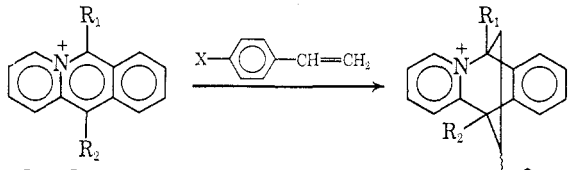
species. Rates of addition of *para*-substituted styrenes to the acridizinium ion follow the inverse electron demand pattern, *p*-nitrostyrene being slowest and *p*-



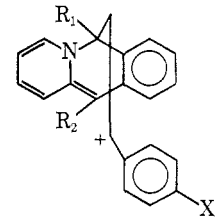
4, $R_1 = R_2 = H$
73, $R_1 = CH_3$; $R_2 = H$
74, $R_1 = H$; $R_2 = CH_3$
75, $R_1 = R_2 = CH_3$

76

methoxystyrene being fastest in the series.

More recently,[50] the effect of the methyl groups at the *meso* positions of the acridizinium ring has been studied. It is known[51] that 9,10-dimethylanthracene reacts with maleic anhydride much more rapidly than does anthracene, and the observation is explicable in terms of electron release. The introduction of a methyl group at the 6 position of the acridizinium ion (**73**) does slow the reaction significantly. On the other hand, introduction of a methyl group into the other *meso* position, position 11 (**74**), results in a greater than tenfold *increase* in the rate of reaction. Reaction rates for the *meso* dimethyl derivative **75** are not as high as for the 11-methyl (**74**) but are significantly higher than for the acridizinium ion (**4**) itself. It is believed that these results can best be rationalized by assuming the intermediacy of a benzyl carbonium ion (**77**) in a reaction which involves two steps.

(50) J. A. Stone, Ph.D. Dissertation, Duke University, 1968.
(51) W. E. Bachmann and M. C. Kloetzel, *J. Am. Chem. Soc.*, **60**, 481 (1938).



77

Reactions of the Benzo[*a*]- and Benzo[*c*]quinolizinium Ions. By comparison with the benzo[*b*]-quinolizinium (acridizinium) ion, very little has been published concerning the chemistry of the angular analogs. The initial paper[22] on the subject of the 7-substituted benzo[*a*]quinolizinium analogs reported that the 7-methyl derivative could be reduced catalytically, presumably to a methylbenzoquinolizidine derivative (**79**), and oxidized by permanganate to phthalic acid.

Richards and Stevens[42] have reported that, on standing in ammonia solution, 7-phenylbenzo[*a*]quinolizinium ion was converted to a pseudo base.

Although preliminary work[52] has been done on the reduction, electrophilic substitution, and ring opening of the benzo[*c*]quinolizinium system, there have as yet been no publications concerning the chemistry of this system.

I wish to acknowledge the support of the National Institutes of Health (National Cancer Institute and National Heart Institute), as well as the support of the National Science Foundation for certain parts of the earlier work in this area.

(52) A. Fozard and C. K. Bradsher, unpublished work.

The Polar Addition of Isocyanates to Carbon–Nitrogen Bonds

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The polar cycloaddition of isocyanates to a great variety of double-bond-containing substrates (dipolarophiles) is an exceedingly useful method of synthesis of heterocyclic molecules.[1] Often one reaction product is obtained in a kinetically controlled reaction, and the reported yields approach theory. However, in the case of slower reacting isocyanates heating is required, which tends to establish thermodynamically controlled equilibria. Some control over the product distribution can be exerted by the choice of reagents and reaction conditions or by removal of lower boiling species from the reaction mixture.

In isocyanates both the C=N and the C=O double bond can participate in polar cycloaddition reactions, but usually reaction products resulting from addition across the C=N double bond are isolated. I have selected the addition of isocyanates to carbon–nitrogen bonds for emphasis in this Account, because the complexities encountered best demonstrate the scope and the limitations of this versatile synthetic method.

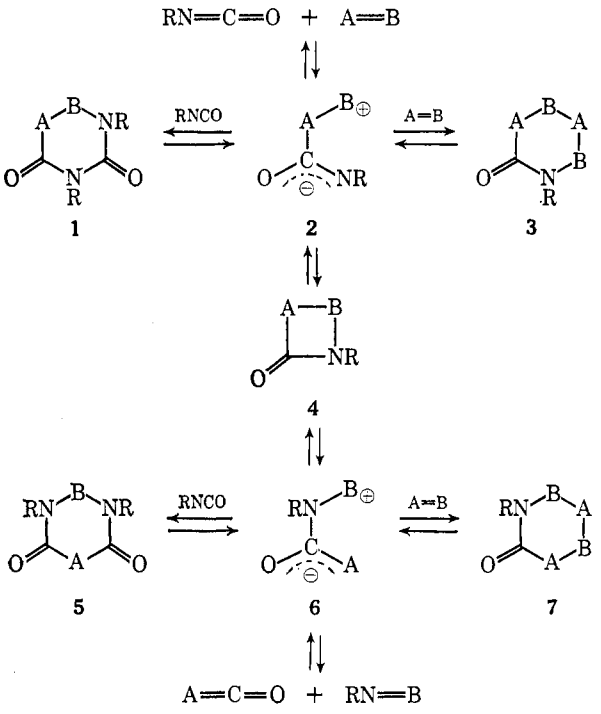
(1) H. Ulrich, "Cycloaddition Reactions of Heterocumulenes," Academic Press, New York, N. Y., 1967, Chapters 1 and 4.

