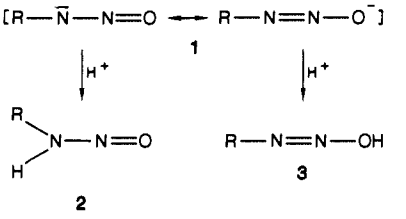
Preparation of a Thallium(I) Diazotate. Structure, Physicochemical Characterization, and Conversion to Novel *N*-Nitroso Compounds

Larry K. Keefer,*[1a] Shui-mei Wang,[1a,b] Takako Anjo,[1a,c] James C. Fanning,[1d] and Cynthia S. Day[1e]

Contribution from the Chemistry Section, Laboratory of Comparative Carcinogenesis, National Cancer Institute, Frederick Cancer Research Facility, Frederick, Maryland 21701, Department of Chemistry, Clemson University, Clemson, South Carolina 29631, and Crystalytics Company, Lincoln, Nebraska 68501. *Received July 27, 1987*

Abstract: Thallium(I) (*E*)-methanediazotate (**4**) has been prepared and characterized. In contrast to previously reported methanediazotates, **4** is a highly crystalline material whose physical properties suggest a considerable degree of covalency: it is readily soluble in certain nonpolar solvents; it melts reversibly at a low temperature; it is monomeric and nonconducting in chloroform solution; and ions corresponding to the formula $Tl(CH_3N_2O)^{\bullet+}$ are found in the electron impact mass spectrum. The crystal structure of **4** revealed Tl–O distances as short as 2.52 (3) Å and confirmed the anti stereochemistry; the monoclinic unit cell, space group $P2_1/c$-C_{2h}^5 (No. 14), had a = 13.233 (6) Å, b = 11.594 (4) Å, c = 6.523 (2) Å, β = 119.45 (3)°, V = 871.5 (6) Å^3, and Z = 8. The compound's advantageous stability and solubility properties provide important new opportunities for probing the solution chemistry of the alkanediazotates. As an illustration of this potential, **4** has been converted in homogeneous media to unusual *N*-nitroso compounds including a quaternary ammonium salt of a primary nitrosamine, an isotopic variant of dimethylnitrosamine in which the methyl group syn to the oxygen is fully deuteriated, and the less stable *Z* conformer of methylbenzylnitrosamine. In contrast to **4**, its *Z* stereoisomer has until now defied isolation but has been identified in situ by reaction with iodomethane-d_3 to produce (*E*)-methyl(methyl-d_3)nitrosamine.

Diazotates **1** and their conjugate acids, the primary nitrosamines **2** and diazo hydroxides **3**, have been invoked as key intermediates in many important transformations of organic[2] and biological[3-11] chemistry. For the most part, their existence in the various



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preparative, degradative, and pharmacological activation reactions in which they are thought to play a role has been inferred indirectly from the identities of the products ultimately observed. Diazotates can be isolated, however, and by now the chemistry of numerous alkali metal derivatives has been extensively explored,[2a,5,12-18] though they have almost invariably proven difficult to purify or analyze satisfactorily.

In this paper, we describe the preparation and properties of what we believe to be the first example of a thallium(I) diazotate. This compound, thallium (*E*)-methanediazotate (**4**), contrasts in a variety of unexpected ways with previously described diazotates.

(1) (a) National Cancer Institute. (b) Present address: GAF Co., Wayne, NJ 07470. (c) Present address: Hatano Research Institute, Kanagawa, Japan. (d) Clemson University. (e) Crystalytics Co.

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(16) Thiele, J. *Justus Liebigs Ann. Chem.* **1910**, *376*, 239-268. This author considered the mechanism by which alkylhydrazines are converted to diazotates by alkyl nitrites in base to involve sequential nitrosation, first of the secondary nitrogen atom and then of the primary amino group. Subsequent removal of the remaining N–H proton by added alkoxide was postulated to produce an anion capable of fragmenting to nitrous oxide and alkanediazotate. In support of this hypothesis, Thiele found that *N*-alkyl-*N*-nitrosohydrazines were converted to the same diazotates by treatment with only 1 mol each of nitrosating agent and base.

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The results suggest that the thallium derivatives of **1** should provide new insight into the chemistry of this important compound type.

Experimental Section

Warning! Most *N*-nitroso[10] and azoxy compounds[11] are potentially carcinogenic, and thallium compounds are considered to be especially poisonous.[19] In addition, alkanediazotates are easily converted to diazoalkanes[2] and should as a consequence be regarded as capable of detonation. While we have prepared compound **4** and studied its reactivity on a great many occasions, encountering uncontrolled reactions only when the material was exposed to acids, we are aware of one injury-producing incident that illustrates the potential hazards of the work described herein.[20] All such materials should, therefore, be handled, stored, and discarded only with proper respect for their toxic or explosive properties.

Reagents and Methods. All chemicals were obtained from Aldrich Chemical Co., except *n*-butyl nitrite (Frinton Laboratories), *tert*-butyl nitrite (K & K Laboratories), iodomethane-d_3 and dichloromethane-d_2 (Merck, Sharp & Dohme), and azoxymethane (National Cancer Institute Chemical Carcinogen Reference Standard Repository, a function of the Division of Cancer Etiology, NCI, NIH, Bethesda, MD 20892).

Gas chromatography (GC) was performed on a Perkin-Elmer Model 996 gas chromatograph equipped with flame ionization detector, a Hewlett Packard Model 3380 A integrator, and a 3-m length by 3-mm-i.d. stainless-steel column of 10% Carbowax 20 M + 2% potassium hydroxide on 80/100-mesh Supelcoport. Helium carrier gas was flow-controlled at 35 mL/min, and temperature was programmed at 24 °C/min to 220 °C after it was held initially at 80 °C for 4 min. Retention times under these conditions were 2.72 min for azoxymethane and 6.11 min for dimethylnitrosamine.

