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The Relative Reactivities of Methanol and Methoxide Ion in Addition to 4-Chlorobenzyne[1]

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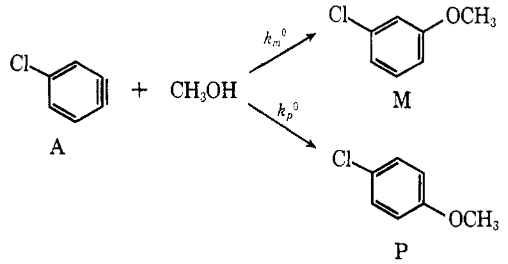
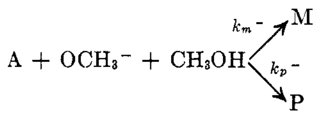
The relative reactivities of CH_3O^- and CH_3OH toward 4-chlorobenzyne can be reckoned from the variation of the chloroanisole *para/meta* ratio with $NaOCH_3$ concentration. The necessary mathematical expression is derived, and a set of experimental determinations gives the expected linear plot. Methoxide ion is estimated to be 157 times as reactive as methanol toward the carbon in 4-chlorobenzyne *meta* to chlorine, and 70 times as reactive toward the position *para* to chlorine.

When 4-chlorobenzyne is generated in methanol solution, it adds methanol to form a mixture of *m*- and *p*-chloroanisoles (eq 1). In neutral methanol, the *p*-/*m*-chloroanisole ratio is about 4.7. However, the *p*-/*m*-chloroanisole ratio decreases as the $NaOCH_3$ concentration in the medium increases; it is about 2.1 in 2 *M* $NaOCH_3$ in methanol.[3]



(1)

The change in *para/meta* ratio indicates that orientation is quantitatively different in the methoxide ion catalyzed addition (eq 2) than in addition of neutral methanol, and that methoxide ion is much more reactive than methanol. If methoxide ion were less reactive or even approximately equally reactive, the chloroanisole product ratio would not have changed much, regardless of what *para/meta* ratio prevailed in eq 2, because even in 2 *M* methanolic $NaOCH_3$ solvent molecules are in great excess.[3]



$$A + OCH_3^- + CH_3OH \begin{cases} \xrightarrow{k_m^-} M \\ \xrightarrow{k_p^-} P \end{cases} \tag{2}$$

The possibility that the altered *para/meta* ratio in 2 *M* $NaOCH_3$ is merely due to a salt effect was vitiated by demonstration that the *para/meta* ratio is essentially the same in 2 *M* $NaClO_4$ in methanol as in the pure solvent.[3]

A Method for Estimating the Relative Reactivities of Methanol and Methoxide Ion.—On the assumption that the reactions portrayed in eq 1 and 2 are first order in CH_3OH and CH_3O^-, respectively, we may write eq 3 concerning *p*-chloroanisole and an analogous expression concerning its *meta* isomer.

$$\frac{d[P]}{dt} = k_p^0[A][CH_3OH] + k_p^-[A][CH_3O^-] \tag{3}$$

Dividing one expression by the other

$$R = \frac{d[P]}{d[M]} = \frac{k_p^0[CH_3OH] + k_p^-[CH_3O^-]}{k_m^0[CH_3OH] + k_m^-[CH_3O^-]} \tag{4}$$

Let us define R as the experimental *p*-/*m*-chloroanisole ratio under any conditions (*cf.* eq 4), R^0 as k_p^0/k_m^0, the product ratio in reaction with neutral methanol, and R^- as k_p^-/k_m^-, the ratio in reaction with methoxide ion. Equation 4 is easily transformed into

$$\left(R - \frac{k_p^0}{k_m^0}\right)k_m^0[CH_3OH] = \left(\frac{k_p^-}{k_m^-} - R\right)k_m^-[CH_3O^-] \tag{5}$$

Rearranging

$$\frac{R^0 - R}{R - R^-} = \frac{k_m^-}{k_m^0}\,\frac{[CH_3O^-]}{[CH_3OH]} \tag{6}$$

According to eq 6, a plot of $(R^0 - R)/(R - R^-)$ *vs.* $[CH_3O^-]$ should be linear with slope equal to $(k_m^-/k_m^0)\cdot(1/[CH_3OH])$. From the slope, k_m^-/k_m^0, the ratio of methoxide to methanol reactivities toward the aryne carbon in 4-chlorobenzyne *meta* to the chlorine atom is

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[1] Financial support by the National Science Foundation is gratefully acknowledged.

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[3] J. F. Bunnett, D. A. R. Happer, M. Patsch, C. Pyun, and H. Takayama, *J. Amer. Chem. Soc.*, **88**, 5250 (1966).