Scope and General Description

The reaction of an isocyanate with a double-bond-containing substrate A=B can occur stepwise or concerted with formation of the cycloadduct **4**, provided **4** is stable under the reaction conditions employed. In stepwise addition an acyclic polar adduct, **2**, is formed, which can be intercepted by either the isocyanate or A=B to yield a six-membered-ring 2:1 adduct,

1 or **3**, again in a stepwise addition sequence. Ring opening of **4** can give rise to the formation of the polar acyclic 1:1 adducts **2** and **6**, and interception of **6** by both substrates (RNCO and A=B) to yield the six-membered-ring 2:1 adducts **5** and **7** can likewise occur. While cycloadducts **3** and **7** are identical, **1** and **5** are different chemical entities (isomers). Fragmentation of **4** (perhaps *via* **6**) gives rise to the formation of two new double-bond-containing substrates A=C=O and RN=B (Scheme I). Of course, dissociation of the six-membered-ring 2:1 cycloadducts can also produce A=C=O and RN=B, but this process occurs only at elevated temperature. The newly generated double-bond-containing substrates can intercept **2** and **6**, and formation of a new set of acyclic 1:1 adducts can be visualized too.

Scheme I

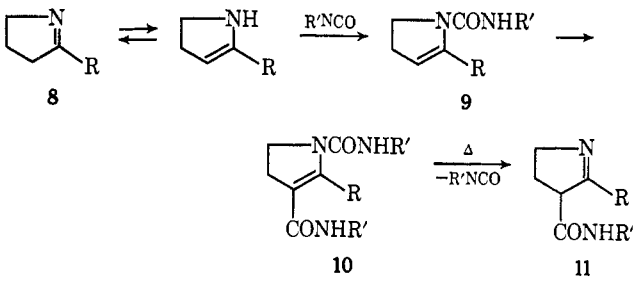


If the lifetime of the initially generated acyclic 1:1 adduct **2** is shorter than the time for rotation around the bond formed, the polar 1,2 cycloaddition is in effect a concerted process. However, the few reported stereospecific cycloaddition reactions of heterocumulenes[2] appear to be exceptions rather than the rule.

The polar 1,4 cycloaddition, which gives rise to the formation of six-membered-ring adducts, proceeds in a stepwise fashion.[3,4] We have recently presented spectral evidence for the formation of an acyclic 1:1 adduct of type **2** in the reaction of arenesulfonyl isocyanates and carbodiimides. A six-membered-ring 1:1:1 adduct derived from the reaction of **2** or **6** with one of the fragmentation products was also isolated in this reaction.[4] The reversibility at elevated temperatures of the processes outlined was perhaps best evidenced in the reaction of N-aryl-N′-dimethylformamidines with aryl isocyanates[5] (see Scheme VI).

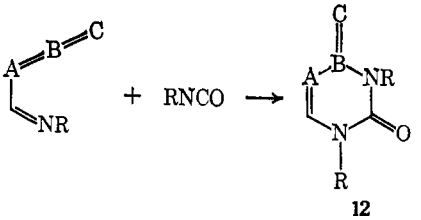
Isolation of the 1,2 cycloadduct **4** is often possible, but mild reaction conditions are essential because of the thermal instability of the four-membered-ring. If a hydrogen substituent is adjacent to the carbonyl function, isomerization of the 1,2 cycloadduct **4** to an acyclic 1:1 adduct can occur.

Scheme II



A completely different reaction pattern emerges if the C=N double bond can be in equilibrium with the corresponding enamine, because addition to the C=C bond becomes competitive. An example of this type of reaction is shown in Scheme II.[6] Here the imine **8** is in equilibrium with the corresponding enamine and the latter undergoes nucleophilic substitution on the nitrogen to generate the enurea derivative **9**. Addition of the isocyanate to the double bond in **9** produces the 2:1 adduct **10**. Heating **10** effects dissociation of the urea function, and the C-substituted cyclic imine **11** is obtained. Thus, if **8** is allowed to react with an isocyanate at an elevated temperature, **11** is the reaction product obtained.

Addition of an isocyanate to a C=N double bond which is adjacent to or part of a cumulative arrangement changes the reaction to a certain degree. For example, if the C=N bond is adjacent to the cumulative double bond system, a Diels–Alder-type 1,4-cycloaddition reaction occurs with formation of the six-membered-ring heterocycle **12** (see also Dimerization of Isocyanates).



If the C=N double bond is part of a cumulative arrangement (isocyanate, carbodiimide, ketenimine), familiar reactions occur which result in the formation

(2) R. Huisgen, L. Feiler, and G. Binsch, *Angew. Chem. Intern. Ed. Engl.*, **3**, 753 (1964); J. C. Martin, V. W. Goodlett, and R. D. Burpitt, *J. Org. Chem.*, **30**, 4309 (1965); F. Effenberger and G. Kiefer, *Angew. Chem.*, **79**, 936 (1967).

(3) R. Huisgen, *ibid*, **80**, 329 (1968); R. Huisgen, M. Morikawa, K. Herbig, and E. Brunn, *Chem. Ber.*, **100**, 1094 (1967).

(4) H. Ulrich, B. Tucker, and A. A. R. Sayigh, *J. Am. Chem. Soc.*, **90**, 528 (1968).

