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Association Phenomena. 6. Effect of Cations on the Rates of Phosphate Transfer by the Metaphosphate Mechanisms. Implications for the Mechanism of Action of Kinases[1]

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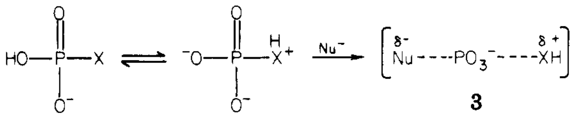
Phosphoroguanidines are excellent models for the chemistry occurring at the active sites of kinases. We have found that mono- and dications have virtually no effect on the rate of hydrolysis of phosphoroguanidines. This is in agreement with a transition state that has predominantly $S_N1(P)$ character. This suggests that there will be no rate inhibition if, as in the mechanism of action of kinases, Mg^{2+} coordinates to the phosphate that is being transferred even though the amount of negative charge at the transferred phosphate diminishes in the transition state as it does when ATP is the phosphate donor in a kinase-catalyzed reaction.

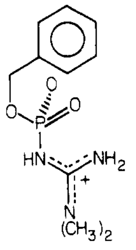
Chemical studies of the mechanism of reaction of kinase substrates have produced a general picture of the preferred reaction pathway.[2] Phosphorocreatine is an outstanding example.[3] The phosphate monoanion is highly reactive, the most reactive of all the phosphorylation substrates. A detailed study has traced the source of the reactivity to the mechanism which appears to apply to all the active phosphorylating agents:[4] first, tautomerism to a highly labile species (**2**) and then bond cleavage to give a highly labile metaphosphate intermediate. In most of these "metaphosphate-type" reactions, there appears to be some nucleophilic participation in the transition state on the basis of competition experiments.[2] In view of these results and the preference for S_N2 reactions at phosphorus,[5] which was experimentally demonstrated on phosphinyl chlorides,[6] it is not surprising that, for most kinases, stereochemical studies demonstrate inversion at phosphorus, consistent with nucleophilic attack at phosphorus by ADP as the bond to the phosphoryl donor breaks.[7,8]



1 2 3

The transition state, **3**, has electrostatic repulsion between the nucleophile (ADP in kinases), Nu, and the partially coordinated metaphosphate ion. The amount of charge on the PO_3 group will depend upon the extent to which the X–P bond is broken in the transition state as we have previously discussed.[2] Kinases uniformly require Mg^{2+}, although other divalent metal cations have activity.[9] As part of our research on the fundamental chemistry of active sites,[10] we now report on the effect of cations on the rate of reaction of a substrate which reacts preferentially by the metaphosphate mechanism:[11,12] *N*,*Nd*-dimethyl-*N'*-phosphoroguanidine (**4**). We have previously shown[2] that competitive capture of metaphosphate gives evidence for the hypothesis that **4** yields a metaphosphate intermediate which has less nucleophilic participation in the transition state **3** than other metaphosphate precursors.

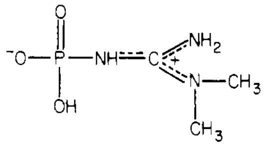
Table I. Association Constants for the Substrate and Sodium, Magnesium, and Guanidinium Ion[a]



B-DMPG

	Na^+	$(NH_2)_3C^+$	Mg^{2+}
$\Delta\delta_{max}$	2 (1)	1.2 (0.5)	–0.9 (0.1)
K (M^{-1})	0.1 (0.04)	0.2 (0.1)	0.8 (0.1)

[a] pH 5, [Cl^-] maintained at 2.00 M with $(CH_3)_4NCl$, 0.01 M phosphate, 0.01 M standard—see Experimental Section.



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Recently, the proposal has been advanced that kinases do not catalyze reactions via a dissociative pathway.[8] Rather, the mechanism is associative, and, furthermore, the transition state is highly symmetrical. This paper presents evidence that the transition state **3** for solution hydrolysis of the creatine kinase substrate, which has much S_N1 character and is therefore by definition highly symmetrical, is not destabilized by cation coordination to the phosphate moiety.