Ultraviolet (UV) data were collected on a Varian Techtron 635 UV-vis spectrophotometer. Infrared (IR) spectra were recorded with a Perkin-Elmer Model 621 infrared spectrophotometer with sample applied to a KRS-5 plate as a mineral oil mull. Proton nuclear magnetic resonance (NMR) spectra were determined by a Varian Model XL-200 NMR spectrometer with tetramethylsilane as internal reference. Thallium spectra were obtained by a General Electric NT-300 NMR spectrometer with a 1280 data system; a broad-band 12-mm tunable probe was used, with sample volumes of 2–5 mL. Mass spectra (MS) were collected by a JEOL Model JMS-01SG-2 mass spectrometer. Solution molecular weight determinations (osmometric) and Karl Fischer (as well as elemental) analyses were performed by Galbraith Laboratories, Knoxville, TN. Conductivity data were collected by a YSI Model 32 conductance meter equipped with an Altex-Beckman Model CEL-GOI glass pipet conductivity cell (cell constant 0.1 cm^{-1}).

Thallium(I) (*E*)-Methanediazotate (4). Thallous ethoxide (20.67 g) was dissolved in 90 mL of peroxide-free anhydrous diethyl ether and mixed with 3.93 g of methylhydrazine and 16.6 g of *n*-butyl nitrite in 25 mL of ether. After mixing, a reddish oil began to form. Moderately vigorous gas evolution ensued, but this could be slowed as desired by cooling in an ice bath. Alternatively, *tert*-butyl nitrite could be used in place of the straight-chain isomer, in which case bubbling was barely detectable. After the solution was stirred in the absence of air overnight (longer if *tert*-butyl nitrite was used), 17.4 g (80% crude yield) of large yellow crystals had formed. These were collected by filtration and recrystallized from dichloromethane or dichloromethane–acetonitrile: mp 59–61 °C; duplicate molecular weight determinations 264, 265 (chloroform) and 528, 547 (pyridine); IR 1709 m, 1320 s (br), 1035 w, 842 m, 680 s, 670 s cm^{-1}; UV (chloroform) strong end absorption with a shoulder at 315 nm (ϵ 570 L/mol·cm); ^{1}H NMR (dichloromethane-d_2) δ 3.43 (s). Observed conductance values were 0.10–0.11 μmho for 1–10 mM solutions in chloroform [compared with 0.11–0.12 μmho for pure chloroform and 65–650 μmho for 1–10 mM solutions of bis(triphenylphosphoranylidene)ammonium chloride ((PNP)Cl) in chloroform] and 5–20 μmho for 1–10 mM solutions in pyridine (compared with 4–15 μmho for pure pyridine and 900 μmho for a 1 mM solution of (PNP)Cl in pyridine). Anal. (CH_3N_2OTl) C, H, N.

Hydrolysis of **4** was studied by adding 1.05 mmol to 80 mL of water at 20.5 °C and trapping the stable gas evolved (presumably nitrogen) from the increasingly basic medium (final pH 11); gas release reached half the theoretical quantity at about 10 min after mixing and was essentially quantitative at 100 min, with thallous hydroxide and methanol assumed to be the other products.

X-ray Data Collection and Structure Determination. Two types of crystals were observed. The large flakes normally isolated upon recrystallization as described above were too thin for satisfactory data collection, but the needles found floating in the recrystallization mixture when the initial solute concentration was kept low proved suitable for diffraction studies. A rectangular parallelepiped (0.25 × 0.40 × 0.90 mm) was selected for data collection. Intensity measurements were made for 1997 independent reflections having $3.00° \leq 2\theta_{Mo K\bar{\alpha}} \leq 55.00°$ ($+h,+k,\pm l$) with graphite-monochromated Mo K$\bar{\alpha}$ radiation using 1.00° wide ω scans on a computer-controlled four-circle Nicolet P_1 autodiffractometer. The intensity data were corrected empirically for absorption effects by ψ scans for four reflections having 2θ between 13.4° and 25.4° and were then reduced to relative squared amplitudes, $|F_o|^2$, by means of standard Lorentz and polarization corrections. The structure was solved by heavy-atom Patterson techniques, and the resulting structural parameters were refined to convergence [R_1 (unweighted, based on F) = 0.054 and R_2 (weighted, based on F) = 0.063 for 927 independent reflections having $2\theta_{Mo K\bar{\alpha}} \leq 55.00°$ and $I > 3\sigma(I)$] with empirically weighted full-matrix least-squares techniques with anisotropic thermal parameters for all non-hydrogen atoms. The top 15 peaks (2.2–1.4 e/Å^3) in the final difference Fourier were within 1.72 Å of a thallium atom; there were no other peaks above the background level (1.1 e/Å^3).

Sodium (*E*)-Methanediazotate (5). An ether solution of methylhydrazine (1.17 g) was mixed with 5.3 g of 25% sodium methoxide in methanol.[16] During the subsequent addition of 5.3 g of *n*-butyl nitrite, extensive precipitation occurred. The resulting slurry was suction-filtered as soon as gas evolution had ceased. The white, slightly hygroscopic powder was washed with ether and dried in a vacuum desiccator. The yield was 1.03 g (50%). Anal. (CH_3N_2ONa) H; C: calcd, 14.64; found, 13.22; N: calcd, 34.15; found 27.59.