(5) H. Ulrich, B. Tucker, F. A. Stuber, and A. A. R. Sayigh, *J. Org. Chem.*, **33**, 3928 (1968).

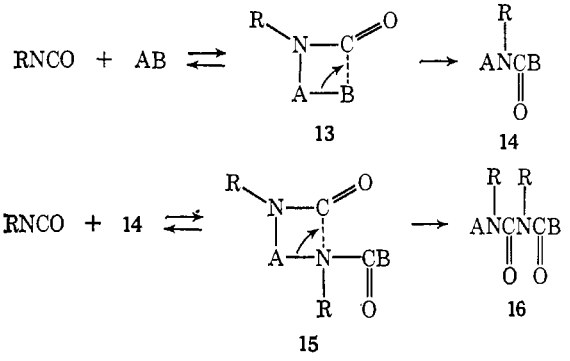
(6) S. J. Love and J. A. Moore, *ibid.*, **33**, 2361 (1968).

of a wide variety of heterocycles. A special case involves the head-to-tail arrangement of two adjacent C=N double bonds (as, for example, in azines), which results in a crisscross 1,3-cycloaddition sequence, forming a bicyclic 1:2 adduct with the isocyanate (*vide infra*).

Last, but not least, addition across a semipolar single bond has to be considered.[1] This type of addition often involves a four-centered transition state with formation of an acyclic 1:1 adduct. The net consequence of the reaction amounts to the insertion of the C=N or C=O double bond of the isocyanate into the semipolar single bond. Although generally quite polar metal–organic bonds are involved, carbon–halogen, carbon–oxygen, and carbon–nitrogen bonds are known to participate. In the case of the carbon–nitrogen bond, one has to consider single-bonded substrates which can easily form a carbonium ion. Such bonding is encountered in amino acetals (aminales)[7] and in certain spiro compounds[5] (see Scheme VI).

For example, stepwise addition of an isocyanate to a single bond A–B leads to formation of an acyclic 1:1 adduct **13**. The reaction is reversible, but if addition to A–B leads to a weakening of this bond a 1,3 rearrangement occurs with formation of the "insertion" product **14**. If the newly formed A–N bond is still reactive, the 2:1 adduct **16** is formed (Scheme III). This reaction proceeds *via* **15** and could in fact lead to linear homopolymerization or cyclic trimerization of the isocyanate.

Scheme III

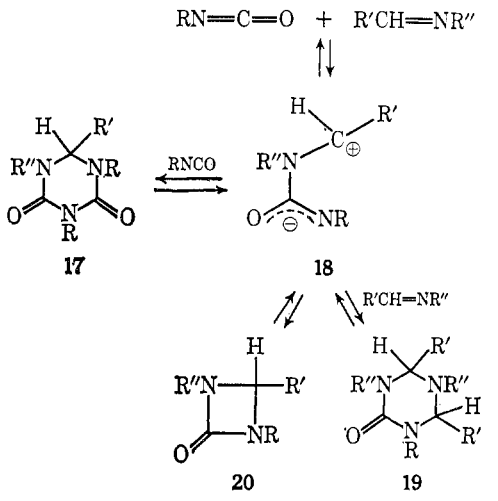


Thus a wide variety of reactions can occur, and it depends largely on the substrate and the reaction conditions which of the numerous possible reaction products are predominantly formed.

Addition of Isocyanates to Imines

The polar addition of isocyanates to imines yields 1:1, 2:1, and 1:2 cycloadducts, depending upon the dipolarophilicity of the C=N double bond of the imine in comparison to the dipolarophilicity of the C=N bond in the isocyanate (Scheme IV). For example, from hexahydrotriazines, which are in a thermal equilibrium with their monomeric imine forms (R′ = H; R″ = alkyl), the cycloadducts **19** are obtained in good yield.[8,9] In contrast, C-substituted imines (R′ = C_6H_5; R″ = C_2H_5) undergo reaction with phenyl isocyanate to produce either **17** or **19** depending upon the reaction

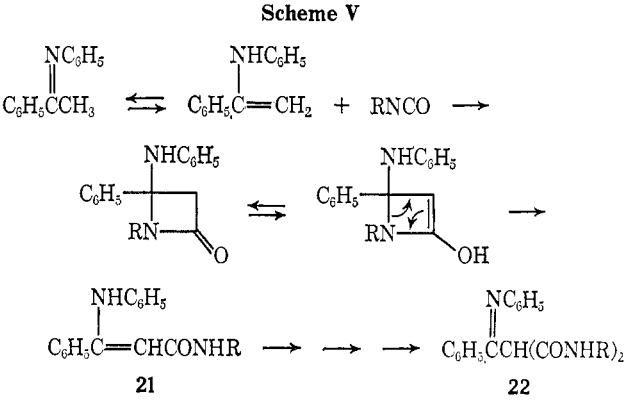
Scheme IV



conditions.[10,11] The cyclic imine 3,4-dihydroisoquinoline and phenyl isocyanate produce cycloadduct **19** exclusively.[10] Sulfonyl isocyanates undergo reaction with imines (R′ = C_6H_5; R″ = aryl or alkyl) to yield predominantly **17**.[9] The cycloadduct **20** is supposedly formed in the reaction of phenyl isocyanate with methyleneaniline (R′ = H; R″ = C_6H_5).[12]

Anils of some ketones undergo reaction with isocyanates *via* the enamine route (see Scheme II) to produce the acyclic 1:1 or 1:2 adducts **21** and **22** (Scheme V).[13,14]

Scheme V



Similarly, endo- and exocyclic imines react preferentially in the enamine form to produce acyclic 1:1 or 1:2 adducts[6,15] (*vide supra*). The 1:1 adducts could result either from attack on the nucleophilic nitrogen

(7) H. Ulrich and A. A. R. Sayigh, *Angew. Chem. Intern. Ed. Engl.*, **5**, 844 (1966).

