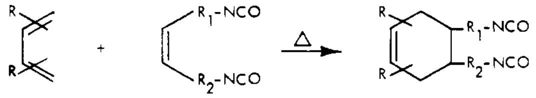
Diels-Alder Reactions of Dienophiles Containing Isocyanate Groups

ROBERT J. KNOPF and THOMAS K. BROTHERTON
Union Carbide Corp., Chemicals and Plastics, Research and Development Department, South Charleston, W. Va.

Olefinic mono- and diisocyanates of the aliphatic series undergo the Diels-Alder reaction with a variety of dienes to afford high yields of conventional adducts; the isocyanate function displays little tendency to compete with the olefinic linkage in adduct formation. Over prolonged reaction times at elevated temperatures, some loss of isocyanate functionality through polymerization is observed, however.

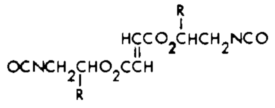
DESPITE intensive activity within the area of isocyanate chemistry over the past decade, few reactions of isocyanate-containing compounds have as yet been described in which the isocyanate function does not participate either intentionally or unintentionally in product formation. Our interest in the synthesis and chemistry of novel cyclic, polycyclic, and polyhalogenated isocyanates led us to explore the possibility of utilizing aliphatic isocyanate-containing olefins as dienophiles in the Diels-Alder reaction illustrated in the following generalized manner, wherein either one or both of the groups R_1 and R_2 may contain an isocyanate substituent.



The literature relative to the behavior of isocyanates toward dienes is sparse, providing little basis for predicting the likelihood of an isocyanate function competing seriously with various types of carbon-carbon double bonds for a given diene species. The isocyanate function in certain aryl isocyanates will behave as a dienophile toward the highly reactive isoindole system (*1*); however, this appears to represent an isolated example. In the reaction with alkoxyacetylenes (*7*), the isocyanate group actually functions in a diene capacity. The highly reactive sulfonyl isocyanates enter into reaction with dienes readily through the isocyanate function, but the products are either anilides of chlorosulfonic acid or four-membered heterocycles formed by cycloaddition (*5*). The aryl thionylamines, ArNSO, which are closely related structurally to aryl isocyanates, have been found to undergo Diels-Alder reactions wherein the thionylamino function can act either as the dienophile (*9*) or as the "diene" (*4*), but in these cases conventional Diels-Alder reactions have been precluded by the absence either of carbon-carbon unsaturation in the dienophile or of typical 1,3-diene functionality. Aliphatic thionylamines do not undergo these reactions.

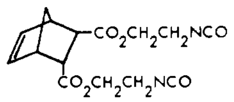
Our investigations during the early 1960's revealed that a large number of Diels-Alder adducts can be prepared from conventional dienes using unsaturated aliphatic mono- and diisocyanates of various types as the dienophiles. Following the termination of our studies in this area, von Brachel and Bayer (*1*) disclosed in the patent literature the formation of Diels-Alder adducts from both allyl isocyanate and 2-isocyanatoethyl methacrylate. The novelty of this approach and its general synthetic utility having been thus disclosed, we wish merely to summarize in this communication our findings, which both corroborate and expand upon those of von Brachel and Bayer.

Dienophiles 1 to 6 contain as a group four different types of unsaturation—namely, α, β-conjugated (1, 2), strained ring (3, 5), cycloalkenyl (4), and acyclic terminal (6). The nine dienes are representative of seven different types—namely, cyclic (7), polyhalogenated cyclic (8, 9), monosubstituted acyclic (10, 11), aromatic (12), unsubstituted acyclic (13), 2,3-disubstituted acyclic (14), and 1,4-disubstituted acyclic (15).