Experimental Section

N,*N*-Dimethyl-*N'*-phosphoroguanidine (DMPG) and the monobenzyl ester of DMPG (B-DMPG) were prepared according

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[1] (a) Prigodich, R. V.; Haake, P. *Inorg. Chem.*, submitted for publication. (b) Prigodich, R. V.; Haake, P. *Inorg. Chem.* **1984**, *23*, 457. (c) Springs, B.; Haake, P. *Tetrahedron Lett.* **1977**, 3223. (d) Knier, B. L.; Haake, P. *Ibid.* **1977**, 3219. (e) Springs, B.; Haake, P. *Bioorg. Chem.* **1977**, *6*, 181.

[2] Reviewed in Allen, G. W.; Haake, P. *Bioorg. Chem.* **1980**, *9*, 325.

[3] Allen, G. W.; Haake, P. *J. Am. Chem. Soc.* **1976**, *98*, 4990.

[4] Reference 2 and (a) Douglas, K. T. *Prog. Bioorganic Chem.* **1976**, *4*, 193. (b) Kenyon, G. L.; Reed, G. H. *Adv. Enzymol.* **1983**, *54*, 367.

[5] Rahil, J.; Haake, P. *J. Am. Chem. Soc.* **1983**, *103*, 1723.

[6] Ossip, P. S.; Haake, P. *J. Am. Chem. Soc.* **1971**, *93*, 6924.

[7] Lowe, G. *Acc. Chem. Res.* **1983**, *16*, 244.

[8] Hassett, A.; Blattler, W.; Knowles, J. R. *Biochemistry* **1982**, *21*, 6335.

[9] (a) Cooperman, B. S. "Metal Ions in Biological Systems"; Sigel, H., Ed.; Marcel Dekker: New York, 1976; Vol. 5, pp 79–126. (b) Walsh, C. "Enzymatic Reaction Mechanisms"; Freeman: San Francisco, 1979; pp 210–239.

[10] Bonicamp, J.; Haake, P. *Tetrahedron Lett.* **1982**, *23*, 3127 and references therein.

[11] Allen, G. W.; Haake, P. *J. Am. Chem. Soc.* **1973**, *95*, 8080.

[12] Kirby, A. J.; Varvoglis, G. *J. Am. Chem. Soc.* **1967**, *89*, 415.

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Table II. Observed Rate Constants for the Hydrolysis of DMPG in the Presence of Divalent Metal Cations

salt	M	pH[a]	μ, N	cationic radius, Å	% assoc[b]	$10^4 k_{\mathrm{obsd}}$, s^{-1}	% std dev
$Mg(ClO_4)_2$	0.33	2.51	1.00	0.65	21 ± 3	5.03	1.8
$MgCl_2$	0.33	1.93	1.00	0.65	21 ± 3	5.02	1.8
$MnCl_2$	0.33	2.00	1.00	0.80		4.81	0.9
$CaCl_2$	0.33	2.49	1.00	0.89		5.42	0.9
$BaCl_2$	0.33	2.50	1.00	1.35		6.67	1.3
$MgCl_2$	0.00	2.00	0.00	0.65	0	5.42	2.9
$MgCl_2$	0.001	2.00	0.003		0.08 ± 0.01	6.09	0.8
$MgCl_2$	0.010	2.00	0.030		0.8 ± 0.1	5.60	0.6
$MgCl_2$	0.100	2.00	0.300		8 ± 1	5.87	2.1
$MgCl_2$	0.33	1.93	1.00		21 ± 3	5.02	1.8
$MgCl_2$	1.00	1.59	3.00		44 ± 6	5.05	1.5
$MgCl_2$	2.5	0.60	7.50		67 ± 8	4.86	1.2

[a] The pH at which k_{obsd} is a maximum for a pH–rate profile between pH 0 and pH 4. [b] % association ([phosphate–cation complex]/[total phosphate]) × 100, equals $[1 + (1/(K[\mathrm{cation}]_{\mathrm{total}}))]^{-1} \times 100$. This is because the phosphate concentration is so low that the fraction of cations in the complex is negligible compared to the total cation concentration.

