high rates that carboxylic esters are cleaved at moderately high temperatures [2], presumably via the $B_{Al}2$ [3] mechanism, that is, displacement of carboxylate by attack of the cyanide on the alcohol carbon atom.

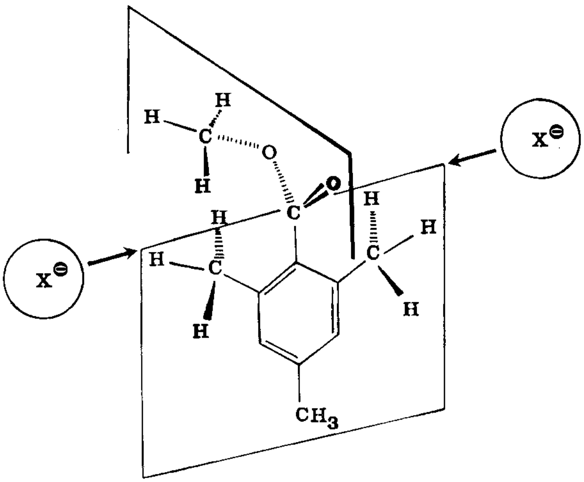


In this paper we report the preparative application of our system towards the cleavage of esters of aromatic and aliphatic acids. In the second part we discuss mechanistic aspects of the reaction.

Competition Experiments. – The methyl ester of 2-benzylcyclopentanone 2-carboxylic acid is 72 times more reactive than the corresponding ethyl ester [2]. We hoped to take advantage of this rate difference to effect selective cleavage of methyl in the presence of ethyl esters.

We carried out competition experiments between methyl and ethyl esters of different acids in order to obtain an objective measure of the methyl selectivity of the system. As a first example the pair methyl mesitoate and ethyl benzoate was investigated.

The use of methyl mesitoate is interesting for two reasons. Esters of mesitoic acid may not be hydrolyzed by nucleophilic attack on the carboxyl group because of steric interference of the *o*-methyl substituents with the entering nucleophile [4]. The cleavage of this substrate may therefore be used as evidence for the $B_{Al}2$ mecha-



nism (see below). The absence of attack on the carboxyl group suppresses at the same time any possible interchange of ester groups according to *Scheme 1*, which would be detrimental to the selective ester cleavage.

Scheme 1

$$R^1COOE^1 + X^- \rightleftarrows R^1COX + E^1O^-$$

$$R^2COOE^2 + E^1O^- \rightleftarrows R^2COOE^1 + E^2O^-$$

$$R^1COOE^1 + E^2O^- \rightleftarrows R^1COOE^2 + E^1O^-$$

The results of the competition experiments are summarized in Table 1. An 1:1 mixture of methyl mesitoate (5.6 mmol) and ethyl benzoate (5.8 mmol) upon treatment with sodium cyanide (5.9 mmol) in HMPT for 24 hours/75° afforded mesitoic acid (85%), unreacted methyl mesitoate (9%) and unreacted ethyl benzoate (93%) [2]. No benzoic acid could be detected. Under similar conditions (Table) a mixture of methyl benzoate and ethylphenyl acetate yielded 77–92% benzoic acid, contaminated in one case with phenylacetic acid (3%). Similar results were obtained with ethyl benzoate and methyl phenylacetate. However, in this case the recovered ester contained 8% ethylphenyl acetate (calculated with respect to phenylacetic ester). The amount of cleavage of ethylester is at least in two cases higher than would be predicted from the kinetic methyl/ethyl rate ratio of 144 (see below). It could be due to partial hydrolysis in the work up or to carbonyl attack by the cyanide. The latter hypothesis is supported by the observation of ester interchange in the experiment with methylphenyl acetate and ethyl benzoate.