TABLE I

REACTIONS OF 1-(4-CHLORO-2-IODOPHENYL)-2-BENZENESULFONHYDRAZIDE WITH $NaOCH_3$ IN CH_3OH AT 59.4°

$[NaOCH_3]_{st}$,[a] M	$[CH_3O^-]_f$,[b] M	[Substrate]$_0$,[c] M	Product yields, %					
			p- and *m*-chloroanisoles	*m*-C_6H_4ClI	C_6H_5Cl	I^-	R[e]	$\frac{R^0 - R}{R - R^-}$
			Part A					
0.10[d]	0	0.10	10.2	59.4	0.7	16.6	4.73	0
0.20	0.10	0.10	13.3	63.5	0.9	19.7	3.71	0.64
0.30	0.20	0.10	14.7	64.2	1.4	21.0	3.23	1.35
0.40[d]	0.30	0.10	15.5	63.4	2.0	21.2	3.01	1.93
0.50	0.40	0.10	16.2	57.4	1.9	24.9	2.85	2.58
0.60	0.50	0.10	16.8	63.5	2.2	22.1	2.72	3.35
0.70	0.60	0.10	17.2	63.7	2.4	22.1	2.65	3.92
0.80	0.70	0.10	17.0	61.5	4.6	23.1	2.58	4.67
0.90	0.80	0.10	17.2	60.1	4.1	23.3	2.52	5.52
1.00	0.90	0.10	18.1	~60	5.1	22.7	2.50	5.87
2.00[d]	1.90	0.10	20.2	66.4	~10	31.2	2.12	∞
			Part B					
0.10	0.08	0.02	18.9	60.4	2.8	23.1	3.76	0.59
0.30	0.28	0.02	19.5	63.5	6.8	25.8	3.04	1.84
0.40	0.38	0.02	20.5	66.1	7.7	27.7	2.85	2.58
0.70	0.68	0.02	16.9	53.1	15.4	33.1	2.58	4.67

[a] $[NaOCH_3]_{st}$ represents the concentration that would have been obtained if there had been no reaction with substrate. [b] $[OCH_3^-]_f$ represents the "free" concentration after acid–base reaction with substrate. [c] The substrate is named in the title of the table. [d] Duplicate runs afforded R values differing by not more than 0.02. [e] *p*-/*m*-Chloroanisole ratio.

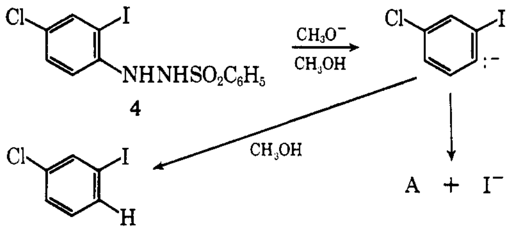
easily reckoned. (The solvent concentration is considered as constant.) The corresponding reactivity ratio toward the position *para* to chlorine is then given by

$$k_p^-/k_p^0 = (R^-/R^0)(k_m^-/k_m^0) \qquad (7)$$

In order to use eq 6 and 7, one must know R^0 and R^-. The former is easily determined by decomposition of a suitable 4-chlorobenzyne precursor in methanol not containing free methoxide ions. The latter may be estimated from the *para/meta* product ratio in a concentrated $NaOCH_3$ solution, providing that the data indicate the methoxide-catalyzed addition to be predominant at that concentration.

Although eq 6 and 7 are derived for the specific case of 4-chlorobenzyne reacting with CH_3O^- and CH_3OH, the principle should be valid for other cases in which two nucleophiles, one the conjugate base of the other, compete for a suitably constituted aryne.

Choice of Chemical System.—A precursor which would afford 4-chlorobenzyne under a wide range of $NaOCH_3$ concentrations was desired. Chlorine derivatives of benzenediazonium 2-carboxylate[4] cannot be used except in neutral methanol because in basic methanol dediazoniation to chlorobenzoic acids eclipses aryne formation.[3] However, 1-(*o*-halophenyl)-2-benzenesulfonhydrazides are decomposed to *o*-halophenyl anions over a wide range of $NaOCH_3$ concentrations,[5,6] and when the halogen is bromine or iodine the *o*-halophenyl anion reacts in part to eject halide ion and form an aryne. (The competing mode of reaction is proton capture from methanol to form an aryl halide.) A greater fraction of halide ion loss occurs the more easily the carbon–halogen bond is broken, and accordingly the easily accessible 1-(4-chloro-2-iodophenyl)-2-benzenesulfonhydrazide (**4**) was chosen as the principal 4-chlorobenzyne precursor for this study; see eq 8.