Table III. Data for the pH-Rate Profiles of DMPG Hydrolysis in 0.33 and 2.50 M $MgCl_2$

0.33 M $MgCl_2$			2.50 M $MgCl_2$		
pH	$10^4 k_{\mathrm{obsd}}$, s^{-1}	% std dev	pH	$10^4 k_{\mathrm{obsd}}$, s^{-1}	% std dev
−0.7	2.40	2.7	0.3	4.25	0.7
−0.4	2.97	0.5	0.6	4.87	1.2
0.25	3.88	2.2	0.9	4.47	1.4
0.91	5.02	1.6	2.7	0.82	3.3
1.87	4.98	1.1			
1.93	5.02	1.8			
3.61	2.67	1.8			

to Allen and Haake.[11] Tetramethylammonium chloride and guanidinium chloride were recrystallized three times from ethanol/water solutions. All other materials were analyzed reagent grade.

An inorganic phosphate assay was used to measure the rate of hydrolysis of DMPG in solutions of guanidinium chloride; it was modeled after the method of Jencks and Gilchrist.[13] The concentration of the $SnCl_2/HCl$ reagent was increased 10-fold in $SnCl_2$. This provided an excess of the reducing agent, and full color development was reached within 10–20 s. Maximum absorbance data was used and this gave excellent Beer's law plots for the stock solutions of inorganic phosphate used in the daily standardization of this procedure. Direct spectrophotometric monitoring of the disappearance of DMPG was used with all other salts. The reactions were followed at 220 nm at a constant cell block temperature of 30.5 ± 0.1 °C in a Cary Model 16 K UV–vis spectrophotometer and Leeds and Northrup Speedomax W recorder. All reactions were initiated by introducing 1.00 mL of 1.25×10^{-2} M DMPG to 25.0 mL of a salt solution. Both solutions were temperature equilibrated to 30.5 °C. pH was buffered with dilute acid and pH readings were taken on a Radiometer Type TTTlc pH meter with a 5-mm standard Beckman combination electrode.

The pseudo-first-order rate constants were calculated by a nonlinear estimation program (NEFO5A.FOR) in which the infinity point and rate constant are unknowns. We have checked this program against cases where the infinity point is known. Where the infinity point is in error, this method has proven better than others we have used. The second-order rate constants were calculated by a least-squares program (LSTSQR.FOR) for linear equations.

NMR Method. Two stock solutions were made, each contained 30% D_2O (made CO_2 free by bubbling Ascarite treated N_2 through the solution for 30 min), 0.01 M trimethyl phosphate, 0.01 M phosphate diester, and 100 μM EGTA (ethylene glycol bis(β-aminoethyl ether)-*N,N'*-tetraacetic acid). One stock solution contained the background electrolyte, tetramethylammonium chloride, and the other contained the chloride salt of the cation of interest. The pH of the stock solutions was adjusted with tetramethylammonium hydroxide. pH readings were not adjusted for ionic strength or % D_2O. Appropriate volumes of the stock solutions were mixed to give the desired final concentrations.

Phosphorus-31 chemical shifts were recorded at 31 ± 1 °C (sample temperature), Varian XL-200, after 32 transients. Wide-band proton noise decoupling was employed and 30% ^2H_2O allowed heteronuclear field-frequency locking on deuterium. The resolution was 0.5 Hz or 0.006 ppm. Three spectra were recorded for each sample and averaged.

