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Ozonation of Carbodiimides

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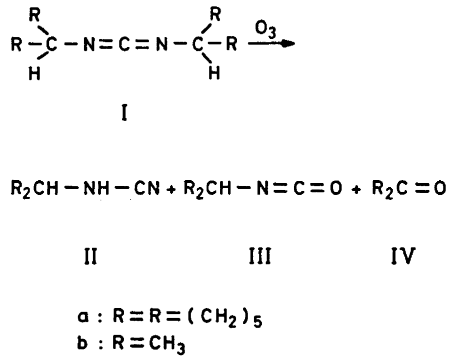
A series of *N,N′*-disubstituted carbodiimides has been ozonized. Ozone consumption was not quantitative, but gradually two mol equivalents could be absorbed. Main products from the reactions were the correspondingly substituted ketones, isocyanates, cyanamides, and molecular oxygen. Minor amounts of nitrocyclohexane, *N,N′*-dicyclohexyl urea, and carbon dioxide were obtained from *N,N′*-dicyclohexyl carbodiimide, and unidentified peroxy functions were observed to an extent of 10 – 15 % from all carbodiimides. As the products indicate both carbon-nitrogen single and double bond cleavage, different reaction paths are incorporated in the proposed reaction scheme.

The reaction of cumulated unsaturated three-atom systems with ozone has not been studied extensively until recently. Ketenes yielded α-lactones as primary products,[1] simple allenes have been shown to give ozonolytic products, *viz.* carbonyl compounds and carbon monoxide,[2] sterically hindered allenes gave in addition products where the carbon-carbon bonds in the allene systems are intact.[3,4] Recently, a report has appeared that shows that ketenimines (both simple and sterically hindered) yielded cleavage products (carbonyl fragments and isocyanides) with no sign of compounds with the carbon chain intact.[5] The present paper will deal with the reaction of ozone with carbodiimides and since the last possible three-atom heterocumulene, an isocyanate, is shown to be a product, its reaction with ozone is touched upon.

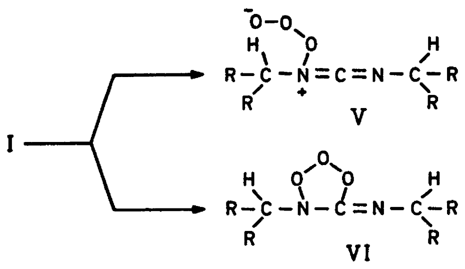
The main products from the ozonation of carbodiimides (I) (of which *N,N′*-dicyclohexyl and *N,N′*-diisopropyl carbodiimides are studied most extensively) are alkyl cyanamides (II), isocyanates (III), carbonyl compounds (IV), and molecular oxygen (Table 1).



Scheme 1.

It is obvious that the observed products must originate from more than one reaction path. Stoichiometrically, it seems reasonable that the cyanamides and the carbonyl compounds are formed in one of these paths, while the isocyanates must have been formed in another reaction.

In one of the most frequent utilizations of carbodiimides, *viz.* the formation of peptide bonds, Khorana [6] suggests a mechanism starting with a nucleophilic attack of a carboxylate



Scheme 2.

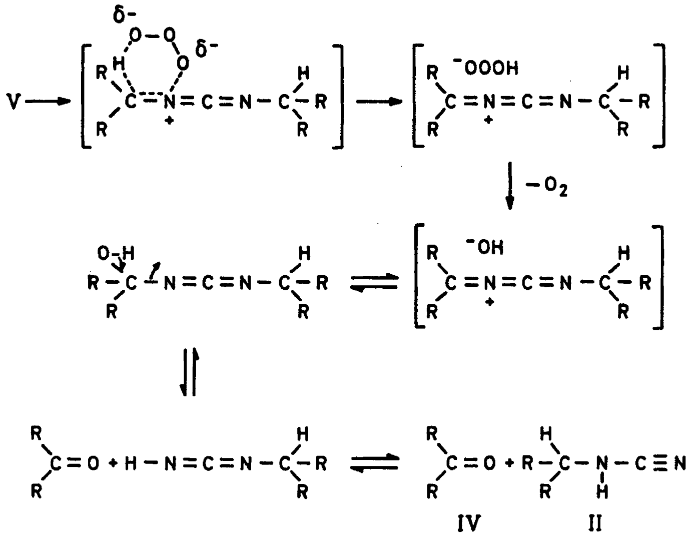
Table 1. Ozonation of *N*,*N'*-dialkyl carbodiimides $R_2CH-N=C=N-CHR_2$.