(8) D. H. Clemens and W. D. Emmons, *J. Org. Chem.*, **26**, 767 (1961).

(9) W. Bartmann, *Chem. Ber.*, **100**, 2938 (1967).

(10) R. Huisgen, K. Herbig, and M. Morikawa, *ibid.*, **100**, 1107 (1967).

(11) N. A. Lange, *J. Am. Chem. Soc.*, **48**, 2440 (1926).

(12) A. Senier and F. G. Shephard, *J. Chem. Soc.*, **95**, 494 (1909).

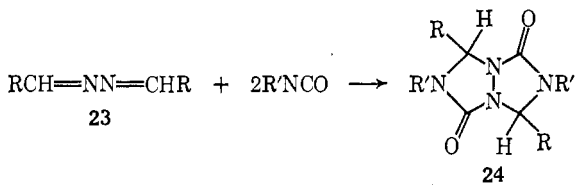
(13) J. Moszew and A. Inasinski, *Roczniki Chem.*, **34**, 1173 (1960); *Chem. Abstr.*, **55**, 15383 (1961).

(14) J. Schoen and K. Bogdanowicz-Szwed, *Roczniki Chem.*, **38**, 425 (1964); *Chem. Abstr.*, **61**, 1827 (1964).

(15) J. P. Chupp and E. R. Weiss, *J. Org. Chem.*, **33**, 2357 (1968).

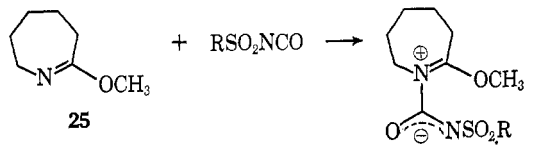
(N-alkyl substituent) or by addition across the activated C=C bond (N-aryl substituent).[15] An exception is 3,4-dihydroisoquinoline which cannot undergo the ene reaction.[10]

From azines **23** and isocyanates the bicyclic adducts **24** are obtained as a result of "crisscross" 1,3-cycloaddition sequences.[9,16,17]



23 **24**

The acyclic 1:1 adduct **26**, obtained in the reaction of 2,6-dimethylphenoxysulfonyl isocyanate with the cyclic imidate **25**, is stable and does not undergo further reaction with either one of the starting materials.[9]



25 **26**

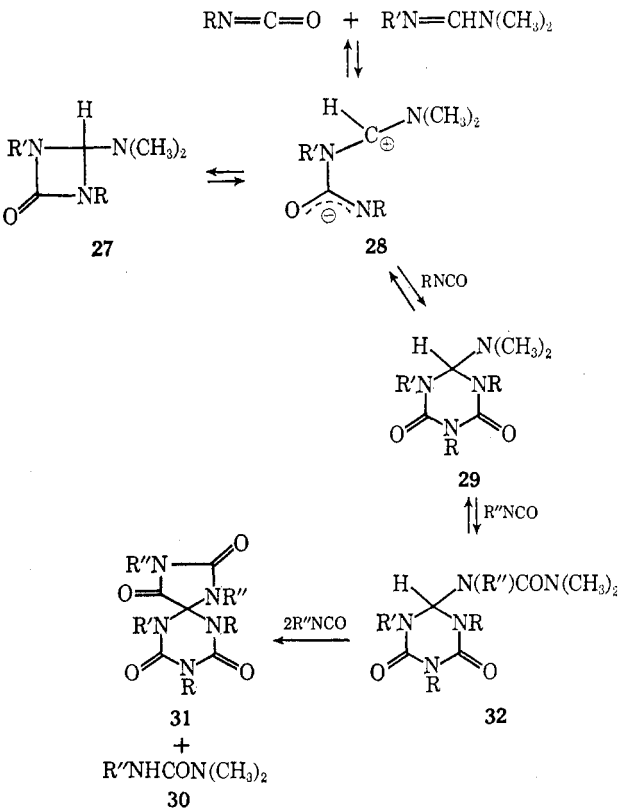
Similarly, stable 1:1 adducts of sulfonyl isocyanates with heterocyclic amines, such as pyridine, picolines, and isoquinoline, are known.[18]

Addition of Isocyanates to Amidines

The reactivity of olefins in polar cycloaddition reactions with isocyanates depends upon the polarization of the double bond. For example, ketene aminals and enamines react faster than olefins (in that order). The same relationship may in fact exist in the C=N double bond system, *i.e.*, amidines and guanidines ought to react more readily than imines.[19] We have observed that N-phenyl-N′-dimethylformamidine undergoes rapid reaction with tosyl isocyanate to afford the 1:1 cycloadduct **27** (R = 4-$CH_3C_6H_4SO_2$; R′ = C_6H_5) in high yield. If the reaction is conducted in chlorobenzene or *o*-dichlorobenzene, and phenyl isocyanate is removed by partial distillation of the solvent, N-tosyl-N′-dimethylformamidine is obtained in 85% yield.[19] The cycloaddition of tosyl isocyanate to N-butyl-N′-dimethylformamidine proceeds in a similar manner.[19]

