a difference-fourier synthesis, but the C–H distances were restrained to 1.08 Å. The final refinements were with anisotropic temperature factors on the non-hydrogen atoms and individual isotropic temperature factors on the hydrogen atoms. A two-block matrix least-squares method was employed, minimizing $\sum w\Delta F^2$ where $w^{-1} = \sigma^2|F_o| + 0.0002|F_o|^2$. The refinement converged at $R = 0.073$, $R_w = 0.074$, for 754 unique observed reflections ($I > 3\sigma(I)$) and 146 least-squares parameters. Four reflections were omitted because of suspected extinction. The final difference maps were flat, without recognizable residual features.

Acknowledgment. T.S.C. and M.T.H.L. are grateful to the NSERC for grant support.

Registry No. 1, 112399-65-2; 1-naphthylacetonitrile, 132-75-2; ethyl 1-naphthylacetimidate hydrochloride, 43002-67-1; 1-naphthylacetamidine hydrochloride, 16275-19-7.

Supplementary Material Available: Tables of atomic positional parameters, anisotropic temperature factors, interatomic distances, interbond angles, and torsion angles (6 pages). Ordering information is given on any current masthead page.

Carbon Leaving Group in Aromatic Nucleophilic Substitution. Quantitative Comparison with a Common Leaving Group

Mario Mattioli, Paolo Mencarelli,* and Franco Stegel[1]

Centro di Studio sui Meccanismi di Reazione e Dipartimento di Chimica, Università di Roma "La Sapienza", 00185 Roma, Italy

Received July 13, 1987

Examples of carbon leaving groups in aromatic nucleophilic substitutions on activated substrates are scarce,[2,3] and as far as we know, no data are reported on the relative mobility of these groups with respect to the usual leaving groups, e.g., NO_2, F, Cl, Br. With the aim to fill this gap, we started a preliminary investigation, some time ago, on the reactivity of 4-(trichloromethyl)quinazoline (**1**) toward nucleophilic reagents.[4] Trihalomethyl groups are well known as leaving groups in the haloform reaction,[5] but they are seldom present as leaving groups in aromatic nucleophilic substitutions.[3]

In a previous paper, we reported that **1** reacts easily with methoxide ion in methanol to give the expected product of aromatic nucleophilic substitution at position 4, i.e., 4-methoxyquinazoline.[4] An accurate spectroscopic investigation of the reaction revealed that during the course of the reaction, at variance with the usual aromatic substitution mechanism, a covalent solvation adduct accumulates. Thus, this reaction seemed to us unfit for a quantitative assessment of the mobility of a trichloromethyl group in the aromatic nucleophilic substitution.

We now report on the reaction of **1** with hydroxide ion in 1:1 MeCN/H_2O and on the quantitative comparison of the reactivity of **1** with that of 4-chloroquinazoline (**2**).

Results and Discussion

Compound **1** reacts rapidly, at room temperature, with tetrabutylammonium hydroxide ion in 1:1 MeCN/H_2O to give 4-hydroxyquinazoline (**3**) as the only product. No spectroscopic evidence was found for the accumulation of an intermediate during the reaction course.

Table I. Kinetic and Activation Data for the Reactions of 1 and 2 with OH^- in 1:1 MeCN/H_2O

compd	k_2 (25 °C), M^{-1} s^{-1}	$\Delta H^{\ddagger}$,[a] kcal mol^{-1}	$-\Delta S^{\ddagger}$,[a] cal deg^{-1} mol^{-1}
1[b]	3.18×10^{-2}	12.6 (0.5)	23.1 (1.6)
2[c]	8.34×10^{-3}	17.0 (0.7)	11.1 (2.2)

[a] Standard deviations in parentheses. [b] $k_2 \times 10^2$, M^{-1} s^{-1} (°C): 2.22 (20.6), 4.27 (28.3), 6.93 (36.2), 11.8 (43.6). [c] $k_2 \times 10^3$, M^{-1} s^{-1} (°C): 5.15 (20.4), 11.7 (28.1), 23.8 (36.1).

Since our aim was to compare the mobility of the trichloromethyl group with that of a more usual one, the chlorine atom was chosen as a reference group. Therefore, the reaction of **2** under the same conditions was studied. Also, in this case an aromatic nucleophilic substitution does occur, but, at variance with the reaction of **1**, 4-hydroxyquinazoline is not the only reaction product. A small amount of 4-(cyanomethyl)quinazoline (**4**) (6–12% yield, depending on the temperature), arising from the reaction of **2** with the conjugated base of MeCN, was in fact found. As for the reaction of **1**, no intermediate was observed in the reaction of **2** with hydroxide ion.

All kinetic measurements were carried out under pseudo-first-order conditions, with a large excess of the nucleophile. The rate constants for the reaction of **2** with OH^- were obtained from the observed rate constants and from the ratio of **3**/**4**, assuming a kinetic scheme of two first-order parallel reactions. Kinetic and activation data for the reactions of **1** and **2** with OH^- in 1:1 MeCN/H_2O are reported in Table I.

