washed with absolute alcohol. The precipitate was dried in an oven at 110°. Analysis indicated that the salt contained only a small amount of water (2–3%). About 0.7 g. of sample was used in each of the runs.

Table I contains a summary of the runs which were made.

TABLE I

	Temperature of reaction tube, °C.	Duration in hours of fluorination period
1	Room temperature	4.5
	Room temperature	7.5
2	300	4
	300	7
3	500	3
	500	8
4	625	3.75
	625	7.5
5	700	4
	700	7.5
6	800	4
	800	7.5

After each run, the sample was tested with hydriodic acid to determine whether any oxidation had occurred. In each instance, the results were negative. This confirms the work of Klemm.[2]

In the preliminary stages of this investigation when a platinum combustion boat was used, praseodymium(III) fluoplatinate was one of the products formed at temperatures above 500°. Detailed information on this and other fluoplatinates will be the subject of a paper now in preparation.

Acknowledgment.—Part of this work was supported by A. E. C. contract.

CONTRIBUTION FROM THE
CHEMISTRY DEPARTMENT OF THE
GEORGE WASHINGTON UNIVERSITY
WASHINGTON, D. C.

Kinetics and Some Hydrogen Isotope Effects of the Reaction of Diphenyldiazomethane with Acetic Acid in Ethanol[1]

BY JOHN D. ROBERTS AND CLARE M. REGAN

RECEIVED DECEMBER 3, 1951

As part of other investigations,[2,3] we have had occasion to study the kinetics and hydrogen isotope effects of the reaction of diphenyldiazomethane with acetic acid in ethanol using the techniques previously developed for other carboxylic acids.[2–5] As might be expected, the reaction of acetic acid with diphenyldiazomethane is very similar to that with benzoic acid in that it is accurately first order in acid as well as diazo compound and shows similar salt and medium effects (*cf.* Table I). All of the data are consistent with the hypothesis that acetic acid and benzoic acid react with diphenyldiazomethane by similar mechanisms involving rate-determining proton transfers from undissociated acid to diazo compound. Indeed, the only very striking difference between the behaviors of the two acids is that a considerably higher fraction of benzhydryl acetate (87%) is formed with acetic acid than benzhydryl benzoate (55%) with benzoic acid[3] (Table II). This difference is likely to be due to steric hindrance since acetic acid with its small methyl group should be more reactive in a direct reaction[3] with diphenyldiazomethane than benzoic acid.

TABLE I

RATES OF REACTION OF DIPHENYLDIAZOMETHANE WITH ACETIC ACID IN ABSOLUTE ETHANOL AT 30.0°

Acetic acid, mole/l.	Diphenyldiazomethane, mole/l.	Salt, mole/l.	k_2, (moles/l.)$^{-1}$ min.$^{-1}$
0.0341	0.00218	....	0.562
.0683	.00328	....	.556
.1472	.00547	....	.578
.1472	.00547	0.033 $LiClO_4$	.624
.1472	.00547	.067 $LiClO_4$	.645
.1472	.00547	.100 $LiClO_4$	.692
.1472	.00547	.033 NaOAc	.523[a]
.1472	.00547	.067 NaOAc	.493[a]
.1472	.00547	.100 NaOAc	.462[a]
.1542[b]	.00526	....	2.12
.1542[c]	.00526	....	1.30
.1787[d]	.00947	....	0.166
.0953[e]	.00526	....	0.553
.0953[e,b]	.00526	....	2.12
.0953[e,c]	.00526	....	1.23
.1759[e,d]	.00947	....	0.151

[a] The same slowing of rate by carboxylate ion was observed with benzoic acid and admits of a similar explanation.[3] [b] Solvent was 82.5% ethanol–17.5% water (by volume). [c] Solvent was 82.5% ethanol–17.5% deuterium oxide (by volume), 38% calculated replacement of O–H groups by O–D groups. [d] Solvent was C_2H_5OD which was prepared as described previously.[5] [e] CD_3COOD used in place of CH_3COOH.