	$R+R=(CH_2)_5$					R = Me		
	GLC[a]	MeOAc		CCl_4		GLC[a]	$(COOEt)_2$	
Compound [b]	Column	Found mM	Calc.[b] mM	Found mM	Calc.[b] mM	Column	Found mM	Calc.[b] mM
Starting material (x)	A	7.5	6.1	7.9	6.8	B,C	1.9	1.6
O_3 consumed (y)		11.0	7.3	9.0	8.1		2.0	2.2
O_2 evolved (z)		7.5	5.2	6.3	6.2		1.7	1.6
R_2CO(u)	A,B	3.0	3.4	4.6	4.8	B,C	1.2	1.3
$R_2CHNHCN$ (a)	D	2.8		4.3		D	1.0	
R_2CHNCO (b)	A,B	1.0		0.8		B,C	0.3	
R_2CHNO_2 (c)	A,B	0.4		0.3			0	
Peroxy comp. (d)		1.5		1.4			0.3	
Urea (e)		0.8		0.3			0	
$a+b+d+e$		6.1		6.8			1.6	
CO_2		0.2 – 0.3		n.c.[c]			n.c[c]	

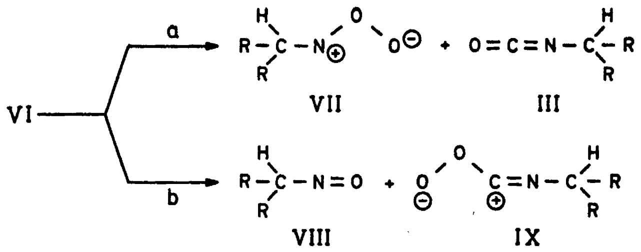
[a]See experimental section for description. [b]See Scheme 7. [c]Not checked.

anion on the central carbon atom, true enough, after activating this position by protonation of one of the imide nitrogen atoms. This indicates that ozone, whose ability to react only as an electrophile is no more questioned, will approach the carbodiimide function at the lone pair of one of the nitrogen atoms. The next step of the reaction may then be the formation of an adduct V or a five membered ring VI (Scheme 2).

There seems to be no way to distinguish between this description of the early phase of the reaction and the π-complex theory very well substantiated by Bailey [7] for the olefinic double bond-ozone reaction except that one emotionally would prefer the first explanation when the more polar carbon-nitrogen double bond is approached by ozone. However, at this point the problem seems more semantic in nature. More important is the further fate of the carbodiimide-ozone primary adducts.



Scheme 3.

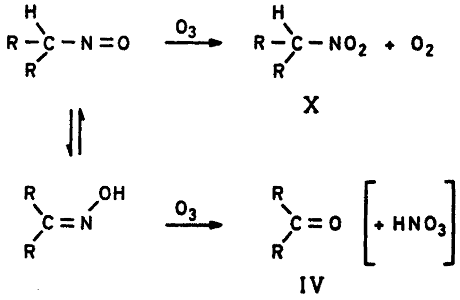


Scheme 4.

In adduct V the relative strength of the nitrogen – oxygen *versus* the oxygen-oxygen bond is of considerable importance. As discussed earlier[8] this should depend on the basicity of the nitrogen atom. As this must be rather low in carbodiimides the strength of the nitrogen-oxygen bond is rather weak, but strong enough to weaken the α-carbon-hydrogen bond (Scheme 3).

