was extracted with ether and dioxane, and the organic extracts were washed with sodium bisulfite. Removal of the solvents gave a yellow solid which was recrystallized from ethanol–water to give 5.0 g (95%) of the iodo acid: mp 129–133 °C; ^{1}H NMR δ 3.6 (s, CH_2), 7.2–7.7 (dd, aromatic), 11.2 (OH); ^{13}C NMR δ 40.5 (CH_2), 92.8, 131.2, 132.7, 137.6 (aromatic), 177.1 (COOH); IR (KBr) 3200–2900 (OH), 1690 (C=O) cm^{-1}. Anal. C, H, I.

(*p*-Iodophenyl)acetic Acid Dichloride. A solution of (*p*-iodophenyl)acetic acid (3.0 g) in 50 mL of chloroform in a three-necked flask protected from the light was treated with dry chlorine gas at 0 °C for 10 min. The dichloride precipitated from the solution and was collected by filtration. The yield of pure product was 86%: mp 88–90 °C dec; ^{1}H NMR δ 3.7 (s, CH_2), 7.2–7.5 (aromatic), 10.0 (OH).

(*p*-Iodophenyl)acetic Acid Difluoride (3). A mixture of 1.5 g of mercuric oxide, 100 mL of methylene chloride, and 2.3 g of dichloride was treated with 2 mL of 48% hydrofluoric acid, and the mixture was shaken vigorously for 8–10 min. The methylene chloride layer was decanted and used immediately. The yield of **3** by titration of the iodine liberated after reaction with potassium iodide was 95%.

Reaction of 3 with 1,1-Diarylethenes. General Procedure.[5] The reaction with 1,1-diphenylethylene is typical. A solution of 2.0 g (11 mmol) of 1,1-diphenylethylene in 8 mL of methylene chloride was added at 0 °C during 10 min to a solution (1 equiv) of **3** in methylene chloride. The mixture was stirred at 0 °C for 3 h. The mixture was extracted with sodium bicarbonate solution, and the organic phase was separated, dried, concentrated, and chromatographed on silica gel (hexane) to give pure 1,1-difluoro-1,2-diphenylethane in 60% yield, mp 64–66 °C (lit.[5] mp 65–66 °C). Unreacted starting material accounted for a 95% material balance.

The sodium carbonate solution was acidified and extracted with ether. The dried ether solution was concentrated to give (*p*-iodophenyl)acetic acid with about 95% recovery.

Yields and spectral data of 1,1-difluoro-1,2-diarylethanes are reported in Table III. Anal. C, H, Br, or Cl.

Preparation of 1,1-Diarylethenes. All 1,1-diarylethenes used in this study were prepared by the dehydration of the appropriate alcohol obtained from a Grignard reaction. All of the compounds are known and had spectral and physical properties consistent with reported values.[14]

Relative Reactivity Studies. To a freshly prepared solution of **3** (3.3 mmol, iodometric analysis) in 20 mL of methylene chloride contained in a polyethylene bottle was added a solution containing at least a 10-fold exess of each of the competing ethene and 1,1-diphenylethene. The mixture was stirred at 0 °C for 1 h and washed with dilute sodium bicarbonate. The methylene chloride solution was analyzed immediately by ^{19}F NMR spectroscopy. Relative areas of the CF_2 triplet signal in the products were used to determine relative ratios. Experiments performed for 30 min, and 3 h gave identical results. The results are reported in Table I. An average of six to eight experiments was performed for each determination. Several substrate ratios were used to substantiate the results.

Migratory Aptitudes. A solution of **3** (10 mmol) and unsymmetrical 1,1-diarylethene **8** (10 mmol) were stirred at 0 °C for 2 h in a polyethylene bottle. The mixture was extracted with sodium bicarbonate solution. The methylene chloride solution was analyzed by ^{19}F NMR for the relative amounts of product, which were confirmed by mass spectrometric analysis of the concentrated methylene chloride solution. The tropylium ion and substituted tropylium ion could be easily detected, and relative peak heights could be used to determine relative product ratios. ^{19}F NMR and mass spectral measurements agreed to within 3% of each other. The results given in Table II represent an average of five runs.

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(13) Holten, P. G.; Cross, D. A.; Bowers, A. *Steroids* **1963**, *2*, 71.
(14) Bergmann, E.; Szmuskovicz, J. *J. Am. Chem. Soc.* **1948**, *70*, 2748.