Application of sodium cyanide/HMPT to the cleavage of mixed dicarboxylic esters should give even better results than the competition experiments. The carboxylate anion derived from methyl ester cleavage should shield the molecule from attack by a second nucleophile because of electrostatic repulsions. Depending upon the proximity of the carboxyl groups and the transmittance of electronic effects within the molecule, this will result in reduced reactivity of the monoanion. For

Table 1. *Selective Cleavage of Methyl Esters in HMPT/75°C*

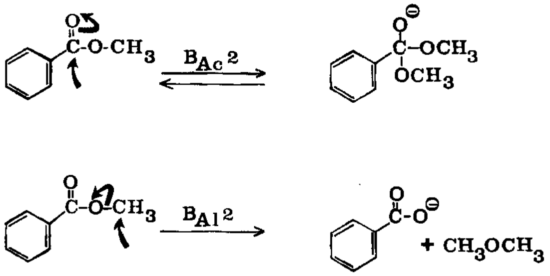
Methyl ester mmol	Ethyl ester mmol	NaCN mmol	Time h.	Acid isolated	Methyl ester recovered	Ethyl ester recovered
Mesitoic 5.6	Benzoic 5.8	5.9	24	Mesitoic a) 85% Benzoic 0%	Mesitoic b) 9%	Benzoic b) 93%
Benzoic 10	Phenylacetic 10	10	40	Benzoic f) 92% Phenylacetic f) 2%	Benzoic 2%	Phenylacetic 85%
Benzoic 10.1	Phenylacetic 10.7	14.8	24	Benzoic c) 77% Phenylacetic c) 3%	Benzoic d) 15%	Phenylacetic d) 79%
Phenylacetic 10.2	Benzoic 10.1	11.1	24	Benzoic 0% Phenylacetic 76%	Phenylacetic e) 13%	Benzoic e) 92% Phenylacetic e) 8%

a) Yields of isolated product with respect to the corresponding ester weighed in.
b) c) d) e) f) Not separated.

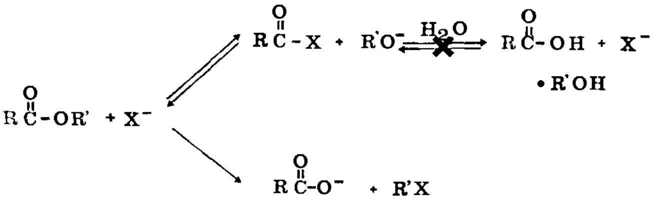
example the σ value of the carboxylate group in the monoanion of phthalic ester is 0.34 units less than that of the corresponding ester. With a ϱ value of 1.75 for the reaction (see below) this corresponds to a factor of 4 in rates between diester and monoanion.

Mechanistic Aspects. – The $B_{Al}2$ mechanism for ester cleavage is very rarely observed. In aqueous media there are only two esters known which hydrolyze by this route, namely β-propiolactones [5] and 2,6-di-*t*-butylmethyl benzoate [6]. In the first case attack on the β carbon atom allows better release of ring strain than does attack on the carboxyl group. In the second example the carbonyl attack is entirely blocked by the bulky *o*-*t*-butyl substituents. Most ester hydrolyses, however, proceed by the well-known $B_{Ac}2$ or $A_{Ac}2$ mechanisms in which the acyl oxygen bond is broken.

The $B_{Al}2$ mechanism is observed if the other possible mechanisms are blocked or made unproductive. In a classical experiment *Bunnet* [7] "forced" the reaction be-



tween sodium methoxide and methyl benzoate in methanol to proceed via the $B_{Al}2$ pathway. Breakdown of the tetrahedral intermediate formed from the addition of methoxide on the carboxyl group yields only the starting materials. However, attack on the alcohol carbon atom leads to the formation of new products, namely dimethyl ether and benzoate ion. The various methods of halolytic ester cleavage which are based on the pioneering work of *Taschner* & *Liberek* [8], *Cherbuliez* [9], and in particular *Eschenmoser* [10], use a similar approach. By transfering the reaction into an aprotic solvent such as pyridine or DMF it is possible to make carbonyl attack a non-productive pathway. Attack of a halide ion on the carboxyl group results in the formation of an acyl halide. This intermediate would be readily hydrolyzed in the presence of water; however, in the absence of water it is forced to return to starting materials, so that the less favourable reaction, that is attack on the alcohol carbonatom, predominates. The cyanide/HMPT system is another application of this principle. The reaction is entirely analogous to that described by *Eschenmoser*, and the mechanism is the same.