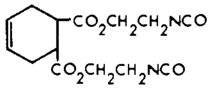


$$\begin{matrix}\mathrm{HCCO_2\overset{\displaystyle R}{\overset{|}{C}}HCH_2NCO}\\ \| \\ \mathrm{OCNCH_2\underset{\displaystyle R}{\underset{|}{C}}HO_2CCH}\end{matrix}$$

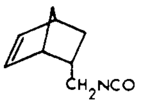
1, R = H
2, R = CH_3



3



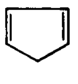
4



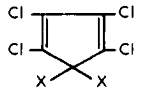
5

$CH_2{=}CH(CH_2)_7CH_2NCO$

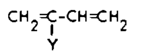
6



7

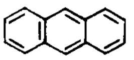


8, X = OCH_3
9, X = Cl



$$\mathrm{CH_2{=}\underset{\displaystyle Y}{\underset{|}{C}}{-}CH{=}CH_2}$$

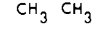
10, Y = Cl
11, Y = CH_3



12

$CH_2{=}CH{-}CH{=}CH_2$

13



$$\mathrm{CH_2{=}\underset{\displaystyle CH_3}{\underset{|}{C}}{-}\underset{\displaystyle CH_3}{\underset{|}{C}}{=}CH_2}$$

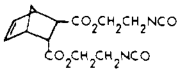
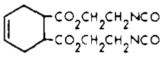
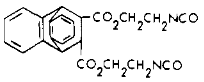
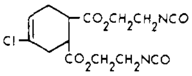
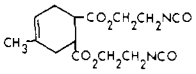
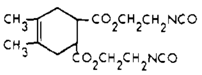
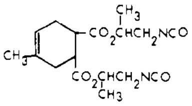
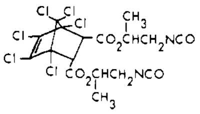
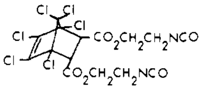
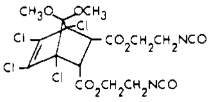
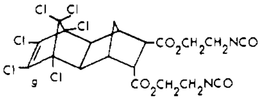
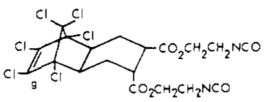
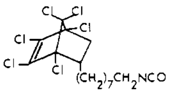
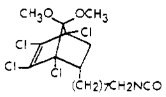
14

$CH_3{-}CH{=}CH{-}CH{=}CH{-}CO_2CH_3$

15

With the exception of those specific cases wherein maximum adduct recovery either was not sought or was especially difficult because of the exceptionally high boiling points of the adducts, surprisingly high yields were obtained in these reactions. The aliphatic isocyanate function apparently displays little tendency to compete with an olefinic linkage for diene and is not destroyed via side reactions, presumably because the reaction system is largely free of species known to catalyze the formation of dimers, trimers, and carbodiimides from isocyanates. However, that some loss of isocyanate functionality is observed over prolonged reaction times at elevated temperatures is evident from the plot (Figure 1) of stripped residue product equivalent weight *vs.* reaction time for the formation of adduct 24 from diene 9 and dienophile 1 at a 2 to 1 molar ratio. The theoretical equivalent weight of the adduct (263.5) is reached after about 13 hours at 190° C., and

Table I. Diels-Alder Reactions of

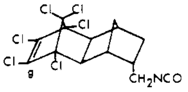
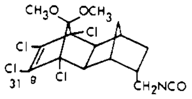
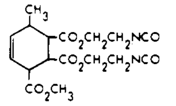
Diene	Dien- ophile	Adduct (No.)		Reaction Temp., ° C.	Reaction Time, Hours	Solvent	Mole Ratio, Diene/ Dienophile	Yield %	B.P., ° C. (Mm.)
7	1	16		170	5	Toluene	4/1	78.7	146-151(0.08-0.15)
13	1	17		150	5	Xylene	3.2/1	72.0	146-151(0.12)
12	1	18		105 25[b]	96 2	Dioxane methylene chloride	1/1 1/1	10.0[c]	
10	1	19		150	4	Xylene	4/1	69.3	178-179(0.15)
11	1	20		150	5	Xylene	4/1	75.2	150-151(0.08)
14	1	21		145	5	Xylene	1.6/1	80.8	160-161(0.07)
11	2	22		150	5	Toluene	4/1	64.4	155-160(0.03)
9	2	23		180	16	None	2/1	28.6	175(0.04)
9	1	24		170	26	None	2/1	25.3	178-203(0.06-0.12)
8	1	25		200	1.5	None	2/1	64.4	205(0.07)
9	3	26[g]		150	17	None	2/1	47.2	<230(0.06)[d]
9	4	27[g]		150	18	None	2/1	51.8	<230(0.10)[d]
9	6	28		155	3	None	1/1	72.3	161-171(0.05-0.10)
8	6	29		155	3	None	1/1	64.2	161-166(0.05)