The rate constant values, at 25 °C, show that **1** is about 4 times more reactive than **2**; that is, the mobility of the trichloromethyl group in this reaction is slightly higher than that of the chlorine atom, which is generally considered a fairly good leaving group in aromatic nucleophilic substitutions.[6a]

On inspection of the activation parameters, an interesting feature emerges. The modest difference in the rate constants is the result of a compensation between the activation enthalpies and activation entropies of the two reactions. In fact, the reaction of **1** is characterized by an activation enthalpy 4.4 kcal mol^{-1} lower than the reaction of **2**, while **2** is favored by an activation entropy less negative by 12 eu. (3.6 kcal mol^{-1} at 25 °C).

Since aromatic nucleophilic substitution on activated substrates with anionic nucleophiles proceeds through an addition–elimination mechanism with the addition as the key step,[6b] the rate constants reported in Table I refer to the addition of the nucleophile to position 4 of the quinazoline ring. With this in mind, we can propose some tentative explanations for the differences in the activation parameters.

From the electronic point of view, the CCl_3 and Cl groups interact differently with the quinazoline ring. The chlorine atom is in fact conjugated with the π system of the ring, particularly with the two electron-withdrawing aza groups. This type of interaction (not possible for the trichloromethyl group) stabilizes the initial state whereas it is lost (at least partially) in the transition state owing to the hybridization change from sp^2 to sp^3 of the carbon atom at position 4. This different electron behavior can be partially responsible for the greater enthalpy of acti-

(1) Deceased October 1986.
(2) Sheperd, R. G.; Fedrick, J. L. *Adv. Heterocycl. Chem.* **1965**, *4*, 145.
(3) (a) Kober, E. *J. Org. Chem.* **1960**, *25*, 1728. (b) Eloy, F.; Lenaers, R. *Helv. Chim. Acta* **1966**, *49*, 1430. (c) Kobayashi, Y.; Kumadaki, I. *Acc. Chem. Res.* **1978**, *11*, 197.
(4) Mencarelli, P.; Stegel, F. *J. Org. Chem.* **1985**, *50*, 5415.
(5) (a) March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley: New York, 1985; p 567. (b) Hudlicky, M. *Chemistry of Organic Fluorine Compounds*; Macmillan: New York, 1962; pp 208–209.
(6) (a) Miller, J. *Aromatic Nucleophilic Substitution*; Elsevier: Amsterdam, 1968; Chapter 5. (b) *Ibid.* pp 18–19.

0022-3263/88/1953-1087$01.50/0

Table II. Standard Heats of Formation of Some α- and β-Substituted Naphthalene Derivatives (gas, 298 K)

compd	$\Delta H_f°$, kcal mol^{-1}
1-methylnaphthalene[a]	27.93
2-methylnaphthalene[a]	27.75
1-(trichloromethyl)naphthalene[b]	10.90
2-(trichloromethyl)naphthalene[b]	6.15

[a] From ref 8. [b] From molecular mechanics calculations (this work).

vation shown by the reaction of **2**. In our opinion, however, another effect arising from the different steric hindrance of the two leaving groups is much more effective. In fact, groups bonded at position 4 of the quinazoline are subjected to a peri interaction with the hydrogen at position 5 as observed in naphthalene derivatives. This destabilizing interaction, effective in the initial state, should decrease in the transition state, as the leaving group is going out of the plane of the ring. This steric effect, which lowers the enthalpy of activation, should be much more important for the bulkier trichloromethyl group than for the chlorine atom.

In order to validate this hypothesis, we tried to evaluate the amount of the peri interaction of the CCl_3 and Cl groups by looking at the standard heats of formation (gas phase) of 1-substituted and 2-substituted naphthalenes, using the latter as a model compounds. Since the standard heats of formation for the (trichloromethyl)naphthalenes are not reported, we recurred to molecular mechanics calculations.[7] The standard heats of formation for α- and β-chloronaphthalene reported in literature[8] are not comparable since they refer to different physical states. Unfortunately, the MMP2 program is not parametrized for calculations on aromatic chloro derivatives. Since the heats of formation of the corresponding methylnaphthalenes are available[8] and considering that the methyl group has a lower steric hindrance than chlorine,[9] they can be used as an alternative to evaluate an upper limit for the amount of peri interaction of a chlorine atom. All these values are collected in Table II. It is evident that the peri interaction is practically negligible for the methyl group ($\Delta\Delta H_f° = 0.2$ kcal mol^{-1}) whereas it is significant for the trichloromethyl group ($\Delta\Delta H_f° = 4.7$ kcal mol^{-1}). The result of this comparison strengthens our hypothesis that the lower enthalpy of activation shown by the reaction of **1** may be due to a peri destabilizing effect.

The differences in the activation entropies are, in our opinion, more difficult to rationalize since solvation effects may play a significant role in determining these differences.

Experimental Section

Melting points are uncorrected. ^{1}H NMR measurements were obtained with a Bruker WP 80 SY instrument. Mass spectra were obtained with a Kratos MS 80 spectrometer. GLC analyses were carried out on a 5830A Hewlett-Packard instrument with a flame-ionization detector and an OV-101 column (5% on Chromosorb WHP 100-120).