Influences of Alkyl Groups on the Rates of Decomposition of *N*-Nitrosoureas in Basic Aqueous Solution

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Alkyl groups exert an important influence on the rate of hydrolysis of the *N*-nitrosoureas in basic solution. Garrett and his associates reported that *N*-cyclohexyl-*N*-nitrosourea decomposes about 40-fold more rapidly than *N*-methyl-*N*-nitrosourea.[1] On the other hand, Lijinsky and Taylor noted that compounds such as *N,N',N'*-trimethyl-*N*-nitrosourea react very slowly.[2] Indeed, the relative rate of hydrolysis of *N*-methyl-*N*-nitrosourea compared to *N,N',N'*-trimethyl-*N*-nitrosourea is 2.17×10^4.[3] Our interest in the factors governing the course of the decomposition reactions of these compounds led us to examine the reactivity of other alkylnitrosoureas.

Results and Discussion

The nitrosoureas were prepared as described previously.[4] The procedures used for the study of the decomposition of these molecules in basic solution were also described previously.[3] All the nitrosoureas examined in this study decomposed in first-order processes at pH 9.75. The kinetic data for the decomposition of the *N*-alkyl-*N*-nitrosoureas in basic solution are summarized in Table I.

Garrett and his associates established that the *N*-alkyl-*N*-nitrosoureas decompose in specific base-catalyzed reactions near pH 7.[1] The rate data provided by these workers indicate that all of the *N*-alkyl compounds with primary alkyl groups decompose at similar rates. Neither the allyl nor the benzyl derivative is significantly more reactive than the methyl derivative. In contrast, *N*-cyclohexyl-*N*-nitrosourea decomposes much more rapidly than *N*-methyl-*N*-nitrosourea.[1] It was our intention to study the rates of hydrolysis of *N*-isopropyl- and *N*-*tert*-butyl-*N*-nitrosourea. Regrettably, these compounds were quite unstable and could not be purified without concomitant decomposition. However, several samples of *N*-isopropyl-*N*-nitrosourea hydrolyzed immeasurably rapidly at pH 9.75 ($k_{obsd} > 1$ s^{-1}). The compound also decomposed upon being allowed to stand in anhydrous chloroform. Isopropylurea was not present in the products of the decomposition reaction.

The fact that secondary alkyl groups accelerate the decomposition reaction while allyl and benzyl groups have only a modest influence on the reaction suggests that steric interactions are significant. To study this aspect of the reaction, we investigated the *N*-methyl-*N'*-alkyl- and *N*-methyl-*N',N'*-dialkyl-*N*-nitrosoureas. The kinetic results are summarized in Tables II and III.

N,N'-Dimethyl-*N*-nitrosourea is much less reactive than *N*-methyl-*N*-nitrosourea, $k_{obsd}(DMNU)/k_{obsd}(MNU) = 3.0 \times 10^{-3}$. Somewhat surprisingly, the other compounds with *N'*-alkyl groups exhibit the same degree of reactivity whether the *N'*-alkyl group is primary, secondary, or tertiary. The introduction of the third methyl group also retards the reaction, $k_{obsd}(TMNU)/k_{obsd}(MNU) = 5.0 \times 10^{-5}$. The *N,N'*-diethyl compound and the other *N',N'*-dialkyl derivative are about tenfold less reactive than the

(1) Garrett, E. R.; Goto, S.; Stubbins, J. F. *J. Pharm. Sci.* **1965**, *54*, 119.
(2) Lijinsky, W.; Taylor, H. W. *Z. Krebsforsch.* **1975**, *83*, 315.
(3) Snyder, J. K.; Stock, L. M. *J. Org. Chem.* **1980**, *45*, 1990.
(4) Snyder, J. K.; Stock, L. M. *J. Org. Chem.* **1980**, *45*, 886.

0022-3263/80/1945-4494$01.00/0

Table I. Observed First-Order Rate Constants for the Decomposition of *N*-Alkyl-*N*-nitrosoureas in Water

N-alkyl group	$10^3 k_{obsd}$, s^{-1} pH 7.75, 35 °C[a]	pH 9.75, 25 °C[b]
CH_3	2.40	35.6
CH_3CH_2	2.38	32.9

[a] Reference 1. [b] This study.