Association Constants.[14] If the concentration of cation–phosphate anion complex is represented by *C*, the total phosphate anion concentration by *P*, and the total cation concentration equals the free cation concentration (because it is much larger than the total phosphate concentration), the association constant, *K*, is given in eq 1. Since only a single sharp resonance was found for

$$K = \frac{C}{M(P - C)} \text{ or } \frac{1}{KM} = \frac{P}{C} - 1 \tag{1}$$

any of the phosphates, exchange of the cation was fast on the NMR time scale. Therefore, the variable *P/C* can be related to chemical shift data as eq 2, where δ_C is the chemical shift of the

$$\delta_{\mathrm{obsd}} = \frac{C}{P}\delta_C + \frac{P - C}{P}\delta_P \text{ or } \frac{P}{C} = \frac{\delta - \delta_P}{\delta_{\mathrm{obsd}} - \delta_P} = \frac{\Delta\delta_{\mathrm{max}}}{\Delta\delta_{\mathrm{obsd}}} \tag{2}$$

complex, δ_P is the chemical shift of the uncomplexed anion, and δ_{obsd} is the observed chemical shift of the phosphate anion in reference to the standard. Therefore, substituting eq 2 into eq 1 and rearranging gives eq 3. A set of data, $\Delta\delta_{\mathrm{obsd}}$ and $\frac{1}{M}$, at varying

$$\frac{1}{\Delta\delta_{\mathrm{obsd}}} = \frac{1}{K\Delta\delta_{\mathrm{max}}}\frac{1}{M} + \frac{1}{\Delta\delta_{\mathrm{max}}} \tag{3}$$

cation concentration, was solved by a weighted least-squares program, where the weighting factor was M^{-2}. The calculated intercept divided by the calculated slope yielded *K*. Standard deviations are $(\Pi \text{ deviations}/(N - 2))^{1/2}$. Standard deviations for slopes, σ_{dsl} and for intercepts, σ_{din}, were determined by the usual methods.[15] The standard deviation for the association constant, σ_K, is a result of the compounding of errors in the determination of the slope and intercept:[15]

$$\sigma_K = \left[\left(\frac{\sigma_{\mathrm{din}}}{\text{slope}}\right)^2 + \left(\frac{(\text{intercept})(\sigma_{\mathrm{dsl}})}{\text{slope}}\right)^2\right]^{1/2}$$

Results

The association constants, which are necessary in order to interpret the rate effects of cations, are found in Table I. The $\Delta\delta_{\mathrm{max}}$ values are the chemical shifts of fully as-

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(13) Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1964**, *86*, 1410.

(14) Prigodich, R. V. Ph.D. Thesis, 1982, Wesleyan University.

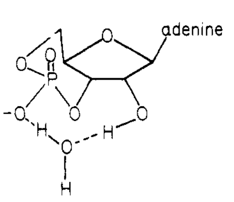
(15) Wilson, E. B., Jr. "An Introduction to Scientific Research"; McGraw-Hill: New York, 1952; pp 219, 272.

Table IV. Observed Rate Constants for the Hydrolysis of *N,N*-Dimethyl-*N*′-phosphoroguanidine in the Presence of Monovalent Cations

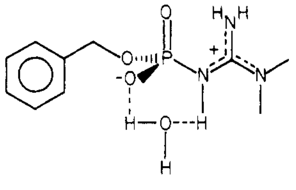
salt	M	pH^a	μ, N	cationic radius, Å	% $assoc^b$	10^4k_{obsd}, s^{-1}	% std dev
$(CH_3)_4NCl$	1.00	2.10	1.00	2.42^c	0^d	3.88	1.0
$(NH_2)_3CCl$	1.00	1.95	1.00	2.22^c	16 ± 8^e	6.05	2.0
CsCl	1.00	2.06	1.00	1.69	9 ± 4^f	7.13	1.2
KCl	1.00	1.99	1.00	1.33	9 ± 4^f	7.57	1.2
NaCl	1.00	1.89	1.00	0.95	9 ± 4^f	6.68	1.0
LiCl	1.00	1.81	1.00	0.60	9 ± 4^f	6.02	1.2
$(CH_3)_4NCl$	5.00	1.80	5.00	2.42	0^d	0.85	1.2
$(NH_2)_3CCl$	5.00	1.97	5.00	2.22	80 ± 40^e	10.4	2.4
NaCl	5.00	1.10	5.00	0.95	30 ± 10^f	19.3	8.3
$NaCl^g$	0.20	2.02	0.20	0.95	2 ± 1^f	6.20	
NaCl	1.00	1.89	1.00	0.95	9 ± 1^f	6.68	1.0
NaCl	5.00	1.10	5.00	0.95	30 ± 10^f	19.3	8.3