(*Z*)-Methylbenzylnitrosamine (10). Benzyl bromide (7.6 mmol) was mixed with 5.0 mmol of **4** and the mixture was allowed to stand at 0 °C for 43 h under a nitrogen atmosphere. The bright yellow crystals turned pale yellow. Chloroform-*d* (1 mL) was added, and the precipitate was removed. The ^{1}H NMR spectrum of the resulting solution included sharp singlets at δ 3.45 (3 methyl H) and 4.63 (2 methylene H); the relative intensity of the two peaks remained at 3:2, but their total intensity diminished slowly while singlets at δ 2.74 (3 methyl H) and 5.09 (2 methylene H) increased correspondingly with time. The quantitative course of reaction was determined in a separate preparation in which a mixture of **4** (5.0 mmol), benzyl bromide (5.5 mmol), and 40 mL of freshly dried ($CaCl_2$) and distilled chloroform was stirred for 100 h at room temperature, filtered, and analyzed by HPLC (μ-Porasil column, hexane/ether/CH_2Cl_2 (15:3:2, v/v/v) mobile phase, 254-nm detector); the yield of **10** under these conditions was 2.0 mmol (40%).

(*Z*)-Methyl(methyl-d_3)nitrosamine (11). Compound **4** (5.76 g) was mixed with 25 g of ice-cold iodomethane-d_3. The solute initially dissolved completely, but cloudiness due to thallous iodide precipitation appeared after only a few minutes at 0 °C. After the solution was stirred in an ice bath for 2 h, 25 mL of 5:2 (v/v) *n*-heptane/diethyl ether was added. The resulting slurry was suction-filtered, and the filter cake was washed with two 5-mL portions of the same solvent and then 5 mL of ether. The combined filtrate was extracted with four successive 5-mL portions of water. The aqueous extracts were mixed with 2 mL of 10 M sodium hydroxide and extracted with four 5-mL portions of dichloromethane. The combined organic layer was analyzed by UV, which revealed that 4.5 mmol (~20% yield) of nitrosamine chromophore was present, and by GC, which showed that the yield of azoxymethane was ≤4%. The solution was dried by passage through cotton, placed in a Kuderna–Danish evaporator, covered with 0.6 mL of water, and concentrated by slightly reducing the pressure inside the Kuderna–Danish apparatus while a small stream of air was introduced at the bottom of the dichloromethane layer via a capillary tube until a homogeneous solution was obtained. The vacuum source for this step was an aspirator connected to the top of the evaporator via a T-tube whose third arm was fitted to the gas inlet of a Bunsen burner, with the rate of evaporation being controlled by adjusting the needle valve of the burner. To minimize conformational equilibration, the temperature of the nitrosamine solutions was kept at or below 0 °C for as much of the 2-h workup procedure

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(20) A colleague has informed us that a 12-mm NMR tube he was opening to recover the 0.3 g of **4**, which had been standing in dichloromethane-d_2 at room temperature for several days after dissolution, violently exploded as the plastic cap was removed, peppering his forearm with glass fragments. It was later ascertained by ^{1}H NMR that similar ampules of the solvent were contaminated with a hydroxylic impurity; subsequent Karl Fischer analysis of a freshly opened ampule indicated the presence of more than 2% water (approximately 10 times the solubility of water in dichloromethane!); the contamination by hydroxylic materials, in combination with the apparent shock sensitivity of the sample and the presence therein of crystal edges formed on partial evaporation of solvent during prolonged standing, suggested that the explosion was due to diazomethane rather than to **4** itself. Indeed, later attempts to detonate **4** deliberately by striking, grinding, or heating it failed uniformly, and even placing it in a direct flame proved to be notably unspectacular. Nonetheless, our colleague's experience does underline the importance of handling any alkanediazotate with all precautions one might normally accord a "stabilized diazoalkane".[17]

as possible. A portion of the 0.4 mL of dark yellow, aqueous nitrosamine solution obtained after removing dichloromethane was extracted with chloroform-*d*: ^{1}H NMR δ 3.05 (s, integral 3.5%), 3.74 (s, integral 96.5%). The molecular ion region of the mass spectrum obtained by GC–MS of the dichloromethane solution contained peaks of *m/z* (relative intensity) 78 (4), 77 (100), 76 (1), 75 (0), 74 (1.5); UV (dichloromethane) 352 nm. The aqueous nitrosamine solution was purified by injecting 0.1-mL aliquots onto the 7-mm-i.d. by 30-cm length μ-Bondapak C_{18} reversed-phase column of a Waters Associates high-pressure liquid chromatography (HPLC) system whose column was jacketed by a stainless steel tube through which coolant was circulated at ≤10 °C. The mobile phase was either water or 0.01 M phosphate buffer (pH 7.3) at a flow rate of 0.5 mL/min.

(*Z*)-*N*-Ethoxy-*N'*-methyl-*N'*-(methyl-*d*$_3$)diazenium Hexafluorophosphate (12). A conformationally stable, crystalline derivative of **11** was prepared by adding 10 mL of a 0.06 M dichloromethane solution thereof to a slight excess (160 mg) of triethyloxonium hexafluorophosphate dissolved in dichloromethane. The resulting mixture was rotary evaporated, leaving a semisolid mass, which was recrystallized from boiling methanol. The yield was 43 mg: mp 92–93 °C; ^{1}H NMR (chloroform-*d*) δ 1.62 (t, 3 H), 3.89 (s, 1.14 H), 4.20 (s, 1.86 H), 5.16 (q, 2 H); these integral ratios were unchanged after 66 h. A sample of the unlabeled analogue was prepared by similar reaction of dimethylnitrosamine with the Meerwein salt and shown to be analytically pure; mp 93.5–94.5 °C. Anal. ($C_4H_{11}N_2OPF_6$) C, H, N, P, F.