Table II. First-Order Rate Constants for the Decomposition of *N*-Methyl-*N'*-alkyl-*N*-nitrosoureas in Water at pH 9.75 at 25 °C

N-alkyl group	$10^4 k_{obsd}$, s^{-1}	*N*-alkyl group	$10^4 k_{obsd}$, s^{-1}
CH_3	1.06	$(CH_3)_2CH$	1.40
CH_3CH_2	1.05	$CH_3CH_2(CH_3)CH$	2.11
$CH_3CH_2CH_2$	1.37	c-C_6H_{11}	2.18
$(CH_3)_2CHCH_2$	1.47	$(CH_3)_3C$	3.06

Table III. First-Order Rate Constants for the Decomposition of *N*-Methyl-*N',N'*-dialkyl-*N*-nitrosoureas in Water at pH 9.75 at 25 °C

N',N-dialkyl groups	$10^7 k_{obsd}$, s^{-1}
CH_3, CH_3	16.4
CH_3CH_2, CH_3CH_2	2.54
$CH_3CH_2CH_2$, $CH_3CH_2CH_2$	1.14
$CH_3CH_2CH_2CH_2$, $CH_3CH_2CH_2CH_2$	1.55
$(CH_3)_2CHCH_2$, $(CH_3)_2CHCH_2$	0.968
$(CH_3)_2CH$, $(CH_3)_2CH$	1.23
c-$(CH_2)_4$[a]	6.73
c-$(CH_2)_5$[b]	1.49

[a] The pyrrolidine derivative. [b] The piperidine derivative.

trimethyl compound. The related *N',N'*-diisopropyl compound is one of the least reactive substances examined in this study.

The reaction mechanism which most satisfactorily describes the base-catalyzed hydrolysis of the nitrosoureas is shown in Scheme I.[3] Under the conditions of these experiments at relatively high buffer concentration, the reaction rate is governed by the second term in the rate equation shown in eq 1. Thus, the ratio k_2k_3/k_{-2} determines the reaction rate. The rate constants k_3 and k_2 will be influenced similarly by the alkyl groups such that the ratio, k_3/k_{-2}, will be less sensitive to substituent effects than the constant k_2. In this situation, the factors governing the rate constants for the formation of the tetrahedral intermediate determine the reaction rate. It is pertinent that the relative reactivities of the mono-, di-, and trimethyl derivatives are essentially the same in neutral solution where the hydroxide ion catalyzed reaction is dominant and in more basic solution, pH 9.75, at high buffer concentration where the buffer-catalyzed reaction proceeds at a limiting rate. These observations indicate that an interpretation of the rate data on the basis of the influences of the alkyl groups on the rate constants for the formation of the intermediate is suitable.

$$k_{obsd} = \frac{k_1k_3[OH^-]}{k_{-2}[BH]} + \frac{k_2k_3[B^-][H_2O]}{k_{-2}[BH]} \quad (1)$$

Spectroscopic work suggests that the mono- and dialkylnitrosoureas have a strong preference for the hydrogen-bonded conformation.[4,5] The concept of stereoelectronic control suggests that the reaction with hydroxide ion proceeds in a specific way to yield the tetrahedral intermediate in which the entering hydroxide ion and the lone pair on the *N'*-nitrogen atom are antiperiplanar (eq 2).[3] The *N*- and *N'*-alkyl groups apparently influence this reaction in three distinct ways. First, the high reactivities of *N*-cyclohexyl- and *N*-isopropyl-*N*-nitrosourea suggest that the steric requirements of the *N*-alkyl groups are important. The rate enhancement caused by these groups may be attributed to torsional interactions between the *N*-alkyl group and the carbonyl group in the starting compounds which are relieved, in part, in the conversion of the nitrosourea to the tetrahedral intermediate. Second, the polar influences of the *N'*-alkyl groups stabilize the nitrosourea and increase the energy requirements for the achievement of the tetrahedral intermediate. Third, this rate-retarding influence of the *N'*-alkyl groups is augmented by the increasing steric requirements for the conversion of the di- and trialkylnitrosoureas to the tetrahedral intermediate. The greatly reduced reactivities of compounds such as the *N*-methyl-*N'*-isopropyl and the *N*-methyl-*N',N'*-diisopropyl derivatives are best accounted for on these bases.

Scheme I

$$CH_3N(NO)CONH_2 + OH^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} CH_3N(NO)C(O^-)(NH_2)OH$$

$$CH_3N(NO)CONH_2 + HOH + B \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} T^- + BH^+$$

$$T^- \xrightarrow{k_3} CH_3N{=}NO^- + HOCONH_2$$

(2)

Experimental Section

Caution: the alkylnitrosoureas are suspected to be carcinogenic substances. Suitable precautions must be observed in work with these compounds.