[a] The pH at which k_{obsd} is a maximum for a pH–rate profile between pH 0 and 4. [b] Percent association, ([phosphate–cation complex]/[total phosphate]) × 100, equals $(1 + (1/(K[\text{cation}]\ \text{total})))^{-1} \times 100$. This is because the phosphate concentration is so low that the fraction of cations in the complex is negligible compared to the total cation concentration. [c] Cation radii calculated from crystal structure data. [d] Association constant, *K*, from ref 10b. [e] Association constant from Table I. [f] Association constant for Na^+ in Table I. [g] Rate constant from ref 11. [h] Guanidinium ion.

sociated phosphate. They are similar to the values we found for other phosphate monoanions;[1b] Mg^{2+} caused an upfield shift while the monocations cause a downfield shift. *K* and $\Delta\delta_{max}$ values for the B-DMPG–Mg^{2+} complex are very near to those same parameters for c-AMP.[1b] This is possible evidence for a water molecule tightly bound to a phosphoryl oxygen and guanidium N–H in a similar manner as proposed for a water molecule bound to the phosphate and ribose hydroxyl in c-AMP.[16]



c-AMP



B-DMPG

DMPG has a maximal rate of hydrolysis at pH 2. But metal ions could shift that maximum because they will change the p*K* of the phosphate.[1e,17] Table II presents the maximal ranges of DMPG hydrolysis between pH 0 and 4 in the presence of divalent cations based upon rate measurements over than interval. There is little variation in rate from cation to cation or between 0 and 2.50 M $MgCl_2$. The pH–rate maximum falls as $MgCl_2$ concentration increases, however. The data for the pH rate profiles of 0.33 and 2.50 M $MgCl_2$ are given in Table III.

Table IV contains the kinetic data for the hydrolysis of *N,N*-dimethyl-*N*′-phosphoroguanidine (DMPG) in the presence of monovalent cations. The rate constants are those that represent the maxima in pH rate profiles which ranged from pH 0 to 4. The observed rate constant in 1.00 M $(CH_3)_4NCl$ is 3.88×10^{-4} s^{-1} and may be considered to be the rate of hydrolysis of uncomplexed[17] DMPG when $\mu = 1.00$ N. Thus, cations seem to give a significant rate increase at very high concentrations of salt.

Discussion

There are two striking and important results: (1) Cations have little effect on the rate of hydrolysis of the DMPG zwitterion (Tables II–IV). (2) At very high salt concentrations, 5 M, significant changes in rate were observed.

To understand the lack of effect of cations on the rate, one must consider the differences in interactions of the cations with the transition state compared to the ground state. Mechanistic studies have shown that the reactive form of DMPG at low pH is the zwitterion.[11] The pK_as of the two ionizable phosphate protons are −0.31 and 4.32 and the guanidinium pK_a is 11.3. At pH 2 and low ionic strength the predominant species is the zwitterion, $DMPG^{\pm}$·. Whether or not PO_3^- is transiently formed or is coupled to the incipient nucleophile in a "loose" transition state, (**3**), the charge separations shown appear applicable because there is a great deal of bond breaking and little if any bond making in the transition state.[2] Therefore, the net charge on the phosphate moiety in **3** must be near unity. Although the reaction proceeds through a dianion, **2**, the important question is the relative energies of interaction of cations with the ground and transition states, and the ground state is not **2** but rather the more stable tautomer **1**. Since there are similar charges (not only on the phosphate but also on the guanidinium ion) in ground- and transition-state structures, the observed lack of effect of cations on rate is in accord with our previous studies.[2,3,5,11] The lack of effect on rate also suggests to us that nucleophilic attack on DMPG is not important in the transition state; if it were, other studies on metal ions suggest that the metal ion would provide catalysis by bringing nucleophile and substrate together in the transition state.[18-20] This result fits very well with our conclusions about the transition-state structure based upon competitive trapping of the metaphosphate intermediate in mixed solvents.[21]