In contrast, phenyl isocyanate undergoes a slow reaction with N-phenyl-N′-dimethylformamidine to produce the 2:1 adduct **29**.[5,20,21] Interestingly, the 2:1 adduct **29** reacts with 1 equiv of phenyl isocyanate to yield **32**,[5,20] which upon further reaction with phenyl isocyanate affords the spiro compound **31** and the N-aryl-N′-dimethylurea **30** (Scheme VI).[5,20] The spiro compounds **31** can be prepared conveniently by heating the appropriate aryl isocyanate in N,N-dimethylformamide (DMF).[5]

Scheme VI



If the 2:1 adduct **29** (R = R′ = C_6H_5) is heated with *p*-tolyl isocyanate at 150° for several hours, the mixed spiro compound **31** (R = R′ = C_6H_5; R″ = 4-$CH_3C_6H_4$) is obtained in low yield. The low yield is explained by the reversibility of all of the reactions with the exception of formation of **31**, which is irreversible under the reaction conditions employed. The mass spectrum of the crude reaction mixture shows parent ions at masses *m/e* 579, 593, 607, 621, 635, and 649, indicating formation of all of the expected spiro compounds. Using two different isocyanates a total of 24 different spiro compounds can be formed.

The addition of phenyl isocyanate to a number of endo- and exocyclic amidines and bicyclic amidines has been observed by Richter, and he has obtained in most cases the 2:1 cycloadducts **29**, the cyclic amidines being considerably more reactive than N-phenyl-N′-dimethylformamidine.[21]

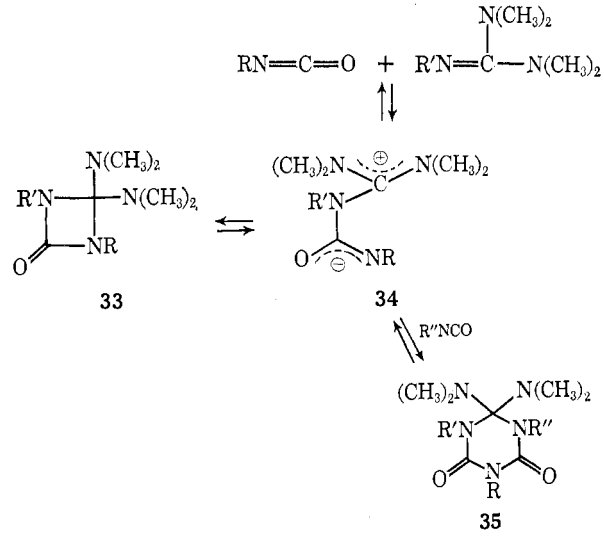
Addition of Isocyanates to Guanidines

The addition of tosyl isocyanate to N,N,N′,N′-tetramethyl-N″-phenylguanidine occurs at room temperature to produce the 1,2-cycloadduct **33**, a compound in which four nitrogen groups are attached to a carbon center.[19] Of course, the formulation of the cy-

(16) I. R. Bailey and A. T. McPherson, *J. Am. Chem. Soc.*, **39**, 1322 (1917).
(17) R. Huisgen, *Angew. Chem. Intern. Ed. Engl.*, **2**, 565 (1963).
(18) Z. Brzowski and W. Zacharewicz, *Roczniki Chem.*, **35**, 1163 (1961); *Chem. Abstr.*, **57**, 16447 (1962); W. Aumüller and R. Weyer, German Patent 1,100,618 (1961); *Chem. Abstr.*, **55**, 24680 (1961); M. Seefelder, *Chem. Ber.*, **96**, 3243 (1963).
(19) H. Ulrich, B. Tucker, and A. A. R. Sayigh, *Angew. Chem. Intern. Ed. Engl.*, **7**, 291 (1968).
(20) E. Dyer, T. E. Majewski, and J. D. Travis, *J. Org. Chem.*, **33**, 3931 (1968).
(21) R. Richter, *Chem. Ber.*, **101**, 3002 (1968).

cloadducts **27** and **33** is based on convention rather than absolute structure proof, and X-ray diffraction studies are needed in order to differentiate from the acyclic polar structure **28** and **34**. Heating in *o*-dichlorobenzene causes fragmentation of **33** with formation of phenyl isocyanate, which is removed with the high-boiling inert solvent, and N,N,N′,N′-tetramethyl-N″-tosylguanidine is obtained in high yield.[19] In contrast, reaction of methyl isocyanate with N,N,N′,N′-tetramethyl-N″-phenylguanidine affords the thermolabile 2:1 cycloadduct **35** (R′ = C_6H_5; R = R″ = CH_3).[22] The reaction can also be conducted in a stepwise fashion by adding phenyl isocyanate to a solution of the guanidine derivative in diethyl ether, followed by methyl isocyanate to produce **35** (R″ = CH_3; R = R′ = C_6H_5) *via* the linear intermediate **34** (Scheme VII).[22]

Scheme VII



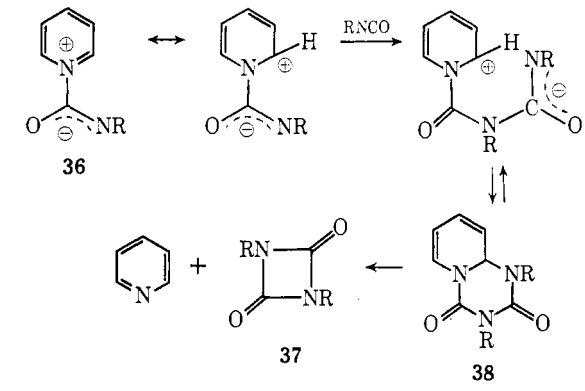
If phenyl isocyanate is treated with a catalytic amount of N,N,N′,N′-tetramethyl-N″-phenylguanidine, trimerization is observed[22].