TLC analyses were performed on Merck 60 F_{254} silica gel plates. Column chromatography separations were carried out on Merck 60 silica gel (70-230 mesh). The kinetic measurements were carried out spectrophotometrically, at different temperatures, in the thermostated cell compartment of a Cary 219 instrument. An excess of tetrabutylammonium hydroxide was present, so that the reactions occurred under pseudo-first-order conditions. The kinetics were followed at 308 nm, a wavelength corresponding to an absorbance maximum of the conjugated base of **3**. The second-order rate constants were obtained by dividing the pseudo-first-order rate constants by the corresponding nucleophile concentrations. The activation parameters were obtained by using the Eyring equation.[10]

4-(Trichloromethyl)quinazoline (1) was prepared as previously described.[4]

4-Chloroquinazoline (2) was prepared from 4-hydroxyquinazoline according to a reported procedure.[11]

Reaction of 1 with Tetrabutylammonium Hydroxide. Tetrabutylammonium hydroxide (16 mL of 1.5 M aqueous solution, 24 mmol) and 3 mL of water were added at room temperature to a solution of **1** (0.376 g, 1.52 mmol) in 12.4 mL of MeCN. After about 5 min, the reaction was complete. TLC analysis (silica gel, 1:1 benzene/ethyl acetate) showed the presence of one product only. The solution was neutralized with aqueous HCl, partially evaporated, and then continuously extracted with ethyl ether for 24 h. The ether solution was dried (Na_2SO_4). Removal of the solvent left a white solid (0.175 g) that was identified as 4-hydroxyquinazoline[11] (yield 79%).

Reaction of 2 with Tetrabutylammonium Hydroxide. Tetrabutylammonium hydroxide (16 mL of 1.5 M aqueous solution, 24 mmol) and 3 mL of water were added at room temperature to a solution of **2** (0.25 g, 1.52 mmol) in 12.4 mL of MeCN. After about 5 min, the reaction was complete. TLC analysis (silica gel, 1:1 benzene/ethyl acetate) showed the presence of two compounds that, after neutralization with aqueous HCl and extraction with ethyl ether, were separated by column chromatography (silica gel, 4:1 benzene/ethyl acetate and ethyl acetate). The minor product was eluted first (25 mg) [mp (CCl_4) 127-128 °C; ^{1}H NMR (CD_3COCD_3) δ 7.2-7.8 (m, 4 H, H6-H8 and CH), 8.30 (two multiplets, 1 H, H-5), 8.55 (s, 1 H, H-2), 9.35 (s, 1 H, NH); IR (Nujol) 2220 cm^{-1} (-CN stretching); mass spectrum ($(M + 1)^+$), m/e 170] and was identified as 4-(cyanomethyl)quinazoline (yield 9.7%). The main product was then eluted (170 mg) and identified as 4-hydroxyquinazoline[11] (yield 77%).

Determination of the Ratios of 3/4 for the Reaction of 2. The reaction was carried out, as reported above, at the same temperature of the kinetic runs (see Table I). After extraction with ethyl ether, the ratio of **3**/**4** was obtained by GCL analysis.

Acknowledgment. We thank Dr. Felice Grandinetti for his assistance in the molecular mechanics calculations.

Registry No. **1**, 99356-81-7; **2**, 5190-68-1; **4**, 112270-68-5; 1-(trichloromethyl)naphthalene, 37827-78-4; 2-(trichloromethyl)-naphthalene, 37827-80-8.

(7) (a) Calculations were performed by using the Allinger MMP2 molecular mechanics program.[7b] (b) Allinger, N. L.; Flanagan, H. L. *J. Comput. Chem.* **1983**, *4*, 399.

(8) Stull, D. R.; Westrum, E. F., Jr.; Sinke, G. C. *The Chemical Thermodynamics of Organic Compounds*; Wiley: New York, 1969.

(9) (a) This can be inferred from the conformational energies[9b] of Cl (0.43 kcal mol^{-1}) and CH_3 (1.70 kcal mol^{-1}) for the axial/equatorial equilibrium in monosubstituted cyclohexane derivatives (b) Testa, B. *Principles of Organic Stereochemistry*; M. Dekker: New York, 1978; p 119.

(10) Bunnett, J. In *Investigation of Rates and Mechanism of Reactions*; Bernasconi, C. F. Ed.; Wiley: New York, 1986; Part I, p 287.

(11) Armarego, L. F. *J. Appl. Chem.* **1961**, *11*, 71.

Reductive Amination of Pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione

Alan P. Marchand,* Paritosh R. Dave, N. Satyanarayana, and Benny E. Arney, Jr.

Department of Chemistry, North Texas State University, Box 5068, Denton, Texas 76203-5068

Received August 27, 1987

Sodium cyanoborohydride is a highly selective reducing agent which is stable to pH 3 in aqueous acidic solution. Its ability to preferentially reduce iminium ions in the presence of ketone or aldehyde carbonyl groups renders it suitable for use as a reagent in the reductive amination

0022-3263/88/1953-1088$01.50/0