These results have application to the mechanism of action of kinases. The stereochemistry has now been

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(16) Bolton, P. H.; Kearns, D. R. *J. Am. Chem. Soc.* **1979**, *101*, 479.

(17) (a) Smith, R. M.; Alberty, R. A. *J. Am. Chem. Soc.* **1956**, *78*, 2376. (b) Smith, R. M.; Alberty, R. A. *J. Phys. Chem.* **1956**, *60*, 180.

(18) Huebner, P. A.; Milburn, R. M. *Inorg. Chem.* **1980**, *19*, 1267.

(19) Atwood, L.; Haake, P. *Bioorganic Chem.* **1976**, *5*, 1165.

(20) We have shown that an S_N2-type reaction between a neutral nucleophile, imidazole, and a phosphate monoanion is catalyzed by cations.[14]

(21) We observed random reaction in mixed solvents with highly reactive phosphoroguanidines except with 2-propanol–water for which steric hindrance would lead to preferential solvation by water. This result implies that metaphosphate is so reactive that it reacts predominantly with the first solvation shell.[2]

shown to be uniformly inversion of configuration at phosphorus.[22] There is an absolute requirement for dications for kinase activity.[9,22] Furthermore, ATP^{3-} is known to hydrolyze via a mechanism analogous to that for DMPG hydrolysis, and it is also known that cation coordination has little effect on the rate of nonenzymic ATP^{3-} hydrolysis.[23] These studies, and the results of this paper indicate that cation coordination has little effect on the rate of phosphoryl donor hydrolyses with significant S_N1 character.

There is evidence for migration of the associated cation during the kinase-catalyzed reaction;[24] kinases may utilize the change in site of cation coordination to catalyze phosphoryl transfer. We find that divalent cations coordinate to the α-, β-, and γ-positions of ATP in solution.[1a,14] Coordination of Mg^{2+} to the α- and β-positions, as well as the transferred phosphoryl moiety, would increase the acidity of the leaving group in both the forward and reverse reactions. Additionally, coordination of a cation would reduce the electrostatic repulsion of the negatively charged substrates. The evidence presented in this paper demonstrates that these rate-enhancing properties of cation coordination at the kinase active site would not be diminished at any rate-inhibiting character intrinsic to cation coordination to a substrate that reacts via a transition state with predominant S_N1 character.

Although the importance of our results is not dependent on whether the mechanism is predominantly dissociative or associative,[8] it is certainly true that the metaphosphate ion is a highly unstable intermediate. As Allen and Haake demonstrated, even in the most reactive metaphosphate precursors, there is a tendency for associative character in the transition state, and we therefore predicted that the enzymic reactions would have some associative character in a predominantly dissociative transition state.

The rate effects of high concentrations of salt are probably related to changes in water structure and therefore solvation of **1**–**3** will be of critical importance to their total energies. With 5 M salt, the structure of water will be greatly altered. If each Cl^- and each Na^+ is solvated by six waters, nearly every water molecule will be tied up with salt solvation, and therefore solvation of **1**–**3** will change. For example, if **1** is solvated less well, its energy will be raised and the rate will increase.

Acknowledgment. We thank Professor Max Tishler for comments and the NIH for a grant.

Registry No. DMPG, 34718-93-9; B-DMPG, 50725-11-6; sodium, 7440-23-5; magnesium, 7439-95-4; guanidinium ion, 25215-10-5; kinase, 9031-44-1.

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[22] Knowles, J. R. *Annu. Rev. Biochem.* **1980**, *49*, 877.