Benzyltrimethylammonium (*E*)-Methanediazotate (13). The quaternary salt, **13**, was prepared by mixing equal volumes of **4** and benzyltrimethylammonium bromide, each as a 0.2 M solution in chloroform-*d*, and filtering the resulting slurry: ^{1}H NMR (−50 °C) δ 3.31 (s, 9 H), 3.38 (s, 3 H), 4.82 (s, 2 H), 7.5 (m, 5 H); ^{13}C NMR (−50 °C) δ 44.3, 52.1, 68.3, 127.1, 128.4, 130.5, 132.0. The absence of additional peaks in either spectrum indicated that the yield of **13** was essentially quantitative. The methanediazotate signal suffered loss of intensity on warming, but all others remained constant. The products of decomposition were characterized by conducting a similar reaction in undeuteriated chloroform while sweeping evolved gas with nitrogen through an ethereal valeric acid solution; this confirmed that diazomethane was produced, though the amount of methyl valerate recovered was small (1.8%) and some methanol appeared to be present in the trapping solution as well. That a diazotate can be converted to a diazoalkane efficiently under nonbasic conditions has been demonstrated by previous workers.[16,17]

Thallium(I) (*Z*)-Methanediazotate (14) and (*E*)-Methyl(methyl-*d*$_3$)nitrosamine (15). Thallous ethoxide (10 mmol) was dissolved in 20 mL of ether, and the resulting solution was cooled to 0 °C in a nitrogen atmosphere. A solution of 10 mmol of *N*-nitroso-*N*-methylurethane in 20 mL of ether was added dropwise over 20 min, during which time a white precipitate was formed. After the solution stood at 0 °C for another 20 min, the presence of **14** was established by adding 20 mL of an ether solution containing 31.7 mmol of iodomethane-*d*$_3$ to convert **14** to **15**. The deep yellow precipitate that formed during the next 43 h at 0 °C was removed, and the filtrate was concentrated to remove most of the ether. The nitrosamine was extracted into cold water and then back-extracted into dichloromethane. The organic layer was dried with anhydrous sodium sulfate and concentrated to remove the dichloromethane. All operations were conducted at 0 °C. The residue was dissolved in chloroform-*d*: ^{1}H NMR δ 3.11 (s, integral 69%) 3.84 (s, integral 31%). After the solution stood overnight at 28 °C, the signals at δ 3.11 and 3.84 became equal in intensity. The yield of **15** under these conditions was estimated from a series of separate preparations with unlabeled reactants; GC indicated that dimethylnitrosamine and azoxymethane were each produced in 7% yield when the reaction mixtures were allowed to stand in ether solution at 0 °C overnight.

Results and Discussion

Historically, diazotates and their conjugate acids have been of tremendous importance, playing a key role in processes of great theoretical interest (for example in studies of carbenium ion chemistry[2]) as well as commercial significance (e.g., in the dyestuff industry[2a]). Diazotates and their conjugate acids are also proven or suspected intermediates in the activation of many potent carcinogens to their ultimately tumorigenic forms,[3,5-11,21,22] as well as in the chemotherapeutic action of certain anticancer drugs.[4,7,8a,22,23]

Unfortunately, it has been difficult to study these important species directly because it has too often proven impossible to purify them adequately after isolation as the alkali metal salts, to dissolve them without decomposition in nonpolar solvents, and to examine them successfully with such useful characterization techniques as melting point, combustion analysis, and mass spectrometry.

We have discovered that replacement of the alkali metal ion by thallium(I) can markedly alter the properties of a diazotate, permitting facile recrystallization, characterization by a full complement of analytical methods, and investigation of its chemistry in solution. We describe below the remarkable properties of **4**, structurally the simplest of the thallium(I) diazotates.

Synthesis and Characterization of 4. The synthesis of Tl(MeN$_2$O) was easily accomplished by mixing the reactants of eq 2 in the indicated proportions and allowing them to stir in ether

$$\mathrm{MeNH\text{-}NH_2} + 2\,n\text{-BuONO} + \mathrm{TlOEt} \longrightarrow \underset{\mathbf{4}}{\mathrm{Tl(MeN_2O)}} + \mathrm{N_2O} + 2\,n\text{-BuOH} + \mathrm{EtOH} \quad (2)$$

solution until the yellow product crystallized. The synthesis was patterned after that of Thiele,[16] who prepared sodium (*E*)-methanediazotate (**5**) by mixing sodium alkoxide with methylhydrazine and a nitrite ester.

Compound **4** contrasted in a variety of important ways with previously reported diazotates. To illustrate these differences, we also prepared a sample of **5** and studied the physical and chemical properties of the two compounds in parallel.

Compound **4** was highly crystalline and proved to be suitable for X-ray diffraction (vide infra), while the sodium compound was a white powder. Compound **4** melted at a low temperature (59–61 °C) and resolidified upon cooling, whereas characteristic melting points have not been observed for **5** and other methanediazotates. The thallous species gave an electron impact mass spectrum that included peaks at *m/z* 262 and 264 attributable to molecular ions of composition Tl(CH$_3$N$_2$O)$^{\bullet+}$ but **5** under similar conditions yielded no spectrum. Unlike **5**, **4** was not noticeably hygroscopic, although the latter darkened slowly upon exposure to air.

Solubility differences between **4** and **5** were particularly noteworthy. Compound **4** proved to be especially soluble in several relatively nonpolar solvents, primarily halogenated hydrocarbons, with solutions as concentrated as 1 M or greater being easily prepared in some cases. Compound **4** could also be recovered unchanged from wet pyridine and dissolved easily in hexamethylphosphoramide (though it appeared to react with dimethyl sulfoxide to form colored products as it dissolved). By contrast, **5** and related diazotates fail to dissolve, or else they dissolve with decomposition, in nearly every solvent except hexamethylphosphoramide and dimethyl sulfoxide, in which they are typically soluble enough to yield easily observable NMR peaks.