(8)

This system involves a complication which, fortunately, is of no consequence to its use for our present purposes. The *m*-chloroiodobenzene formed (see eq 8) undergoes partial loss of iodine under the conditions employed, forming chlorobenzene and iodide ion.[3,7] This side reaction should not have any effect on the reactions of 4-chlorobenzyne. Indeed, the *p*-/*m*-chloroanisole ratio in 2 *M* $NaOCH_3$–CH_3OH from the system of eq 8 was earlier shown to be substantially the same as from other 4-chlorobenzyne precursors.[3]

Experiments to Estimate Relative Reactivities.—Our experiments concerning reactions of **4** with $NaOCH_3$ in CH_3OH are summarized in Table I. This table comprises two series of runs, differing in the initial concentration of substrate. Inasmuch as a rapid acid–base reaction occurs on mixing, the data are best considered with reference to $[OCH_3^-]_f$, the free methoxide ion concentration remaining after the acid–base reaction. The *p*-/*m*-chloroanisole ratios (R) in the two series at nearly equal $[OCH_3^-]_f$ are virtually the same.

Qualitatively, the data of Table I show the same trend toward lower *p*-/*m*-chloroanisole ratios at higher methoxide concentrations that was noted earlier in a less extensive set of data concerning the same substrate.[3] Quantitatively, a plot of $(R^0 - R)/(R - R^-)$ *vs.* $[OCH_3^-]_f$ is linear, as called for by eq 6. It is presented as Figure 1. The slope by linear regression analysis is 6.67, and the correlation coefficient 0.998. From the density of methanol at 59.4° (0.754 g/ml[8]), the concen-

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[4] M. Stiles and R. G. Miller, *J. Amer. Chem. Soc.*, **82**, 3802 (1960).

[5] J. F. Bunnett and D. A. R. Happer, *J. Org. Chem.*, **31**, 2369 (1966).

[6] J. F. Bunnett and H. Takayama, *J. Amer. Chem. Soc.*, **90**, 5173 (1968).

[7] J. F. Bunnett and C. C. Wamser, *ibid.*, **89**, 6712 (1967).

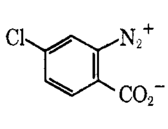
[8] "International Critical Tables," Vol. III, 1928, p 27.

tration of CH_3OH is 23.6 M. From this value, the slope in Figure 1 and eq 6 and 7, k_m^-/k_m^0, is reckoned as 157 and k_p^-/k_p^0 as 70. These are the relative reactivities of methoxide ion and methanol toward the carbons *meta* and *para* to chlorine in 4-chlorobenzyne. These results may alternatively be expressed as rate coefficients relative to k_m^0 (1.0) as follows: k_p^0, 4.7; k_m^-, 1.6×10^2; k_p^-, 3.3×10^2.

We stress that these results depend on the validity of the assumptions made in deriving eq 6. Chief among them is the assumption that the neutral and base-catalyzed methanol additions are first order in methanol and methoxide ion, respectively. However, it is noteworthy that if the respective reaction rates were proportional to $[CH_3OH]^2$ and to $[OCH_3^-][CH_3OH]$, eq 6 would still be valid because $[CH_3OH]$ would cancel from both numerator and denominator in forming eq 4.

The numerical values of the various rate coefficient ratios derived from our data also depend on the R^0 and R^- values chosen for use in the computations. The values we have used are from the data of Table I, namely, 4.73 for R^0 and 2.12 for R^-. Each of these represents the average of two independent determinations which differed by not more than 0.02 in R value. In other experiments,[3] R^0 and R^- values differed somewhat according to the aryne precursor and the experimental conditions employed. We do not fully understand those variations, but we note that the R^0 and R^- values used in the present computations are close to the average of other determinations.

Orientation of CH_3OD Addition.—From decomposition of 5-chlorobenzenediazonium 2-carboxylate (**5**) in methanol-O-*d* at reflux, *p*- and *m*-chloroanisoles were obtained in a *para/meta* ratio of 4.0. The similarity of this product ratio to that in ordinary methanol suggests that sundering of the O–H bond of the alcohol and/or bond formation by hydroxy hydrogen to aryne carbon are not involved prior to or during rate-limiting steps. The alternative, previously rejected on other grounds,[3] of concerted addition *via* cyclic transition states **6** and **7** would, of course, be subject to a kinetic isotope effect in regard to the formation of both isomers, and if each reaction were equally affected one might think the *para/meta* ratio to be unaffected. However, the change of hydrogen isotope would change the relative degrees of C–O and C–H bond formation in concerted, cyclic transition states, and consequently the charge distribution in the transition states, and therefore the *para/meta* ratio.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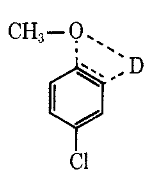
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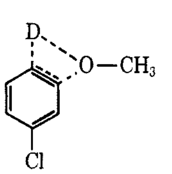
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Reaction Mechanism.—The facts that the *p-/m*-chloroanisole ratio is higher for neutral methanol addition than for methoxide-catalyzed addition and that methoxide ion is more reactive than neutral methanol indicate that additions of both nucleophiles occur stepwise *via* rate-limiting transition states such as **8** and **9**. The arguments have been presented previously,[3] and are not repeated here.