Preparations. *N*-Isopropyl-*N*-nitrosourea was prepared by the nitrosation of isopropylurea obtained from the reaction of isopropylamine with *N,N'*-dimethyl-*N*-nitrosourea. The initial product exhibited an absorption at 237 nm and had distinctive NMR signals [δ 1.33 (d, CH_3), 5.01 (m, CH), 5.29 (br, NH), 6.81 (br, hydrogen bonded NH)]. These results together with the infrared spectrum secure the assignment of structure. However, a satisfactory elemental analysis could not be obtained.

The methods of preparation and the physical properties of the other nitrosoureas used in this investigation have been reported.[4]

Kinetic Experiments. The methods employed in this investigation were described previously.[4] The data reported in Tables I–III were obtained for the reaction at pH 9.75 in 0.2 M sodium borate buffer at 25 °C.

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(5) The conformational preference is reinforced by amide resonance and a strong intramolecular hydrogen bond as well as the relationship between the carbonyl group and the *N*- and *N'*-alkyl groups.

the American Cancer Society.

Registry No. *N*-Methyl-*N*-nitrosourea, 684-93-5; *N*-ethyl-*N*-nitrosourea, 759-73-9; *N,N'*-dimethyl-*N*-nitrosourea, 13256-32-1; *N*-methyl-*N'*-ethyl-*N*-nitrosourea, 72479-13-1; *N*-methyl-*N'*-propyl-*N*-nitrosourea, 72479-16-4; *N*-methyl-*N'*-isobutyl-*N*-nitrosourea, 72479-18-6; *N*-methyl-*N'*-isopropyl-*N*-nitrosourea, 72479-15-3; *N*-methyl-*N'*-*sec*-butyl-*N*-nitrosourea, 72479-17-5; *N*-methyl-*N'*-cyclohexyl-*N*-nitrosourea, 16813-38-0; *N*-methyl-*N'*-*tert*-butyl-*N*-nitrosourea, 72479-14-2; *N,N',N'*-trimethyl-*N*-nitrosourea, 3475-63-6; *N*-methyl-*N',N'*-diethyl-*N*-nitrosourea, 50285-72-8; *N*-methyl-*N',N'*-dipropyl-*N*-nitrosourea, 72479-19-7; *N*-methyl-*N',N'*-dibutyl-*N*-nitrosourea, 72479-21-1; *N*-methyl-*N',N'*-diisobutyl-*N*-nitrosourea, 72479-22-2; *N*-methyl-*N',N'*-diisopropyl-*N*-nitrosourea, 72479-19-7; *N*-methyl-*N*-nitroso-1-pyrrolidinecarboxamide, 67084-42-8; *N*-methyl-*N*-nitroso-1-piperidinecarboxamide, 72479-20-0; *N*-isopropyl-*N*-nitrosourea, 16830-14-1; isopropylurea, 691-60-1.

Substituent Effect during the Synthesis of Substituted [2.2]Paracyclophane by Photoextrusion of Carbon Dioxide from a Cyclic Diester

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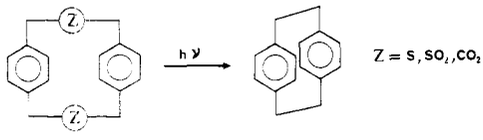
The continued interest in strained molecules such as [2.2]paracyclophanes has stimulated the search for a very effective synthesis. Several recent papers have shown that photoextrusion reactions of sulfur,[1-3] sulfur dioxide,[2,4] or carbon dioxide[5] from the sulfide, sulfone, or ester precursors, readily available by established synthetic methods, are very useful and high yield processes.



During our studies of photochemical reactions in organized media such as liquid crystals, we have been interested in the photodecarboxylation of dilactones (Z = CO_2) reported by Kaplan and Truesdale[5] for the synthesis of unsubstituted [2.2]paracyclophane. We report in this paper a drastic effect of substituents located on benzene rings during such a photodecarboxylation.

The synthesis of cyclic diesters **1** and **2** was accomplished from dibromo compounds and the trimethylammonium salt of 1,4-benzenediacetic acid in refluxing acetonitrile under high dilution conditions (giving higher yields than the heterogeneous condensation of the silver salt of the diacid).[5] The products were isolated by chromatography, and their physical properties, listed in Table I, are entirely consistent with the assigned structures.