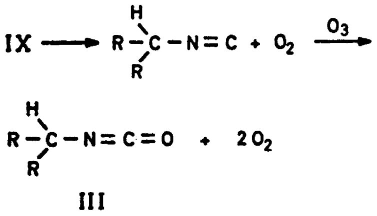
The first two equilibria involved are analogous to those in the Mannich reaction. Monosubstituted carbodiimides are unstable relative to their tautomers, the cyanamides.[9] As seen from Table 1, the yields of ketones IV are somewhat higher than those of the cyanamides II. Since the cyanamides are found rather unreactive towards ozone compared to the carbodiimides and since the other reaction path primarily involves the carbon-nitrogen double bond forming intermediate VI, analogous to the one proposed for ozonolysis of simple allenes, the excess of ketones IV must have been formed through extensive rearrangement of VI or through secondary reaction of some primary products with ozone. The latter reaction is obvious from the amount of ozone absorbed in reaction. In principle, intermediate VI could break down in two ways (Scheme 4).

An entity like VII would most likely rearrange to the corresponding nitro compound. Thus, one should expect path *a* to give equal amounts of isocyanates and nitro compounds, which is not observed. On the other hand, if path *b* is preferred several things may happen. Firstly, nitroso compounds should react with ozone to give nitro-compounds. In addition they rearrange easily to oximes (provided an α-hydrogen is available) which again react easily with ozone with good yields of correspondingly substituted carbonyl compounds.[10] (Scheme 5).



Scheme 5.

Path *b* is analogoues to the main reaction way proposed for simple allenes,[2] but a similar breakup of intermediate IX to give nitroso compound VIII and carbon monoxide does not take place, as the latter is not a reaction product. However, IX may give molecular oxygen and isonitriles, which upon ozonation give good yields of isocyanates[11] (Scheme 6).

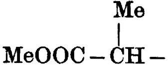


Scheme 6.

The existence of the all-carbon analogue of IX is indicated very strongly by Hartzler[12] by observing the formation of an α-hydroxy ester by ozonolysis of an allene in ethanol.

None of the reaction paths so far proposed do explain the formation of 4 – 10 % disubstituted ureas. This would necessitate the presence of

Table 2. Reactivity of carbodiimides $R_1-N=C=N-R_2$ with ozone.[a]

	R_1	R_2	Consumed O_3 (mmol)	NMR-position of α-hydrogen[b]
1.	*t*-Bu	*t*-Bu	1.6	–
2.	*t*-Bu	Me	2.2	2.92
3.	*t*-Bu	Et	3.3	3.20
4.	*t*-Bu	i-Prop.	6.7	3.48
5.	*t*-Bu	 $\mathrm{MeOOC-\overset{\overset{\textstyle Me}{|}}{C}H-}$	5.6	3.87
6.	i-Prop.	i-Prop.	7.9	3.47
7.	Cyclohexyl	Cyclohexyl	10.6	3.1

[a] 10 mmol carbodiimide dissolved in 25 ml MeOAc, 18 mmol O_3 passed through the solution at −40°C. [b] Chemical shift in ppm (δ-values in CCl_4) relative to tetramethylsilane.

water and/or acids, and as the solvents used were carefully predried, these reagents must have been formed during ozonation. As mentioned above, the ozone absorption is not quantitative and as ethyl acetate is found to yield carboxylic acids upon ozonation,[13] urea formation in this solvent is understandable. Oxidation of carbon tetrachloride by ozone should not give any hydrogen-containing species capable of initiating urea formation.[6] However, the nitric acid formed (Scheme 5) may be responsible for the urea in this solvent.

From Table 1 it can be seen that the reaction path outlined in Scheme 3 is more important than any other. Thus factors influencing the rate of this reaction, may have great effect on the ozone consumption. In fact, *N,N′*-di-*tert*-butyl carbodiimide, where no α-hydrogen is available reacts very sluggishly with ozone and no cyanamide is detected. A further comparison of reactivity of several carbodiimides towards ozone is given in Table 2.