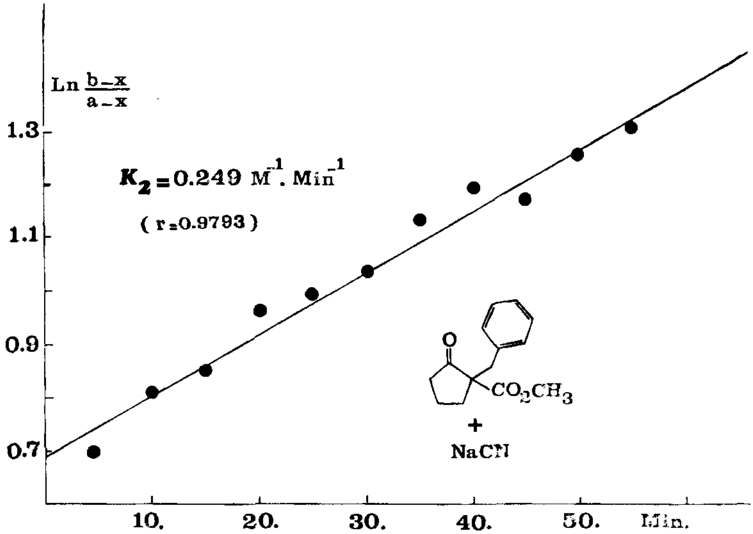


Fig. 1. *Reaction of sodium cyanide with 2-benzyl-2-carbomethoxycyclopentanone in HMPT/75°.*
Sample run second-order conditions
$[NaCN]_0 = 0.113\,M$; $[Ester]_0 = 0.0627\,M$

---

[1] The change in the methyl/ethyl rate ratio could be due to a «looser» transition state [12] for the better leaving group, 2-benzylcyclopentanone 2-carboxylate.

Kinetic studies have been performed under second-order conditions with 2-benzylcyclopentanone 2-carboxylic esters [2] at 75°. The reaction follows second-order kinetics (Fig. 1). The methyl ester is more reactive than the ethylester by a factor of 72.

Similar results were obtained from kinetic studies under pseudo first-order conditions with excess sodium cyanide and esters of substituted benzoic acids (Fig. 2). The results are summarized in Table 2. The methyl/ethyl rate ratio in this system was 144, twice as high as with 2-benzylcyclopentanone 2-carboxylate1).

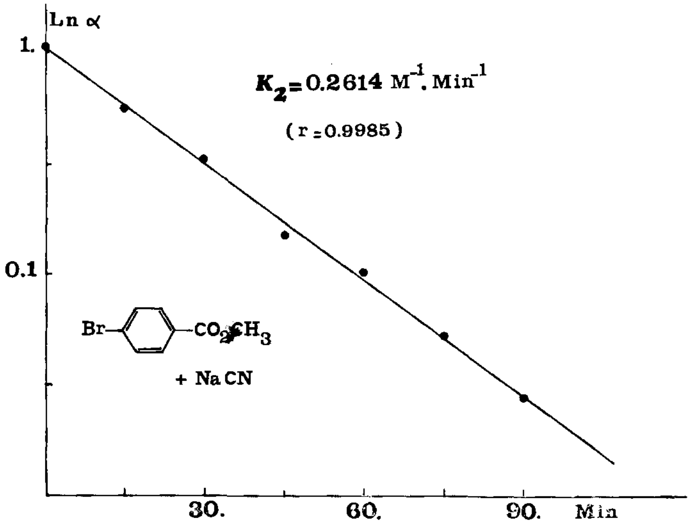


Fig. 2. *Reaction of sodium cyanide with* p-*bromo-methyl benzoate in HMPT/75°*. Sample run pseudo first-order conditions