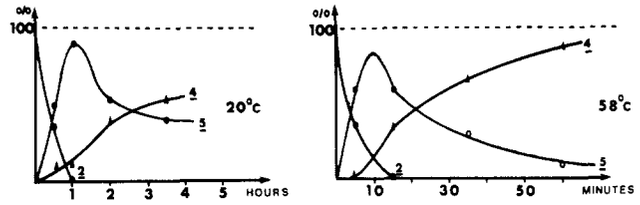
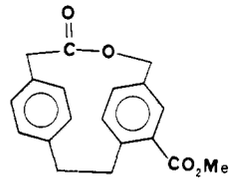


Figure 1.

While the parent diester (R = H) is readily photochemically decarboxylated into the corresponding paracyclophane[5] (70% yield), the dilactones **1** and **2** showed, under the same conditions, decarboxylation yields strongly dependent on the nature of R.

We actually observed that a methoxy group strongly enhanced the decarboxylation process as compared to a carbomethoxy group: complete disappearance of the starting dilactone required 12 min in the case of **1** and 1 h in the case of **2** when irradiation was conducted in quartz (MeOH, 20 °C). In addition, the dilactone **2** is first monodecarboxylated, leading only to the monolactone **5**[6]



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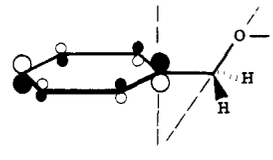
which is indeed difficult to decarboxylate further, as shown in Figure 1 and Table II, although this decarboxylation process was strongly temperature dependent: 6 times faster at 58 °C than at 20 °C (Table II). No such monodecarboxylation was detected from compound **1**.

Irradiation conducted in Pyrex ($\lambda > 300$ nm) led to an 86% yield of paracyclophane **3** from compound **1** (ϵ_{300nm} 978) in 50 min (20 °C) and only to a 36% yield of monolactone **5** from **2** (ϵ_{300nm} 283) in 20 h (20 °C).

The results obtained by Givens[8] during a photodecarboxylation study of esters showed that efficient CO_2 loss requires a phenyl substitution β to the oxygen atom as shown in **6**. This can be translated in terms of orbital interactions: the π_{arom}–σ^*_{C-O} hyperconjugation stabilizes conformer **6** and weakens the C–O bond.



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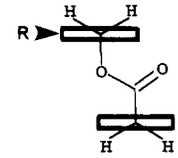

7

Likewise, in our case, the conformation **7** of the dilactone is both electronically (π–σ^* interaction) and sterically favored, which is consistent with the easy decarboxylation. The observed substituent effect is in agreement with this model: a methoxy group raises the aromatic π level,

(1) V. Boekelheide, I. D. Reingold, and M. Tuttle, *J. Chem. Soc., Chem. Commun.*, 406 (1973).
(2) W. Rebafka and H. Staab, *Angew. Chem., Int. Ed. Engl.*, **12**, 776 (1973).
(3) R. Gray and V. Boekelheide, *Angew. Chem., Int. Ed. Engl.*, **14**, 107 (1975).
(4) R. S. Givens, R. J. Olsen, and P. L. Wylie, *J. Org. Chem.*, **44**, 1608 (1979).
(5) M. L. Kaplan and E. A. Truesdale, *Tetrahedron Lett.*, 3665 (1976).

(6) TLC as well as ^1H and ^{13}C NMR spectroscopy indicate that only one isomer was formed and that the decarboxylation was regioselective. Structure **5** was demonstrated by 250-MHz ^1H NMR by comparison of the chemical shifts of benzylic protons linked to oxygen in molecules **2** and **5** [in **2**, δ_{AB} 5.50 (benzylic protons ortho to CO_2Me), 5.08 (benzylic protons meta to CO_2Me); in **5** δ_{AB} 5.02] and by the magnitude of the nonequivalence observed for the methylene ortho to CO_2Me in **4** and **5** [in **4**, δ_A 4.11, δ_B 2.88; in **5**, δ_A 4.04, δ_B 2.87]. A conformational study of these molecules will be published shortly (submitted for publication in *Can. J. Chem.*).
(7) H. J. Reich and D. J. Cram, *J. Am. Chem. Soc.*, **91**, 3534 (1969).
(8) R. S. Givens and W. F. Oettle, *J. Am. Chem. Soc.*, **93**, 3301 (1971).

0022-3263/80/1945-4496$01.00/0