Its excellent solubility properties have greatly facilitated analytical characterization of the new diazotate. It could be recrystallized conveniently by various solvents and solvent combinations. The recrystallized material was of reproducibly high purity, as reflected both in the characteristic melting point and in the elemental analysis, which corresponded satisfactorily to the formula Tl(CH$_3$N$_2$O). Decomposition of **4** could be easily detected, both by discoloration of the bright yellow solid or its solutions and by the appearance of bubbles and/or insoluble material in its otherwise homogeneous solutions.

In contrast, **5** and other alkali metal diazotates have proven especially difficult to characterize analytically.[24] Their low solubility and/or high reactivity in the usual solvents have thwarted efforts to purify them by standard methods such as chromatography or recrystallization. To prepare crystals of potassium

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(24) Previous comments on the difficulty of achieving and verifying the analytical purity of diazotates can be found in ref 2a, 5, 13b, and 17.

(25) (a) Suhr, H. *Chem. Ber.* **1963**, *96*, 1720–1725. (b) Hassaneen, H. M.; Abdelhamid, A. O.; Fahmi, A. A.; Shawali, A. S. *J. Heterocycl. Chem.* **1985**, *22*, 395–400.

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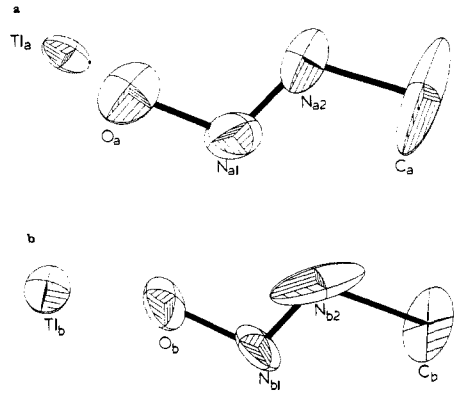

Figure 1. Perspective ORTEP[40] drawing for the solid-state structure of $Tl(CH_3N_2O)$ with the two crystallographically independent formula units shown in a and b. Atoms are represented by thermal vibration ellipsoids drawn to encompass 50% of their electron density.

(*Z*)-methanediazotate (**6**) for X-ray diffraction studies, for example, the material had to be handled with special techniques (sealed capillary, nitrogen atmosphere) after painstaking recrystallization from dimethyl sulfoxide or liquid ammonia.[18,27] In addition, the low solubility renders problematical many of the most useful spectral characterization methods. To illustrate this point, consider the ^1H NMR spectroscopy of diazotates,[5,7,15d,18,25] by now widely adopted as a mainstay analytical tool for examining this class of compound. For the typical sample, the dimethyl-d_6 sulfoxide or hexamethylphosphoramide-d_{18} solution may yield a single ^1H NMR peak at the proper chemical shift, tempting the analyst to conclude that the sample at hand is pure. However, careful inspection may reveal that the solution is cloudy, indicating incomplete dissolution of a proportion that is difficult to determine. If the solid consists only of undissolved diazotate, then no compromise of the sample's purity is implied. But if it contains some insoluble decomposition product such as an alkali metal hydroxide, produced on disproportionation of the "exceptionally air- and moisture-sensitive" diazotate[27] to diazomethane gas, the contamination may not be detectable by ^1H NMR even if extensive. For this reason, we have adopted elemental combustion analysis as the only fully reliable index of purity for the alkali metal diazotates. It has been our experience that the quality of such substances may show considerable variation from one supposedly identical synthesis to another, particularly as reflected in the percent nitrogen value observed, which is diminished from the expected value to the extent that either of the two main gaseous decomposition products (diazoalkanes or dinitrogen) is formed. In our hands, percent nitrogen values for the alkali metal methanediazotates have never exceeded 90% of theoretical (for example, see the Experimental Section). Similar results have been reported by previous authors.[24] These findings underscore the difficulty of adequately purifying and characterizing alkali metal diazotate preparations and illustrate an important potential advantage of working with the thallium derivative, which does not appear to share their analytical limitations.

Structure and Bonding in 4. The crystal structure of **4** was determined. The unit cell was monoclinic, space group $P2_1/c\text{-}C_{2h}^5$ (No. 14), with a = 13.233 (6) Å, b = 11.594 (4) Å, c = 6.523 (2) Å, β = 119.45 (3)°, V = 871.5 (6) Å^3, and Z = 8. ORTEP diagrams of the two crystallographically independent $Tl(CH_3N_2O)$ units are shown in Figure 1. The X-ray data revealed that the diazotate moiety of $Tl(CH_3N_2O)$ is essentially planar (within 0.01 Å), with none of the C, N, or O atoms lying more than 0.4 standard deviation from the least-squares mean plane defined by the C–N–N–O system. In this respect, **4** is like most of the other diazotates whose structures have been determined thus far by crystallographic methods (Table I).[26-30] The only compound we

Table I. Summary of Structural Data for Crystalline Diazotates, M(C–N^A–N^B–O)

	$Tl(CH_3N_2O)$ unit		literature values						
	a	b							
diazotate confgn	trans	trans	cis	trans	cis	trans	cis	trans	
ref	this work		26	26	27	28	29	30	
C–N^A, Å	1.48 (7)	1.54 (7)	1.465 (19)	1.466 (20)	1.477 (10)	1.388 (7)	1.455 (15)	1.420 (7)	
N^A–N^B, Å	1.24 (5)	1.15 (5)	1.288 (17)	1.278 (17)	1.246 (8)	1.330 (6)	1.296 (13)	1.327 (6)	
N^B–O, Å	1.35 (4)	1.34 (4)	1.255 (17)	1.241 (22)	1.306 (7)	1.239 (6)	1.318 (11)	1.249 (7)	
shortest M···O, Å	2.52 (3)				2.650				
shortest M···N, Å	2.88 (4)				2.900				
C–N^A–N^B, deg	117 (4)	112 (4)	119.2 (12)	117.6 (13)	116.2 (5)	108.1 (4)	119.2 (9)	113.6 (4)	
N^A–N^B–O, deg	111 (3)	107 (3)	115.9 (14)	118.0 (15)	119.8 (5)	117.6 (4)	118.8 (9)	113.1 (4)	
C–N^A–N^B–O coplanar?	yes	yes	C is 0.204 Å out of NNO plane	C is 0.165 Å out of NNO plane	"Das Anion ist sehr genau eben"	M–N^B–O, M–N^B–N^A, and N^A–N^B–O angles sum to 359.9°	"diazotate group···planar"	"essentially coplanar"	

(27) Huber, R.; Langer, R.; Hoppe, W. *Acta Crystallogr.* **1965**, *18*, 467–473.