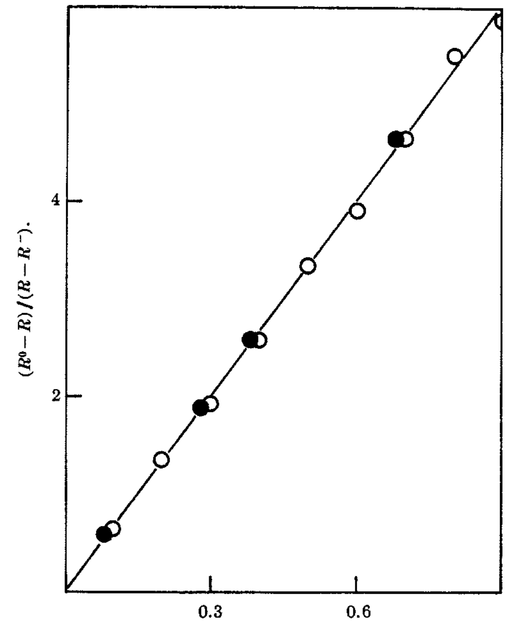
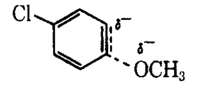


Figure 1.—Plot used to evaluate k_m^-/k_m^0; see eq 6. Data of Table I: ○, part A; ●, part B.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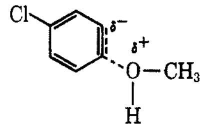
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Experimental Section

Materials.—1-(2-Iodo-4-chlorophenyl)-2-benzenesulfonhydrazide (**4**) was prepared as previously described,[3] and 5-chlorobenzenediazonium 2-carboxylate (**5**) after Stiles, Miller, and Burckhardt.[9] Methanol-O-*d* was prepared after Streitwieser, Verbit, and Stang[10]; it was estimated from its infrared spectrum to be 94% deuterated on oxygen.

Reactions of 4 with $NaOCH_3$ in CH_3OH.—The hydrazide **4** (0.409 g, 0.001 mole) in a 25-ml round-bottomed flask was mixed with methanolic $NaOCH_3$ (10 ml) with swirling under dry, oxygen-free nitrogen at room temperature. The hydrazide dissolved to form a solution of color varying from pale yellow with 0.1 M $NaOCH_3$ to reddish pink with 2 M $NaOCH_3$. A water-cooled condenser capped by a soda lime drying tube was affixed, and the flask was placed in a thermostat at 59.4° for 1 hr. To the cooled flask, 1.0 ml of a pentane solution containing 1×10^{-5} mole of bromobenzene and 5×10^{-5} mole of *o*-chloroanisole and then 10 ml of pentane were added through the condenser. Water (10 ml) was added, the layers were separated, the aqueous layer was extracted with a further 5 ml of pentane, and the combined pentane extracts were washed twice with water and dried over anhydrous $MgSO_4$. The dried pentane extract was analyzed by glpc on a column of 10% Carbowax 20M on Chromosorb P (80–100), at a column temperature of 115°. Relative molar responses were determined to be: chlorobenzene identically equal to bromobenzene, the three chloroanisole isomers identically equal to each other, and *o*-chloroanisole/*m*-chloroiodobenzene 1.00/0.78. Comparison of observed peak areas, corrected for molar response, and retention times with those of the bromobenzene and *o*-chloroanisole standards enable quantitative determination of yields. Iodide ion was determined by titration of the aqueous extracts with $AgNO_3$.

Registry No.—Methanol, 67-56-1; methoxide ion, 3315-60-4; A, 14091-35-1; **4**, 14173-17-2.

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[9] M. Stiles, R. G. Miller, and U. Burckhardt, *J. Amer. Chem. Soc.*, **85**, 1792 (1963).

[10] A. Streitwieser, Jr., L. Verbit, and P. Stang, *J. Org. Chem.*, **29**, 3706 (1964).