Dienophiles Containing Isocyanate Groups

M.P., ° C. (Solvent)	n_D^{30}	Microanalysis		Derivatizing Reagent	M.P., ° C.	Microanalysis	
		Calcd., %	Found, %			Calcd., %	Found, %
	1.4950[a]	C, 56.2 H, 5.0 N, 8.8	C, 55.5 H, 5.1 N, 9.0	$C_6H_5NH_2$	169.5–170	C, 64.0 H, 5.9 N, 11.1	C, 64.0 H, 6.0 N, 11.1
	1.4864	C, 54.5 H, 5.2 N, 9.1	C, 54.6 H, 5.3 N, 9.1	n-$C_4H_9NH_2$	99–101	C, 58.2 H, 8.4 N, 12.3	C, 58.1 H, 8.5 N, 12.3
101.5–103 (50/50 benzene/ heptane)		C, 66.7 H, 4.6 N, 6.5	C, 67.3 H, 4.7 N, 6.3	n-$C_4H_9NH_2$	161–162	C, 66.4 H, 7.3 N, 9.7	C, 66.8 H, 7.0 N, 9.4
	1.5000	C, 48.9 H, 4.4 N, 8.2 Cl, 10.3	C, 49.3 H, 4.4 N, 8.2 Cl, 10.8	n-$C_4H_9NH_2$	116–117	C, 54.1 H, 7.6 N, 11.5	C, 54.0 H, 7.7 N, 11.2
	1.4856	C, 55.9 H, 5.6 N, 8.7	C, 56.5 H, 5.9 N, 8.7	n-$C_4H_9NH_2$	101–103	C, 58.8 H, 7.3 N, 9.7	C, 58.8 H, 7.0 N, 9.4
	1.4912	C, 57.1 H, 6.0 N, 8.3	C, 56.8 H, 6.0 N, 8.5	n-$C_4H_9NH_2$	132	C, 59.8 H, 8.7 N, 11.6	C, 59.7 H, 8.8 N, 11.9
	1.4760	C, 58.3 H, 6.3 N, 8.0	C, 57.6 H, 7.0 N, 8.1				
	1.5308	C, 36.8 H, 2.5 N, 5.0	C, 37.1 H, 2.7 N, 4.6				
	1.5329	C, 34.2 H, 1.9 N, 5.3	C, 34.2 H, 1.7 N, 4.9	n-$C_4H_9NH_2$	154–155	C, 41.0 H, 4.8 N, 8.3 Cl, 31.6	C, 41.1 H, 4.9 N, 8.3 Cl, 31.0
	1.5240	C, 39.4 H, 3.1 N, 5.4 Cl, 27.4	C, 39.1 H, 3.1 N, 4.9 Cl, 28.6	$C_6H_5NH_2$	164–165	C, 49.4 H, 4.3 N, 7.9 Cl, 20.2	C, 49.5 H, 4.3 N, 7.9 Cl, 19.9
		C, 40.5 H, 2.7 N, 4.7 Cl, 35.9	C, 41.0 H, 2.6 N, 5.0 Cl, 34.3				
	1.5429	C, 39.3 H, 2.8 N, 4.8 Cl, 36.6	C, 39.4 H, 2.8 N, 4.7 Cl, 36.9				
	1.5230	C, 42.4 H, 4.2 N, 3.1 Cl, 46.9	C, 42.8 H, 4.2 N, 3.2 Cl, 46.5				
	1.5075	C, 48.6 H, 5.6 N, 3.3 Cl, 31.9	C, 48.7 H, 5.5 N, 3.1 Cl, 31.6				

(*continued on page 424*)