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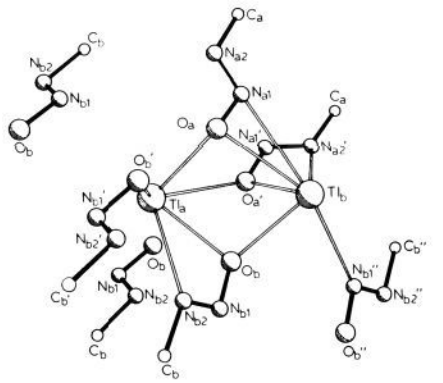
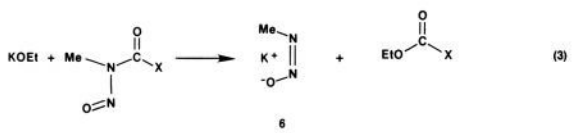


Figure 2. Perspective ORTEP[40] drawing showing the (primary) coordination spheres of the two crystallographically independent thallium atoms in crystalline **4**. All atoms are represented by arbitrary-sized spheres for purposes of clarity.

have found in the literature for which significant departures from diazotate planarity have been reported was the interesting octahedral platinum(IV) complex characterized by Freeman, in which the carbon atoms of both the diazotate groupings lay approximately 0.2 Å out of the respective N–N–O planes.[26]

As a corollary of their planarity, diazotates are expected to display considerable double-bond character in their N–N linkages and thus to exist in either cis or trans configurations.[2a,d] Of the five crystalline diazotates examined previously by X-ray methods, two can be classified as trans, two are cis, and one, the bis(diazotate) mentioned above, has both cis and trans linkages (see Table I). It has been widely accepted that diazotates prepared via the alkylhydrazine (eq 2) must be of the trans configuration because they have long been known to be isomeric with those prepared by the action of an alkoxide on an *N*-alkyl-*N*-nitroso-*N*-acyl derivative (eq 3)[2a,d] and because the product (**6**) of the latter



(3)

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synthetic route has been determined to be cis by X-ray crystallography.[27] As presented in Figure 1, the C and O atoms are clearly on opposite sides of the N=N bond in crystalline **4**. The present study is the first in which the fully reasonable, but as yet only indirectly tested, assumption of trans stereochemistry for a diazotate prepared from the corresponding alkylhydrazine has been directly confirmed by X-ray methods.

One of the most interesting suggestions implicit in the X-ray data concerns the nature of bonding between the thallium(I) and the heteroatoms of **4**. Since thallous ion has been likened to the alkali metal cations but is known to have considerable covalent character when bonded to oxygen or nitrogen atoms, which are in turn bonded to alkyl groups,[31] it was not clear how the metal–diazotate bonds in **4** might compare with the presumably ionic interactions in the potassium derivative, **6**. Consistent with a degree of ionic bonding, both crystallographically independent Tl atoms in crystalline **4** were found to be within 3.3 Å of six (Tl_a) or seven (Tl_b) oxygen or nitrogen atoms of several symmetry-related diazotate moieties, as shown in Figure 2; the Tl–O and Tl–N distances for each metal varied by at least 0.48 and 0.29 Å, respectively. Clearly, the solid-state structure of **4** contains extensive 3-dimensional association rather than the presence of discrete molecular metal–diazotate units.

Both Tl ions do, however, have "tight" 1,3-chelate-type interactions with a single diazotate ligand on the coordination sphere, which is similar to that previously observed between a bis(perfluorophenyl)zinc group and a tetramethyltetrazene molecule.[32] Interestingly, the Tl–O and Tl–N(2) bonds involving the "chelated" diazotate are the shortest Tl–O and Tl–N bonds on both Tl coordination spheres. Presumably, retention of such an interaction in the gas phase and in solution would explain both the mass spectral data and the relatively high solubility of **4** in low-polarity solvents.

The differences in crystal structure data (summarized in Table I) between **4** and the other diazotates including **6** further support the possibility of significant covalent character to the thallium diazotate chelate linkage in **4**. The shortest Tl–O distance found in **4** was 0.13 Å less than the smallest K–O separation in **6**,[27] while the ionic radius of Tl is 0.10 Å greater than that of potassium.[31] Thus, the shortest Tl–O separation is 0.23 Å smaller than would be expected if thallium bonding were identical with that of the K^+ ion. A qualitatively similar shortening of the closest metal–nitrogen distance was also observed, but it was smaller in magnitude (0.12 Å rather than 0.23 Å), suggesting a relatively stronger interaction of thallium with oxygen than with nitrogen in the diazotate moiety of **4**. In any case, the metal–oxygen separations in both **4** and **6** were significantly smaller than the metal–nitrogen distances, consistent with the smaller size of oxygen and localization of the negative charge on oxygen. It is perhaps also noteworthy that the N–N–O angles in **4** were more acute than those of any other diazotate, presumably because of chelation to thallium.