Dimerization of Isocyanates

The dimerization of aryl isocyanates to produce 1,3-diaryl-2,4-uretidinedione (**37**) is perhaps the most simple case of 1,2 cycloaddition of an isocyanate. However, if this reaction would occur to any extent, isocyanates would not be stable in the monomeric form. The only cases of a slow noncatalyzed aryl isocyanate dimerization involve 4,4′-diisocyanatodiphenylmethane, which dimerizes at a faster rate in the solid state than in the liquid state,[23] and 2,4-tolylene diisocyanate.[24]

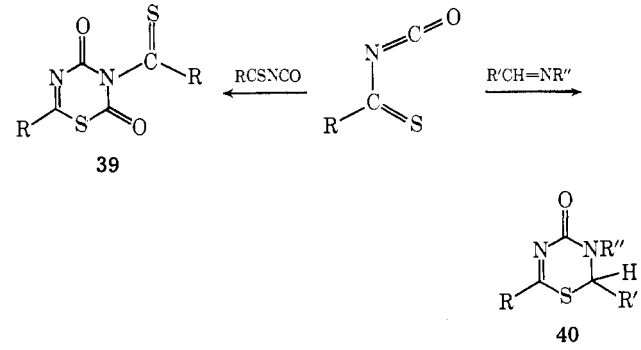
Specific catalysts for dimer formation are trialkylphosphines, pyridine, certain pyridine derivatives, and N,N,N′,N′-tetramethyl-N″-phenylguanidine. Recently, Buckles and McGrew[25] proposed a mechanism for the dimerization of phenyl isocyanate in the presence of tributylphosphine, based on kinetic data. However, the typical base catalysis scheme does not explain the specificity of certain bases with regard to dimer formation. The three groups of catalysts for dimer formation have a common ability to form a five- or a six-membered-ring 2:1 adduct, which can collapse to dimer with regeneration of the catalyst.[26] This sequence is outlined in Scheme VIII, and I have selected

Scheme VIII



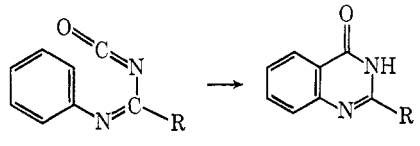
pyridine as the catalyst example. The initial addition of pyridine to the isocyanates affords the polar 1:1 adduct **36**, which can add a second isocyanate in a stepwise 1,4-polar addition to form the 2:1 adduct **38**; the latter could eliminate the catalyst with concerted formation of aryl isocyanate dimer (**37**). The feasibility of formation of similar stable 2:1 cycloadducts of phenyl isocyanate has been demonstrated by Huisgen and coworkers[10] in the reaction with isoquinoline.

If the isocyanate contains a thiocarbonyl or an imidoyl group adjacent to the cumulative system, a different type of dimer can be formed, resulting from addition of the cumulative C=N double bond to the 1,4 system. For example, generation of thioacyl isocyanates results in rapid formation of the corresponding dimers **39**.[27] However, the monomeric thioacyl isocyanate can be trapped by addition of an azomethine to the reaction mixture to yield the cycloadduct **40**.[28]

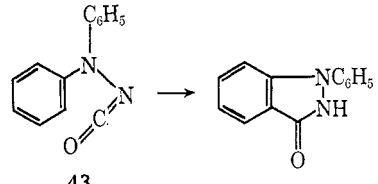


(22) R. Richter, *Tetrahedron Letters*, 5037 (1968).
(23) Unpublished results of our laboratory.
(24) A. Davis, *Makromol. Chem.*, **66**, 196 (1963).
(25) R. E. Buckles and L. A. McGrew, *J. Am. Chem. Soc.*, **88**, 3582 (1966).
(26) W. G. Bentrude and W. D. Johnson, *ibid.*, **90**, 5924 (1968), have obtained pentacovalent five-membered ring phosphoranes in the reaction of dimethylketene with trivalent phosphorus derivatives. Heating of the cyclic phosphoranes to 60° produces dimethylketene dimer in quantitative yield.
(27) J. Goerdeler and H. Schenk, *Chem. Ber.*, **98**, 2954 (1965).
(28) J. Goerdeler and K. Jones, *ibid.*, **99**, 3572 (1966); J. Goerdeler and R. Weiss, *ibid.*, **100**, 1627 (1967).