Table I. Diels-Alder Reactions of Dienophiles

Diene	Dienophile	Adduct (No.)		Reaction Temp., °C.	Reaction Time, Hours	Solvent	Mole Ratio, Diene/Dienophile	Yield, %	B.P., °C. (Mm.)
9	5	30[g]		145	3.75	None	1/1	46.9	
8	5	31[g]		145	4	*o*-Dichlorobenzene	1/1	60.4	<195(0.03)
15	1	32		150	4.5	None	1.9/1	66.4	202(0.35)

[a] Value given is at 22° C. [b] $AlCl_3$-catalyzed method (see Experimental section). [c] No attempt to achieve maximum adduct recovery. standing. [f] Value given is at 20° C. [g] Structures are not intended to imply known ring junction geometry.

the theoretical conversion of diene is reached after 15 hours. Extension of the reaction beyond this point to 19 hours serves to raise the equivalent weight to 304 and substantially to increase the viscosity of the residue product. Inasmuch as the diene conversion is 96 to 97% of theory at the point of theoretical adduct equivalent weight, loss of isocyanate functionality through polymerization of adduct, rather than of starting dienophile, apparently accounts for the observed increase in equivalent weight. At a temperature of 170° C., this adduction is complete in 40 hours, whereas at 200° C., less than 7 hours are required.

The sole cases in which attempted adduct formation were completely unsuccessful were those of dienophiles 1 and 5 with 2,4-hexadienal (sorbaldehyde) as the diene. After about 1 hour at 140° C., both charges had polymerized to gelatinous masses, although at no time were the polymerizations sufficiently rapid to generate noticeable exotherms.

Several of the diisocyanates described herein—e.g., 17 and 24—were screened for toxicological properties and found to be far less toxic than such commonly used diisocyanates as hexamethylene diisocyanate, tolylene diisocyanate, and 4,4'-methylene-bis(phenylisocyanate).

EXPERIMENTAL

Melting points were determined with a Mel-Temp (Laboratory Devices, Inc.) capillary tube apparatus and are uncorrected. Microanalyses were performed by the analytical section of the Research and Development Department of Union Carbide Chemicals Division, South Charleston, W. Va. Infrared spectra were obtained on a Perkin-Elmer Model 21 spectrophotometer. Evaporative distillations were carried out with a Rota-Film molecular still (Arthur F. Smith Co.) modified to utilize a refluxing solvent as the heating medium in place of an electric mantle.

The dienes used in this study were all purchased from laboratory supply houses with the exception of 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene, which was prepared by the method of Newcomer and McBee (*6*) and methyl sorbate, which was prepared by the method of Wheeler (*8*). All purchased dienes were used without additional purification. The ester dienophiles 1 and 2 were prepared in this laboratory and characterized by infrared spectra, microanalysis, wet chemical analysis (reaction with excess di-*n*-butylamine followed by back-titration with a standard hydrochloric acid solution), and derivative formation. Their preparation is described in Belgian Patent **635,304** and in French Patent **1,370,869** (both to Union Carbide Corp.) (*2*). The strained ring dienophile 5 was prepared in this laboratory as described in U. S. Patents **3,141,900** and **3,231,595** (*3*) (to Union Carbide Corp.) and agreed in all physical properties with the product described by von Brachel and Bayer (*1*). Dienophile 6 was purchased from Aldrich Chemical Co. and was used as received. Dienophiles 3 and 4 are products of this study and were characterized as indicated in Table I.

Adduct Preparations. The specific adduct preparations described below are selected as being representative of the various types and serve to illustrate the general procedures used throughout.

Bis(2-isocyanatoethyl)-4-cyclohexene-*trans*-1,2-dicarboxylate (17). A mixture of 140 grams (0.55 mole) of 1, 94 grams (1.74 moles) of 13, and 200 ml. of xylene (mixed isomers) was heated for 5 hours at 150° C. in a steel rocker bomb. Following completion of the reaction, the solvent was removed by stripping (10 mm. of Hg) and the resulting residue was further stripped to 110° C. at 1 mm. of Hg. Evaporative distillation of this residue at 190° C. (0.05 mm. of Hg) afforded 132 grams of straw-colored liquid which, when subsequently refined through a goose-necked still head, gave 122 grams (72.0%) of colorless, odorless liquid, b.p. 146° to 151° C. (0.12 mm. of Hg), n_D^{30} 1.4864. The infrared spectrum (neat) exhibited bands at 3.25 (C—H), 4.45 (NCO), 5.8 (ester C=O), 6.06 (C=C), 8.0 and 8.53 (ester C—O), and 15.2 μ (*cis*-RCH=CHR).