These indications of substantial thallium–diazotate association in crystalline **4** led us to attempt to determine the type of bonding the compound might display in solution. Its high solubility in solvents of low polarity such as dichloromethane suggested that a similar tendency toward covalency might persist in the dissolved state. Consistent with this prediction, the specific conductance of **4** in chloroform was identical with that of the solvent and much smaller than the values found for similar concentrations of an ionic onium halide. In addition, the molecular weight as determined by osmometry in chloroform was 264, or exactly one formula weight for $Tl(CH_3N_2O)$. We conclude that **4** is monomeric and essentially nonionic in chloroform solution.

Pyridine solutions of **4** also displayed little conductivity, despite the higher dielectric constant and coordinating capability of this solvent. The molecular weight was found to be twice the formula weight, indicating dimerization in this solvent. By analogy with the thallium(I) alkoxides, in which a tetrameric structure has been confirmed by observation of ^{203}Tl–^{205}Tl coupling,[33] we expected to find the superposition of a doublet and a singlet in the ^{205}Tl NMR spectrum. Instead, a singlet (width at half-height 400–500 Hz) was observed for a 0.1 M solution of **4** in pyridine at ambient temperature. This resolution seemed fully adequate for observation of the anticipated coupling, since J (^{203}Tl–^{205}Tl) for the alkoxides is >2000 Hz.[33] It is possible that spin–spin interaction among the thalliums, if it exists, may be unobservable at this temperature because thallium interchange is too rapid. Consistent with fast exchange, the signal broadened considerably (width at half-height ca. 4000 Hz) when the temperature was lowered to −30 °C. No suggestions of doublet character could be found even at this low temperature, however, thwarting spectral confirmation of the dimeric nature of **4**.

One other datum that may be relevant to the question of bonding in **4** is its UV spectrum, which in chloroform consists of a low-intensity shoulder at 315 nm on a high-intensity band, which extends into the far UV. A similar shoulder (at 263 nm) for thallium(I) oxalate in water has been attributed to covalent attachment between the metal and the carboxylate function.[34] Bands assigned to thallium(I) transitions might be expected at

(29) Alcock, N. W.; Goodman, P. D.; Kemp, T. J. *J. Chem. Soc., Perkin Trans. 2* **1980**, 1093–1095.
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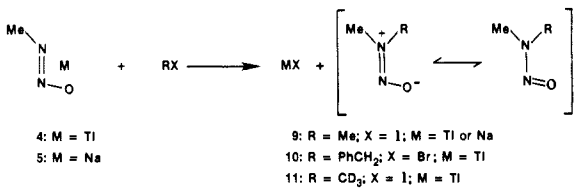
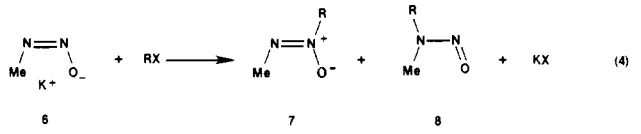
Scheme I. Synthesis of Nitrosamines by Alkylation of (*E*)-Methanediazotates



195–245 nm,[34] but none was observable because the solvent is not transparent in this region.

We believe that the evidence suggests a greater degree of covalent metal–oxygen bonding in the thallium(I) compound **4** than in previously described alkanediazotates (Table I), all of which display either ionic bonding or covalent metal–nitrogen association. While the possibility of noncovalent ion-pair bonding in **4** cannot be excluded on the basis of available data, the results obtained seem consistent with the published generalizations that the Tl–X bond appears to be more covalent than the bond to alkali metal ions in similar compounds and that thallium compounds tend to be polymeric rather than ionic in the solid phase.[31,34]

Stereoselective Synthesis of Thermodynamically Disfavored Nitrosamine Conformers. It is well established that diazotates can be reacted with certain electrophiles to form a variety of useful products.[35,36] One example that illustrates both the synthetic utility of the diazotate group and its interesting ambident nature is the reaction of **6** with alkylating agents. As shown in eq 4, these



reactions have typically yielded both azoxyalkanes **7** and nitrosamines **8** among the stable products, with the product ratio depending on such factors as polarity of the reaction solvent and steric requirements of the alkyl groups. The stereochemistry of azoxyalkane synthesis according to eq 4 has been extensively studied, confirming that configuration is retained in the transformation, i.e., that *Z* diazotates give as products azoxyalkanes having the same stereochemistry, with the attacking electrophilic carbon atom being bound to the nitrogen bearing the oxygen atom. This stereoselective reactivity has been ingeniously exploited for the preparation of several important azoxyalkanes.[2d,35]

It is also well established that the N–N linkages of nitrosamines such as **8** have enough double-bond character to permit *syn*- and *anti*-alkyl groups to be distinguished;[37] when R ≠ Me, *Z* and *E* conformers of compounds having structure **8** can normally be individually recognized in the equilibrium mixtures by NMR[37] and sometimes even isolated by selective crystallization or by chromatography.[38]

We have been interested in the possibility of stereoselectivity in the formation of nitrosamines by diazotate alkylation as in eq 4 but have been able to find no mention of data relevant to this point in the prior literature. Compound **4** (Scheme I) seemed to be an appropriate substrate for such studies. We now report that it can be smoothly alkylated under a variety of conditions and that the nitrosamine products are those in which the configuration of the diazotate moiety is retained.

We began our studies of **4** alkylation as a route to nitrosamine formation with a kinetic comparison between **4** and **5** as substrates for electrophilic attack by iodomethane. In chloroform, both gave dimethylnitrosamine (**9**) as the major product, but there was a large difference between the rates of the two reactions. In the presence of 1 M iodomethane in chloroform-*d* solution, 0.25 M **4** was found by NMR to be converted to **9** at an initial rate of about 0.01 M/h at room temperature, reaching a plateau after 1 day of between 50 and 60% of the theoretical yield. By contrast, **9** was produced from **5** at an initial rate of only 10^{-4} M/h under these conditions. It seemed likely that much or all of this rate difference might be attributable to the fact that **4** at this concentration was completely soluble in the reaction medium while the reaction of **5** was forced to proceed heterogeneously, preventing the reactants from being adequately accessible to one another. For this reason, we attempted both reactions in hexamethylphosphoramide-d_{18} as well, since both **4** and **5** are soluble in this medium. As predicted, results for the two compounds were much less dissimilar in this solvent. The rates for formation of **9** at room temperature were too fast to follow conveniently by NMR for both **4** and **5** under these conditions, and the observed yields reached plateaus at about 20% of theory for both compounds. Interestingly, the yields of azoxymethane were small in all of the above methylation reactions.