Imidoyl isocyanates react similarly to afford dimers, resulting from a 1,4-cycloaddition sequence.[29] Interception of the monomeric imidoyl isocyanate by phenyl isocyanate as the dipolarophile has also been reported.[29] An exception to the generally encountered dimerization is the intramolecular cycloaddition which occurs in N-arylimidoyl isocyanates (**41**). For example, generation of **41** by a variety of methods results in the isolation of the cycloadduct **42**.[30]



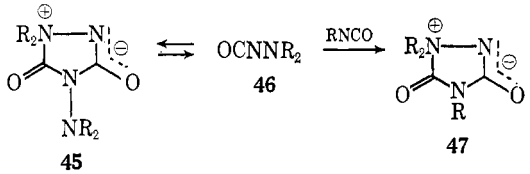
41 **42**



43 **44**

A similar intramolecular cycloaddition reaction has been encountered in the generation of diphenylamino isocyanate (**43**), and cycloadduct **44** has been obtained exclusively.[31]

A third type of dimerization has been observed with dialkylamino isocyanates. For example, dimethylamino isocyanate (**46**, R = CH_3) undergoes rapid dimerization to produce the cyclic hydrazinium ylide **45**.[32] Likewise, trapping of **46** with a different isocyanate is possible, and the cyclic ylide **47** is formed in good yield.[32]

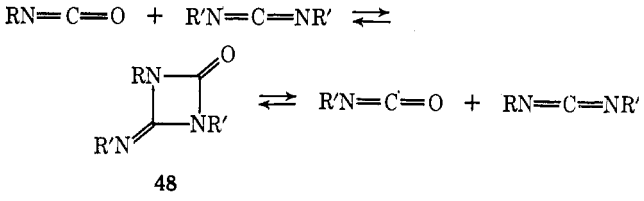


45 **46** **47**

The asymmetrical isocyanate dimers, resulting from addition of the C=N double bond across the C=O double bond of a second isocyanate molecule, are supposed to be intermediates in the base-catalyzed formation of carbodiimides from isocyanates.[33]

Addition to Carbodiimides

The cycloaddition of an aryl isocyanate to diphenylcarbodiimide occurs at elevated temperature to produce cycloadduct **48**.[33,34] The thermolabile 1,2 cycloadduct **48** can undergo fragmentation at elevated temperature to produce a new set of heterocumulenes. The course of this exchange reaction can be controlled by removing the lowest boiling isocyanate from the reaction mixture.[33]

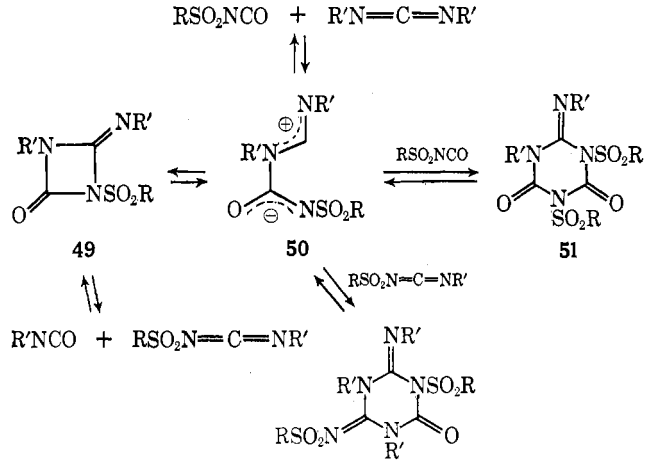


48

While benzoyl isocyanates add to carbodiimides in 1,2 fashion,[35] thioacyl isocyanates undergo a 1,4-cycloaddition reaction.[36]

A considerably more complex reaction pattern emerges in the reaction of sulfonyl isocyanates with dialkylcarbodiimides. The intermediate polar 1:1 adduct **50** can be detected by infrared and nmr spectroscopy, and the lifetime of **50** is long enough to be intercepted by the sulfonyl isocyanate to form the 2:1 adduct **51**. Also interception of a polar 1:1 adduct by the sulfonylcarbodiimide (formed by the collapse of the 1:1 cycloadduct **49**) occurs and the 1:1:1 cycloadduct **52** is isolated (Scheme IX).

Scheme IX



49 **50** **51**

The addition to the dialkylcarbodiimide can be controlled by proper choice of substituents. For example, in N-methyl-N′-*t*-butylcarbodiimide addition occurs across the C=N double bond adjacent to the methyl group. Furthermore, the mode of addition determines the product distribution. If the dialkylcarbodiimide is added slowly to excess sulfonyl isocyanate a higher than 50% yield of **51** can be obtained. The reverse addition produces about 20% of each of **51** and **52**.

Addition of Isocyanates to C–N Single Bonds

The first example of the reaction of an isocyanate with a carbon–nitrogen single-bond-containing sub-

(29) U. v. Gizycki and G. Oertel, *Angew. Chem.*, **80**, 362, 363 (1968).
(30) L. I. Samarai, W. A. Bondar, and G. I. Derkach, *ibid.*, **79**, 897 (1967).
(31) R. Stolle, *Ber.*, **57**, 1063 (1924); R. Stolle, N. Nieland, and M. Merkle, *J. Prakt. Chem.*, [2] **116**, 192 (1927).
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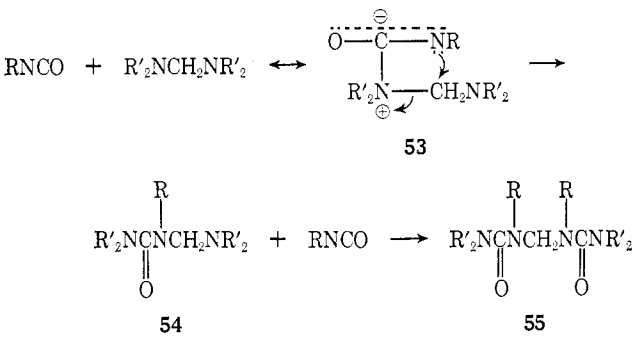
(33) W. Neumann and P. Fischer, *Angew. Chem.*, **79**, 801 (1962).
(34) W. J. Farrissey, Jr., R. J. Ricciardi, and A. A. R. Sayigh, *J. Org. Chem.*, **33**, 1913 (1968).
(35) R. Neidlein, *Arch. Pharm.*, **297**, 623 (1964).
(36) J. Goerdeler and H. Schenk, *Angew. Chem. Intern. Ed. Engl.*, **2**, 552 (1963).