TABLE II

ACETIC ACID CONSUMPTION IN DIPHENYLDIAZOMETHANE REACTION AT 30.0° IN ABSOLUTE ETHANOL

Acetic acid, mole/l.	Diphenyldiazomethane, mole/l.	Salt, mole/l.	Eq. acid consumed/eq. of diphenyldiazomethane[a]
0.0440	.000915	....	0.88
.0440	.00915	....	.86
.0440	.00915	0.070 $LiClO_4$	.83
.0440	.00915	.070 $LiClO_4$	.82

[a] Determined by the procedure of ref. 3.

As part of our program of research on isotope effects,[3,5] several hydrogen isotope effects on the acetic acid–diphenyldiazomethane reaction were measured and are listed in Table I. Substitution of C_2H_5OD for ordinary ethanol as the solvent (with consequent replacement of O–H by O–D in the carboxyl group of the acetic acid) caused a very substantial decrease in the reaction rate (3.5-fold for acetic acid as compared with 3.6-fold for benzoic acid[5]) as expected for a rate-determining proton transfer. Similar replacement of 38% of the O–H bonds by O–D bonds in 82.5% ethanol–17.5% water brought about a 39% decrease in the reaction rate with acetic acid as compared with 38% with benzoic acid.[3] In a number of experiments

---

(1) Supported in part by the program of research of the United States Atomic Energy Commission.

(2) J. D. Roberts and C. M. Regan, *Anal. Chem.*, **24**, 360 (1952).

(3) J. D. Roberts, W. Watanabe and R. E. McMahon, THIS JOURNAL, **73**, 760 (1951).

(4) (a) J. D. Roberts, E. A. McElhill and R. Armstrong, *ibid.*, **71**, 2923 (1949); (b) J. D. Roberts and W. Watanabe, *ibid.*, **72**, 4869 (1950).

(5) J. D. Roberts, C. M. Regan and I. Allen, *ibid.*, **74**, 3679 (1952).

with CD_3COOD[6] in ordinary or deuterated ethanol, it was found that introduction of three deuteriums in the α-position does not alter the reactivity of acetic acid much beyond the experimental error.

In most cases the reactions were slower, but even the largest effect was under 10%. These results confirm the expectation that there should be no very significant difference in electrical or other effects between CH_3– and CD_3– groups on the carboxyl hydrogen.

---

(6) We are indebted to Dr. Donald J. Cram for the preparation of this material by the procedure of C. L. Wilson, *J. Chem. Soc.*, 492 (1935).

DEPARTMENT OF CHEMISTRY AND LABORATORY
FOR NUCLEAR SCIENCE AND ENGINEERING
MASSACHUSETTS INSTITUTE OF TECHNOLOGY
CAMBRIDGE 39, MASSACHUSETTS

Urea Derivatives Related to Procaine

BY NORMAN RABJOHN AND J. Z. SHAHABEDDIN[1]

RECEIVED MARCH 14, 1952

Numerous substituted ureas have been prepared and found to possess physiological properties; however, very few of these are of the diaryl type.