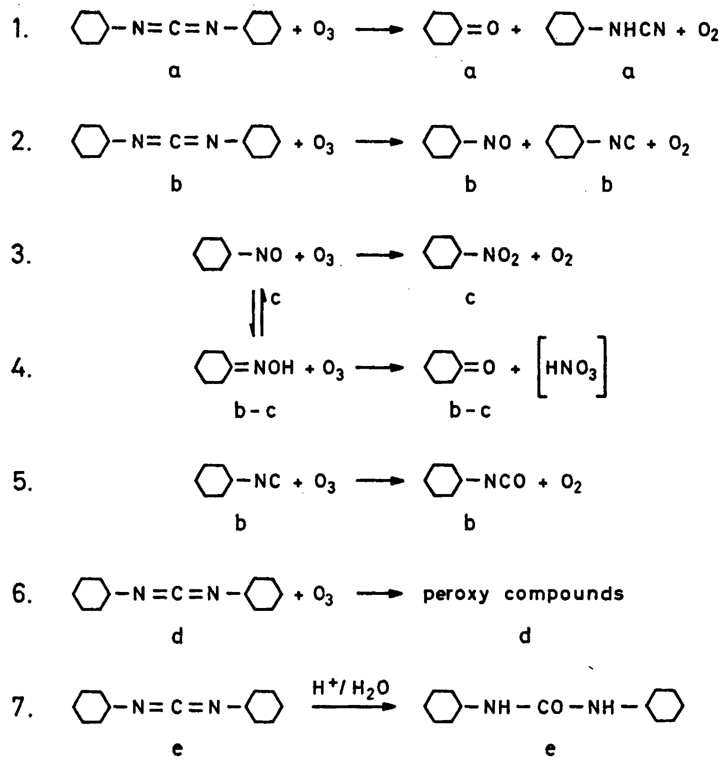
The first four entries in Table 2 show that decreased electron density at the α-hydrogen (as indicated by their resonance position in NMR) is linked in a qualitative manner to the ozone absorption. The increase in reactivity going from compound 4 to 6 merely reflects that there are two α-hydrogens in 6. That compound 5, having the α-hydrogen with lowest electron density, reacts slower than 4, must mean that the primary attack on the nitrogen lone-pair is reduced inductively by the ester group. Why compound 7 should react faster than 6 is not easy to explain. Steric effects may come into play here.

The apparent discrepancy in the amounts of ozone used and oxygen produced compared to consumption of starting material when ozonizing in methyl acetate (Table 1) is probably due to reaction with the solvent. This reaction, however, cannot be solely responsible for the peroxidic content (~20 %) as this is found to be of same order of magnitude in carbon tetrachloride where solvent attack is normally considered slow. Treatment of the ozonized solution with triphenyl phosphine did not increase the amount of any of the compounds in Table 1, although triphenyl phosphine oxide was formed to the same extent as the peroxidic content. This indicates severe breakdown of some species to lower molecular weight peroxy compounds.

A summary of the reaction schemes is given in Scheme 7 (using *N,N′*-dicyclohexyl carbodiimide as an example.

From these sequences can be obtained:
Consumed starting material: $x=a+b+d+e$
Consumed ozone: $y=a+b+c+(b-c)+b+d$
Production of oxygen: $z=a+b+c+b$
Produced cyclohexanone: $u=a+(b-c)$
where a is the yield of cyanamide, b the yield of isocyanate, c the yield of nitro compound, d the total peroxydic content, and e the yield of urea. The results are entered in Table 1.

Examination of the figures in Table 1 indicates that only 80–85 % of the starting materials have been accounted for (including unknown peroxy compounds). Some of this discrepancy may be due to systematic errors in the analytical procedures used. However, as such error may go both ways, the actual reasons must be sought elsewhere. The authors feel that the real causes



Scheme 7.

may be twofold. Firstly, the ozone reactions with the starting materials are not quantitative. Thus primary products may react further at rates comparable with those of the primary reaction; secondary reaction that it not accounted for by the postulated reaction schemes. Even secondary reaction products may react with ozone, being a powerful oxidizing agent, to give low volatility products not separable in GLC from solvent peaks. Secondly, some of the reaction products, *viz.* the cyanamides and the isocyanates are known to dimerize and, indeed, in some cases, especially using copper columns both dimers and trimers of cyanamides were formed in the gas chromatograph detected on a combination instrument GLC – MS. If further oligomerization were to take place during ozonization, they might be of too low volatility to be detected. In view of these analytical difficulties, the authors feel confident that the present results give a fairly good description of the reaction of carbodiimides with ozone.