strate has been observed by Oda and his coworkers.[37] These authors have observed that O,N-acetals of formaldehyde form 1:1 adducts with isocyanates in the presence of a Lewis acid catalyst. In the case of the N,N-acetals of formaldehyde, addition of phenyl isocyanate occurs at room temperature, and a catalyst is not required.[7] Thus, the 1:1 adducts **54** are obtained in high yield. Arenesulfonyl isocyanates react considerably faster than aryl isocyanates, and if a second equivalent of the arenesulfonyl isocyanate is added to **54** the 2:1 adducts **55** are obtained. The reaction proceeds in a stepwise fashion as indicated in Scheme X.[7]

Scheme X



Interestingly, acetals of N,N-dialkylamides seem to react with phenyl isocyanate preferentially across the C–O bond to form cyclic 1:2 adducts (O,N-acetals of parabanic acids).[38] Brederek and his students[39] have proposed a mechanism for the addition of isothiocyanates to acetals of N,N-dialkylamides which involves initial formation of a 1:1 adduct, similar to **53**. However, instead of insertion into the C–N bond, a rearrangement involving the attached proton is supposed to account for the isolated product. In contrast, the aminales of N,N-dialkylamides (see Scheme VI) undergo the reaction sequences shown in Scheme X.[5]

Summary and Outlook

The reaction of isocyanates with carbon–nitrogen-bond-containing substrates exemplifies the complexities which are sometimes encountered in polar cycloaddition reactions. The exact mechanism involved in many of the processes discussed is not known, but the six-membered heterocycles are generated in a stepwise fashion. The role of the four-membered-ring 1:1 cycloadduct as an intermediate in the fragmentation reaction is clear,[40] but again nothing is known about the exact nature of this process. Elucidation of the structure of 1:1:1 cycloadducts, such as **52**, may provide further insight. Although the observed product distribution is dependent upon the equilibria involved, the lifetimes of the polar acyclic 1:1 and 2:1 adducts, the relative dipolarophilicities of the reagents, and the stabilities of the cycloadducts seem to be the most important variables.

As a general rule delocalization of the developing negative charge seems to stabilize the ionic 1:1 adducts (for example, some of the 1:1 adducts of arenesulfonyl isocyanates are stable compounds). Furthermore, arenesulfonyl isocyanates are better dipolarophiles than alkyl and aryl isocyanates. In some instances a selective 1:1:1 addition, using three substrates which differ in their dipolarophilicity, is possible (*vide supra*). On the other hand if two different aryl isocyanates of about equal dipolarophilicity are used (phenyl isocyanate and *p*-tolyl isocyanate), complete exchange with formation of all of the expected isomeric adducts is indicated.

Structural features in the substrate can alter the course of the initial reaction considerably. For example, if a C=N double-bond-containing substrate can tautomerize to the corresponding enamine, addition across the C=C double bond can compete with the reaction across the C=N double bond. Furthermore, rapid tautomerization of the 1,2 cycloadduct (provided a hydrogen is adjacent to the carbonyl group in the four-membered-ring cycloadduct) can give rise to the exclusive formation of stable acyclic 1:1 adducts.

If the reactions are conducted at elevated temperature, thermodynamically controlled equilibria are established, and some control over the distribution of products can be achieved by removing the lowest boiling species from the reaction mixture. The effect of solvents on the product distribution has not been investigated.

Although the limitations of the polar addition reactions of isocyanates with suitable substrates are evident, the synthetic usefulness of these reactions in the formation of acyclic and cyclic adducts as well as new double bond systems (*via* the exchange reaction) is clearly indicated, especially since a host of new products can be prepared by simply mixing compounds, which often can be purchased readily from commercial sources.

I thank my colleagues at The Upjohn Company, Donald S. Gilmore Research Laboratories, for their many contributions and for stimulating discussions, and I wish to single out Dr. A. A. R. Sayigh for his encouragement.

(37) R. Oda, M. Nomura, S. Tanimoto, and T. Nishimura, *Bull. Inst. Chem. Res. Kyoto Univ.*, **34**, 224 (1956); *Chem. Abstr.*, **51**, 6528 (1957).

(38) H. Brederek, G. Simchen, and E. Göknel, *Angew. Chem. Intern. Ed. Engl.*, **3**, 704 (1964).

(39) H. Brederek, G, Simchen, and S. Rebsdat, *Chem. Ber.*, **101**, 1872 (1968).

(40) One of the reviewers has suggested that the four-membered-ring cycloadduct may undergo direct reaction with the substrates, but experimental evidence does not substantiate this assumption. For example, the four-membered-ring aryl isocyanate dimers do not undergo reaction with a different isocyanate to produce a 2:1 adduct. Reaction occurs only at elevated temperature, and fragmentation is indicated by the mixture of products obtained.