$[NaCN] = 0.155\,\text{M};\ [Ester]_0 = 1.69 \times 10^{-2}\,\text{M}$

Table 2. *Rate constants for the reaction* $R^1COOR^2 + NaCN$ *in HMPT/75°C*

R^1	R^2	σ_p [13]	$k_2 \times 10^2$ M^{-1} min^{-1}	Standard deviation for k_2
p-OCH$_3$-∅	CH$_3$	−0.268	2.40	0.07
p-CH$_3$-∅	CH$_3$	−0.170	3.92	0.08
∅	CH$_3$	0.0	7.07	0.21
p-F-∅	CH$_3$	0.062	9.79	0.29
p-Cl-∅	CH$_3$	0.227	18.19	0.41
p-Br-∅	CH$_3$	0.232	26.14	1.04
p-CF$_3$-∅	CH$_3$	0.532	78.35	3.91
p-CN-∅	CH$_3$	0.674	79.14	4.74
∅	C$_2$H$_5$	–	4.91×10^{-2}	0.14×10^{-2}
∅-CH$_2$	CH$_3$	–	2.35	0.06
2-benzylcyclopentanone-2-yl	CH$_3$	–	24.90	0.59
CH$_3$(CH$_2$)$_4$	CH$_3$	–	0.395	0.012

The methyl/ethyl rate ratio is in agreement with the proposed $B_{Al}2$ mechanism. The fact that methyl esters are more reactive than ethyl esters has been previously observed by *Taschner* & *Liberek* in the lithium iodide/pyridine system [8]. The ratio is in the range commonly observed for S_N2 reactions [11]. The proposed mechanism is further supported by the isolation of acetonitrile from cleavage of 2-methyl-2-carbomethoxycyclopentanone [2], and by the selective cleavage of methylmesitoate in the presence of ethyl benzoate. *Eschenmoser* has already pointed out the absence of steric hindrance in the cleavage of methyl esters of tertiary carboxylic acid by lithium iodide in collidine [10], and he arrived at the same mechanistic conclusion.

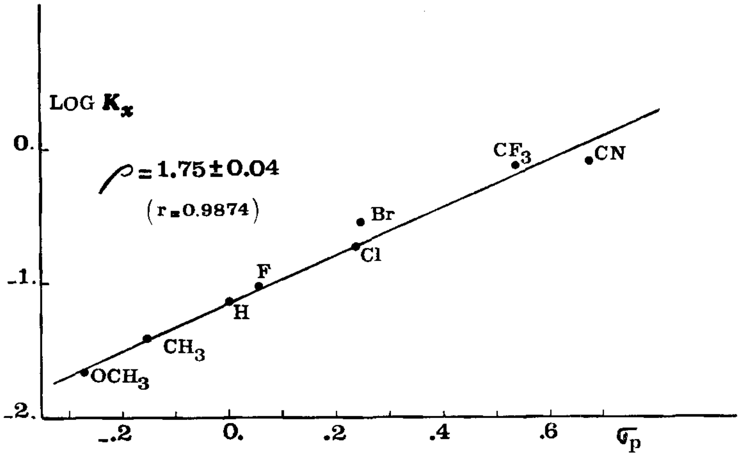


Fig. 3. *Plot of log* k *against* Hammett's *σ constants*

A plot of the rate constants of the substituted methyl benzoates with sodium cyanide (Fig. 3) against *Hammett's* [13] σ constants gives a straight line with a slope of 1.75, considerably lower than is observed in the basic hydrolysis of methyl esters ($\varrho \cong 2.4$) [14]. This could be explained by the increased distance between the reaction center and by the better charge delocalization in the developing carboxylate in comparison with the developing alkoxide during basic hydrolysis. Substitution reactions between benzyl tosylate and halide ions in DMF have a ϱ value of 1.88 [15] A correlation of the pertinent rate constants wih *Taft's* σ* values yields a straight line with a slope of *ca.* 1.5, which demonstrates the decreased reactivity of esters of aliphatic as compared to aromatic esters.

We thank the *Fonds National Suisse de la Recherche Scientifique* for financial support in the early stages of this work.