Reaction of this diisocyanate with *n*-butylamine gave bis[2-(*n*-butylureylene)ethyl]4-cyclohexene-*trans*-1,2-dicarboxylate, m.p. 99–101° C. (ethanol).

Bis(2-isocyanatoethyl)-*trans*-9,10-ethanoanthracene-11,12-dicarboxylate (18). METHOD A. A mixture of 51 grams (0.2 mole) of 1, 36 grams (0.2 mole) of recrystallized 12 (90 to 95% purity grade), and 250 ml. of dioxane was refluxed for 4 days in a nitrogen atmosphere. The resulting amber solution was stripped free of solvent to leave a reddish-orange viscous sirup which could not be induced to crystallize. Repeated batch extractions with a 1 × 200 cc. portion of heptane followed each time by decantation, chilling, and filtration gave 1 to 2 grams per extraction of fine white needles, m.p. 99–101° C. Extraction was discontinued after 9 grams of material had been thus obtained. One recrystallization from 50/50 benzene-heptane raised the melting point to 101.5–03° C.

METHOD B. A solution of 25.4 grams (0.1 mole) of 1, 17.8 grams (0.1 mole) of 12, and 13.3 grams (0.1 mole) of aluminum chloride in 500 cc. of methylene chloride was allowed to stand for 2 hours at room temperature. The

Containing Isocyanate Groups (*Continued*)

M.P., °C. (Solvent)	n_D^{30}	Microanalysis Calcd., %	Microanalysis Found, %	Derivatizing Reagent	M.P., °C.	Microanalysis Calcd., %	Microanalysis Found, %
123–125 (Ethyl acetate)		C, 39.8 H, 2.6 N, 3.3 Cl, 50.5	C, 39.8 H, 2.7 N, 3.4 Cl, 50.4				
88–96[e]	1.5441	C, 46.5 H, 4.1 N, 3.4 Cl, 34.4	C, 46.4 H, 4.3 N, 3.5 Cl, 34.6				
	1.4914[f]	C, 53.7 H, 5.3 N, 7.4	C, 53.5 H, 5.4 N, 7.7				

[d] Evaporation distillations using refluxing 1,2,4-trichlorobenzene as heating medium. [e] Viscous liquid distillate crystallized slowly on

product was recovered by pouring the solution onto ice and allowing the product to be extracted into the methylene chloride phase. The extract was dried over sodium sulfate, and removal of the solvent afforded a sirup similar to the above from which the adduct could be isolated by repeated heptane extractions as described.

The adduct reacted exothermally with *n*-butylamine to give bis[2-(*n*-butylureylene)ethyl]*trans*-9,10-ethanoanthracene-11,12-dicarboxylate, m.p. 161–62° C. (ethanol).

Bis(2 - isocyanatoethyl) - 5,6,7,8,11,11 - hexachloro - 5,7 - methano - 1,2,3,4,5,8,9,10 - octahydronaphthalene - *trans* - 2,3- dicarboxylate (27). A mixture of 277 grams (0.9 mole) of adduct 17 and 491 grams (1.8 moles) of hexachlorocyclopentadiene (9) was heated with stirring for 18 hours at 150° C. in a nitrogen atmosphere. Excess diene was removed from the crude product by stripping to a kettle temperature of 125° C. at full pump vacuum. Evaporative distillation at 230° C. (0.1 mm. of Hg) afforded 271 grams (51.8%) of a reddish-brown viscous liquid, n_D^{30} 1.5429, having an indicated purity of 99.1% by wet chemical analysis.