[23] Miller, D. L.; Westheimer, F. H. *J. Am. Chem. Soc.* **1966**, *88*, 1507. Ramirez, F.; Marecek, J. F.; Szamosi, J. *J. Org. Chem.* **1980**, *45*, 4748.

[24] (a) Petersen, R. L.; Gupta, R. K. *Biophys. J.* **1979**, *27*, 1. (b) Banks, R. D.; Blake, C. C. F.; Evans, P. R.; Haso, R.; Rice, D. W.; Hardy, G. W.; Merett, N.; Phillips, A. W.; *Nature (London)* **1979**, *279*, 773. (c) Reed, G. H.; Barlow, C. H.; Burns, R. A. *J. Biol. Chem.* **1978**, *253*, 4153. (d) Mildvan, A.; Cohn, M. *Adv. Enzymol.* **1970**, *33*, 1.

Highly Reactive Metallic Nickel: Reductive Homocoupling Reagent for Benzylic Mono- and Polyhalides

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Metallic nickel, prepared by the reduction of nickel halides with lithium in glyme using naphthalene as an electron carrier, was found to be a useful reagent for the homocoupling of benzylic mono- and polyhalides. Benzyl halides reacted with metallic nickel at room temperature to give the corresponding 1,2-diarylethanes in good to high yields and functional groups on the aromatic ring such as methoxy, chloro, bromo, nitro, cyano, and alkoxycarbonyl groups were not affected under the conditions employed. Benzylic monohalides (1-(chloromethyl)- or 2-(bromomethyl)naphthalene, chlorodiphenylmethane, and 9-bromofluorene) also underwent coupling reactions with metallic nickel at room temperature to give the corresponding ethane derivatives. On the other hand, benzylic di- and trihalides such as α,α-dibromotoluene and α,α,α-trichlorotoluene yielded mixtures of cis and trans isomers of substituted ethenes. The intermediate of the reaction, benzylnickel complex, was trapped with electron deficient olefins such as methyl acrylate and acrylonitrile.

Introduction

Recently, transition metals in a low oxidation state have been used extensively as reagents for the reductive homocoupling reaction of benzylic halides. For example, titanium,[1] vanadium,[2] chromium,[3] and tungsten[4] have been employed as reagents for this purpose and were prepared in situ by reducing the appropriate metal halide with lithium aluminum hydride. Nickel(I),[5] cobalt(I),[6] and vanadium(II)[7] complexes or metal carbonyls of nickel,[8,9] cobalt,[10] iron,[11-13] molybdenum,[14] and tungsten[4] as well as

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[1] Olah, G. A.; Prakash, G. K. S. *Synthesis* **1976**, 607.

[2] Ho, T.-L.; Olah, G. A. *Synthesis* **1977**, 170.

[3] Okude, Y.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1977**, 3829.

[4] Fujiwara, Y.; Ishikawa, R.; Teranishi, S. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 589.

[5] Hashimoto, I.; Tsuruta, N.; Ryang, M.; Tsutsumi, S. *J. Org. Chem.* **1970**, *35*, 3748.

[6] Yamada, Y.; Momose, D. *Chem. Lett.* **1981**, 1277.

[7] Cooper, T. A. *J. Am. Chem. Soc.* **1973**, *95*, 4158.

[8] Yoshisato, E.; Tsutsumi, S. *J. Org. Chem.* **1968**, *33*, 869.

[9] Kunieda, T.; Tamura, T.; Takizawa, T. *J. Chem. Soc., Chem. Commun.* **1972**, 885.

[10] Seyferth, D.; Millar, M. D. *J. Organometal. Chem.* **1972**, *38*, 373.

[11] Coffey, C. E. *J. Org. Chem.* **1961**, *83*, 1623.

[12] Nakanishi, S.; Oda, T.; Ueda, T.; Otsuji, Y. *Chem. Lett.* **1978**, 1309.

0022-3263/84/1949-2093$01.50/0