TABLE I

UREA DERIVATIVES OF PROCAINE, $XC_6H_4NHCONHC_6H_4CO_2C_2H_4N(C_2H_5)_2$

X	M.p., °C.	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
			Bases				
H[a]	94–96	91	$C_{20}H_{25}O_3N_3$	67.58	67.67	7.09	7.14
2-CH_3[a]	87–89	96	$C_{21}H_{27}O_3N_3$	68.26	67.86	7.37	7.44
2-Cl[a]	86–88	87	$C_{20}H_{24}O_3N_3Cl$	61.61	61.68	6.20	6.44
3-Cl[a]	88–90	88	$C_{20}H_{24}O_3N_3Cl$	61.61	61.51	6.20	6.49
2.5-Cl[b]	155–156	89	$C_{20}H_{23}O_3N_3Cl_2$	56.61	56.39	5.46	5.53
4-Br[c]	174–176	87	$C_{20}H_{24}O_3N_3Br$	55.31	55.63	5.57	5.48
2-NO_2[c]	101–102	91	$C_{20}H_{24}O_5N_4$	59.99	60.30	6.04	6.26
4-NO_2[c]	156–158	84	$C_{20}H_{24}O_5N_4$	59.99	59.71	6.04	6.21
			Hydrochlorides				
H	202–204	97	$C_{20}H_{26}O_3N_3Cl$	61.29	61.26	6.68	6.88
2-CH_3[c]	174–175 (picrate)	92	$C_{27}H_{30}O_{10}N_6$	54.17	54.29	5.05	5.13
2-Cl	195–197	91	$C_{20}H_{25}O_3N_3Cl_2$	56.34	56.66	5.91	6.09
3-Cl	193–195	92	$C_{20}H_{25}O_3N_3Cl_2$	56.34	56.31	5.91	5.91
2,5-Cl	221–223	91	$C_{20}H_{24}O_3N_3Cl_3$	52.13	52.36	5.25	5.13
4-Br	215–217	86	$C_{20}H_{25}O_3N_3ClBr$	51.02	51.36	5.35	5.12
2-NO_2	202–203	97	$C_{20}H_{25}O_5N_4Cl$	54.98	55.11	5.77	6.09
4-NO_2	221–223	87	$C_{20}H_{25}O_5N_4Cl$	54.98	54.96	5.77	5.97

Crystallization solvents: [a] Ethyl acetate-petroleum ether (60–70°). [b] Ethyl acetate. [c] Absolute alcohol.

In connection with an investigation[2] of the effect of change in structure of the 4-amino group in procaine on its pharmacological activity, we prepared 4,4′-di-(β-diethylaminocarboethoxy)-carbanilide[3] and tests[4] indicated that it is relatively active as a local anesthetic.

Accordingly, we have undertaken the syntheses of a number of diarylureas related to procaine by the reaction of the latter with various aryl isocyanates. The melting points, percentage yields, and analytical data for these compounds are recorded in Table I. As yet, they have not been tested for possible physiological properties.

Experimental[5]

Materials.—The aryl isocyanates were purchased from the Eastman Kodak Co. and were purified by distillation or crystallization immediately prior to use. The procaine base was prepared by treating the hydrochloride (Merck and Co., Inc.) with alkali, dissolving the resulting dihydrate in benzene and distilling the solution to a low volume. Upon cooling the residue, the desired base was obtained in almost quantitative yield; m.p. 58–59°.

Preparation of 4-(β-Diethylaminocarboethoxy)-carbanilide and its Hydrochloride.—This procedure is representative of the methods employed for the preparation of the compounds listed in Table I. To 11.8 g. (0.05 mole) of procaine base, dissolved in a mixture of 50 ml. of anhydrous benzene and 25 ml. of anhydrous toluene, was added 5.95 g. (0.05 mole) of phenyl isocyanate. The reaction mixture warmed spontaneously and was refluxed then for about 30 minutes. It was allowed to cool, and placed in a refrigerator until crystallization was completed. The white crystals were removed by filtration, washed with anhydrous benzene and dried to give 16.2 g. (91%) of a product which melted at 90–94°. Four recrystallizations from a mixture of ethyl acetate and petroleum ether (60–70°) raised the melting point to 94–96°.

A sample (1.78 g.) of the purified substituted carbanilide was dissolved in 10 ml. of anhydrous ether and dry hydrogen chloride was passed through the solution. The precipitated hydrochloride was removed on a buchner funnel and dried over solid potassium hydroxide; wt. 1.94 g. (97%); m.p. 202–204°.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF MISSOURI
COLUMBIA, MISSOURI

---

(1) Abstracted in part from a thesis submitted by J. Z. Shahabeddin to the Graduate College of the University of Missouri, 1952, in partial fulfillment of the requirements for the degree of Master of Arts.

(2) N. Rabjohn, T. R. Hopkins and R. C. Nagler, THIS JOURNAL, **74**, 3215 (1952).

(3) U. N. Narayana Rao, B. H. Iyer and P. C. Guha, *Current Sci.* (*India*), **19**, 180 (1950); *C. A.*, **44**, 11025 (1950).

(4) The authors are indebted to the McNeil Laboratories for screening this compound.

(5) All melting points are uncorrected. The semimicro analyses were performed by Mr. P. D. Strickler.