5,6,7,8,9,9 - Hexachloro - 1,2,3,4,4a,5,8,8a - octahydro - 2 - isocyanatomethyl - 1,4,5,8 - dimethanonaphthalene (30). A mixture of 136.5 grams (0.5 mole) of diene 9 and 74.5 grams (0.5 mole) of 2-isocyanatomethylnorborn-5-ene (5) was heated with stirring in a nitrogen atmosphere for 3.75 hours at 145° C. The cooled kettle contents solidified to a tacky mass which smelled strongly of unreacted diene. Trituration of the mass with 60° to 70° C. petroleum ether allowed the removal of unreacted starting materials and afforded 99 grams (46.9%) of a light tan solid melting from 116° to 122° C. One recrystallization from ethyl acetate raised the melting point to 123–25° C. and the adduct crystallized in the form of fine white needles.

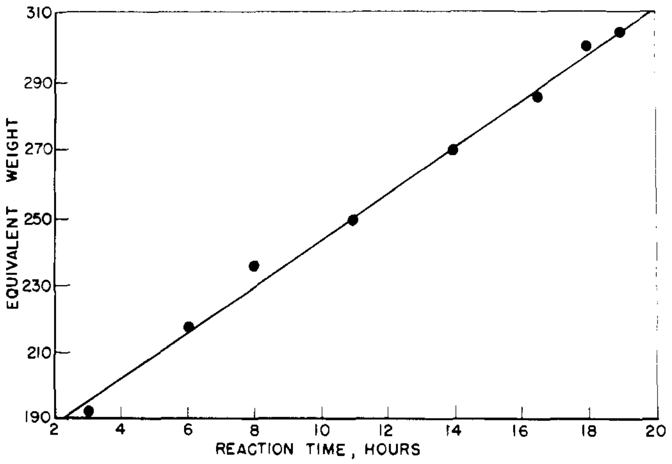


Figure 1. Formation of adduct 24 at 190° C.
Equivalent weight vs. reaction time

8 - (1,4,5,6 - Tetrachloro - 7,7 - dimethoxynorborn - 5 - en - 2 - yl) - octylisocyanate (29). A mixture of 13.2 grams (0.05 mole) of 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene (8) and 9.05 grams (0.05 mole) of 9-decenyl isocyanate (6) was heated for 3 hours at 155° C. in an atmosphere of nitrogen. Following removal of the unreacted starting materials by stripping to 150° C. at 1 mm. of Hg pressure, the residue was evaporatively distilled at 190° C. (0.07 mm. of Hg) to give 14.35 grams of a mobile yellow liquid. Redistillation of this material through a goose-necked still head served to remove a small fore-fraction and to afford the refined product as a pale yellow liquid, b.p. 161° to 166° C. (0.05 mm. of Hg), n_D^{30} 1.5075, in a yield of 38.6%.

ACKNOWLEDGMENT

The authors express their appreciation to D. L. Griffin and W. W. Runyan for performing a portion of the experimental work, to H. L. Joyce for interpretation of infrared spectra, and to H. Bias and J. R. Loy for performing the microanalytical work.

LITERATURE CITED

(1) Brachel, H. von., Bayer, O. (to Farbenfabriken Bayer Co.), U. S. Patent **3,222,387** (Dec. 7, 1965).
(2) Brotherton, T.K., Lynn, J.W. (to Union Carbide Corp.), Belgian Patent **635,304** (July 23, 1963); French Patent **1,370,869** (July 24, 1963).
(3) Brotherton, T.K., Lynn, J.W. (to Union Carbide Corp.), U. S. Patent **3,231,595** (Jan. 25, 1966), **3,141,900** (July 21, 1964).
(4) Collins, G.R., *J. Org. Chem.* **29**, 1688 (1964).
(5) Hoffmann, H., Diehr, H.J., *Tetrahedron Letters* No. **27**, 1875 (1963).
(6) Newcomer, J.S., McBee, E.T., *J. Am. Chem. Soc.* **71**, 946 (1949).
(7) Nieuwenhius, H., Arens, J.F., *Rec. Trav. Chim.* **76**, 999 (1957).
(8) Wheeler, D.H., *J. Am. Chem. Soc.* **70**, 3468 (1948).
(9) Wichterle, O., Racek, J., *Chem. Listy* **47**, 1766 (1953); *CA* **49**, 1053 (1955).

RECEIVED for review November 21, 1966. Accepted March 8, 1967.