Experimental Part

Materials. Hexamethyl phosphoric triamide (*Fluka*) was refluxed with phosphorous pentoxide and distilled. A second distillation from calcium hydride under nitrogen atmosphere afforded HMPT without water or dimethyl amine. The solvent was stored over molecular sieves (4Å) and used within one week after purification. Sodium cyanide (*Merck*) was dried for one day at 200°/10 Torr. The pure substituted methyl benzoates (*Fluka*) were purified by recrystallization or distillation. The *p*-trifluoromethyl, *p*-cyano and *p*-fluoromethyl benzoates were prepared by refluxing the corresponding acids in methanol containing a catalytic amount of sulfuric acid. The purity was confirmed by physical and spectral data.

Kinetic measurements. Pseudo first-order conditions. In a typical kinetic study 400–600 mg of sodium cyanide was dissolved in a 50 ml volumetric flask (0.16–0.24 M). 100–150 mg of the ester (0.01 M–0.02 M) and 100 mg of internal standard (0.01 M) (naphthalene or tetradecane) were weighed in a three-neck flask equipped with condenser and a magnetic stirrer. The system was kept under a nitrogen atmosphere. At the start of the reaction the solution of sodium cyanide thermostated to 75° ± 0.02° was poured into the three-neck flask. At appropriate time intervals a three-ml sample was removed with a syringe and transferred to a separating funnel containing 100 ml of water and 50 ml of diethyl ether. After strong shaking the organic layer was washed with 100 ml of water and then dried over 1 g of magnesium sulfate. After 10 min. the magnesium sulfate was filtered and the solution was concentrated to 2–3 ml using a rotatory evaporator without vacuum. A sample of 2 μl was injected in a *Perkin-Elmer* VPC model 990, coupled with a digital integrator (*Infotronics* Model CRS 208). A 4% SE 30 on chromosorb column of 2.5 m was used for all the esters, except *p*-fluoro- and *p*-trifluoromethyl-benzoate, at 150–180° with a helium flow of 80 ml/min. For the other esters a carbowax 20 M on chromosorb column, thermostated at 140–165° was used. Integrations were carried out in triplicate (maximum deviation 1%). Plots of the log of α_t with

$$\alpha_t = \frac{\text{area of unreacted ester}}{\text{area of internal standard}}$$

gave excellent straight lines to at least 3 half-lives. The slope (which equals k_{obs}) was determined by leaat-squares analysis with a computer programme. The correlation coefficients were in all cases higher than 0.99. Second order rate constants were obtained by dividing k_{obs} by the corresponding salt concentration. The rate constants in Table 2 are averages of at least 3 runs with a standard deviation of 2 to 5% of the means.

Second-order conditions. The stock solutions of nucleophile (0.11–0.12 M) in 100 ml of dry HMPT under nitrogen atmosphere were thermostated at 75 ± 0.02° in a *Lauda* NBS thermostat. At time zero, 1 ml of ester solution (0.05–0.06 M) in HMPT was introduced with a syringe and the solution was continually stirred. At appropriate time intervals a 5 ml sample was removed, quenched with 100 ml of water and extracted with 50 ml of pentane. The organic layer was washed with 100 ml of water. After drying with magnesium sulfate, the pentane was removed on a rotatory evaporator at 45° without vacuum, and a sample was taken up in 0.5 ml carbon tetrachloride for NMR analysis. The unreacted methylester was determined by measuring the NMR. signals for the methyl group ($\tau = 6.35$ ppm) of the ester with respect to the signal of the aromatic protons ($\tau = 2.9$ ppm) on a *Perkin-Elmer* R12 instrument. For each sample five integrations were taken which gave a mean value with an error of ± 5%. Rate constants were obtained from the equation (1)

$$k_2 = \frac{1}{t\,(a-b)} \ln \frac{b\,(b-x)}{a\,(a-x)} \tag{1}$$

with a and b representing the initial concentrations of esters and nucleophiles respectively and x the concentration of nucleophile at time t. A plot of ln b–x/a–x versus time gave good straight lines with a slope of k_2 (a–b) (Fig. 1). Correlation coefficients calculated by a least squares treatment[2]) were around 0.99. Rate constants obtained directly from eq (1) agreed with those calculated by the least squares treatment within 5%.