EXPERIMENTAL

General. The ozone source was a Welsbach T23 Ozone Generator giving 0.77 – 0.80 mmol ozone/min. Oxygen analyses were performed using a Beckman F3 oxygen analyzer as described in the literature.[14]

Gas liquid chromatography (GLC) analyses were performed on Varian Aerograph, model 1520, using column A: 2.4 m × 3 mm copper column with 20 % SE30 on Chromosorb WHMDS (60 – 80 mesh); column B: 2.4 × 3 mm copper column with 10 % PEG 4000 on Chromosorb WHMDS (60 – 80 mesh); column C: 2.4 m × 3 mm copper column with 10 % SE52 on Chromosorb WHMDS (60 – 80 mesh) and on Hewlett-Packard 5700 A, using column D: 4.5 m × 3 mm glass column with 10 % OV17 on Chromosorb WHMDS (60 – 80 mesh). The gas chromatographs were equipped with Disc integrators on the recorder systems for quantitative analyses.

Materials. Solvents used were pure and anhydrous. *N*,*N*′-Dicyclohexyl and *N*,*N*′-diisopropyl carbodiimide were commercially available (Koch-Light Laboratories Ltd. and Aldrich Chem. Co., Inc., respectively) and were distilled prior to use. The other carbodiimides were synthesized according to standard procedures.

The proper isothiocyanates were prepared from the amines,[15] and the disubstituted thioureas were formed on reaction between these isothiocyanates and the proper amines.[16] Treatment of the thiourea with yellow mercuric oxide yielded the carbodiimides.[16]

N-t-*Butyl*-N′-*(1-methoxycarbonyl)ethyl thiourea* was synthesized accordingly from alanine methylester and *t*-butyl isothiocyanate. M.p. 84.0 – 84.5 °C (CCl_4 – pentan), yield 85 %. (Found: C 48.90; H 8.08; N 12.54. Calc. for $C_9H_{18}N_2O_2S$: C 49.51; H 8.31; N 12.83). MS: *m/e* 218 (M+) NMR (δ values, CCl_4): 1.48 (s, 9 H); 1.49 (d, 3 H, $J \sim 8$ Hz), 3.75 (s, 3 H) 5.02 (q, 1 H, $J \sim 8$ Hz) 6.5 – 6.8 (m, broad, 2 H) IR (KBr): 3300 (s), 1740 (s).

N-t-*Butyl*-N′-*(1-methoxycarbonyl)ethyl carbodiimide*. B.p. 92.5 – 93.0 °C/10 mmHg. Yield 85 %. (Found: C 58.16; H 8.62; N 14.98. Calc. for $C_9H_{16}N_2O_2$: C 58.57; H 8.69; N 15.20). MS: *m/e* 184 (M+). NMR (δ values, CCl_4): 1.30 (s, 9 H); 1.40 (d, 3 H, $J \sim 8$ Hz); 3.73 (s, 3 H); 3.87 (q, 1 H, $J \sim 8$ Hz). IR (liq.-film) 2110 (s), 1790 (s).

Standards for GLC, cyanamides,[17] isocyanates,[18] nitro compounds[19] were synthesized according to literature.

Ozonation of carbodiimides. In a typical run, 2.06 g (10 mmol) *N,N′*-dicyclohexyl carbodiimide was dissolved in 25 ml methyl acetate and 18 mmol ozone (with nitrogen as carrier gas[14]) passed through the solution at – 40 °C (ozonation in carbon tetrachloride at 0 °C and in diethyl oxalate at – 40 °C). The exit gases were analyzed for oxygen,[14] carbon monoxide,[2] and carbon dioxide. Approximately 10 mmol of ozone were absorbed by the solution. Qualitative and quantitative analyses were run on GLC (columns and results, Table 1). Urea estimation was done gravimetrically by letting a definite volume of reaction solution stand under dry condition for one week and correcting for estimated solubility. Peroxide contents were determined in a conventional way with sodium iodide in acetonitrile with perchloric acid present or by reaction with triphenyl phosphine to give the phosphine oxide, both estimated quantitatively on Column D.

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