BIBLIOGRAPHY

[1] *P. Müller & B. Siegfried*, Helv. *55*, 2965 (1972).
[2] *P. Müller & B. Siegfried*, Tetrahedron Letters 3565 (1973).
[3] *C. K. Ingold* "Structure and Mechanism in Organic Chemistry", 2nd Ed., Cornell University Press, Ithaca, N.Y. (1969) p. 1142.
[4] *H. L. Goering, T. Rubin, M. S. Newman*, J. Amer. chem. Soc. *76*, 787 (1954).

---

[2]) We thank *J.-C. Perlberger* for the computer programme.

[5] *A. R. Olson & R. J. Miller*, J. Amer. chem. Soc. *60*, 2690 (1938).
[6] *L. R. Barclay, N. D. Hall & G. A. Cooke*, Can. J. Chemistry *40*, 1981 (1962).
[7] *J. F. Bunnet, M. M. Robison & F. C. Pennington*, J. Amer. chem. Soc. *72*, 2378 (1950).
[8] *E. Taschner & B. Liberek*, Roczniki Chem. *30*, 323 (1956).
[9] *E. Cherbulliez, J. P. Leber & M. Bouvier*, Helv. *36*, 1203 (1953).
[10] *F. Elsinger, J. Schreiber & A. Eschenmoser*, Helv. *43*, 113 (1960).
[11] *C. K. Ingold* "Structure and Mechanism in Organic Chemistry», 2nd Ed., Cornell University Press, Ithaca, N.Y. (1969).
[12] *E. C. F. Ko & A. J. Parker*, J. Amer. chem. Soc. *90*, 6447 (1968).
[13] *D. H. McDaniel & H. L. Brown*, J. org. Chemistry *23*, 420 (1958).
[14] a) *H. H. Jaffé*, Chem. Rev. *53*, 191 (1953); b) *H. van Bekkum, P. E. Verkade & B. M. Wepster*, Rec. Trav. chim. Pays Bas *78*, 815 (1959).
[15] *J. Delhoste*, Bull. Soc. chim. France, 133 (1974).

---

108. Photoelectron Spectroscopy of *peri*-Amino Naphthalenes

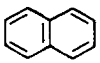
by **John P. Maier**

Physikalisch-Chemisches Institut der Universität Basel

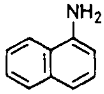
(16 XI. 73)

Summary. The He I photoelectron spectra of *peri*-amino and dimethylamino naphthalenes are presented. The differences in the ionization energies of the π-bands are interpreted by separation of the perturbation of the amino substituent into an inductive destabilization and conjugative stabilization. This affords the assignment of the photoelectron bands of ionization energies below 11 eV and an estimation of the dihedral angle in the *peri*-dimethylamino derivatives. The data on the *peri*-amino naphthalenes indicate some angular distortion in contrast to 2-aminonaphthalene.

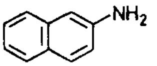
Introduction. – *peri*-Substituted naphthalenes provide an example of molecules where intramolecular crowding can be considerable. The proximity of the *peri*-substituents (*i.e.* 1,8 positions) often results in unique physicochemical properties [1]. For example, 1,8-bis(dimethylamino)naphthalene (**8**) has been found to have an abnormally high basicity, $pK_a = 12.34$ [2], which has been associated with relief, of steric strain and of nitrogen lone-pairs interactions, on protonation.



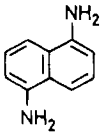
1



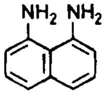
2



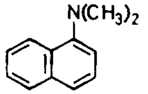
3



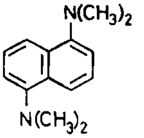
4



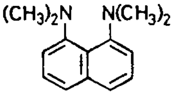
5



6



7



8