These results suggested that **4**, with its unusual bonding characteristics and high solubility in nonpolar media, might hold considerable promise as a synthon for novel *N*-nitroso compounds. As one test of this possibility, crystalline **4** was mixed with excess benzyl bromide. The solid dissolved easily, following which an abundance of thallous bromide began to precipitate. After standing at room temperature, the reaction mixture was evaporated, and the residue was dissolved in chloroform-*d*. Of the many peaks in the ^{1}H NMR spectrum of the crude product, two of the strongest were singlets at 3.45 and 4.63 ppm in an integral ratio of 3:2. These peaks corresponded in chemical shift and relative area to those of the methyl and methylene resonances, respectively, of the *Z* conformer of methylbenzylnitrosamine, **10**. On standing, the intensities of both peaks decreased while two other signals (2.74 and 5.09 ppm, also in an integral ratio of 3:2, as expected for the *E* conformer), which were originally very small, grew correspondingly until they were about twice the size of the peaks for the *Z* conformer. Evidently, the solvolysis of **4** in benzyl bromide led stereoselectively to the less stable conformer of **10**.

The synthetic utility of **4** was further demonstrated by conversion to **11**, a derivative of **9** in which the *syn*- and *anti*-methyl groups have been rendered isotopically distinguishable. Such a compound was desired for biological studies, e.g., for investigating the stereochemistry of enzymatic attack on dimethylnitrosamine during metabolic activation to its proximately carcinogenic form. To accomplish this preparation, a 1 M solution of **4** in iodomethane-d_3 was prepared and allowed to stir at 0 °C. Again, the thallium halide began to precipitate soon after mixing. When UV and GC–MS revealed 2 h later that the yields of **11** and azoxymethane-d_3 were 20% and 4%, respectively, the reaction was quenched, and the desired product was purified by low-temperature HPLC. The ^{1}H NMR spectrum of **11** consisted of a large singlet at 3.7 ppm and a very small singlet at 3.1 ppm, indicating that the conformational purity of the product was high (*Z*:*E* = 96:4). As expected, solutions of **11** underwent equilibration on standing, the ^{1}H NMR signals eventually becoming equal in intensity. A typical half-life for this interconversion was 2 h at 37 °C and pH 7.4. However, the conformational integrity of **11** could be preserved indefinitely when stored as the frozen aqueous solution at −20 °C or colder.

Rotation about the N–N bond could also be prevented by reacting **11** with an ethyl Meerwein salt (eq 5). The crystalline onium derivative, **12**, showed no observable tendency to isomerize, consistent with a formal bond order of 2 for the N–N linkage.

Quaternary Ammonium Diazotate Preparation. Our success in the above synthetic attempts encouraged us to look further at

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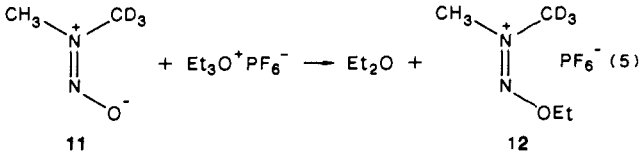
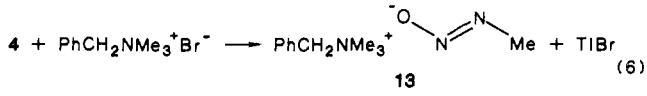


11 12

the general applicability of thallium(I) diazotates in preparative chemistry. As an illustration of its potential for syntheses other than those of dialkylnitrosamines, we investigated metathesis reactions to determine whether thallium could be replaced by onium ions. In view of the affinity of thallium(I) for halide and the insolubility of the resulting TlX, it seemed reasonable to speculate that ionic, chloroform-soluble organic halides should form ionic salts of the primary nitrosamines **2** and diazo hydroxides **3** in transformations like that represented in eq 6.

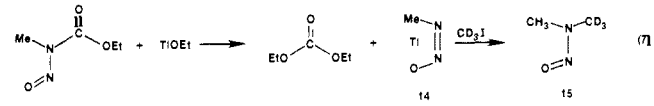


13 (6)

This proved to be a rather general phenomenon. For instance, when solutions of **4** and benzyltrimethylammonium bromide in chloroform-*d* were mixed in equimolar proportion, thallous bromide immediately precipitated, leaving a solution of benzyltrimethylammonium (*E*)-methanediazotate (**13**). This appears to be the first reported example of a quaternary ammonium diazotate, although an interesting secondary ammonium salt of a cyclopropanediazotate has been described.[39] While the three-membered ring may confer unusual stability on the latter alkanediazotate ion, **13** and related diazotates have proven difficult to study due to their instability. In chloroform-*d* solution, for example, **13** decomposed rather rapidly with loss of the diazotate methyl signal from the NMR spectrum. The decomposition was accompanied by generation of diazomethane, although this product was recovered in small yield. Further work on the synthesis of onium diazotates is planned, with the aim of determining the degree to which their instability may be related to the poorly solvating characteristics of the solvents used thus far for these necessarily ionic substances, rather than to stereochemical or other factors.

Thallium(I) (*Z*)-Methanediazotate (14). Definitive answers to some of the questions implicit in the results described above will not be possible until data are available for thallium diazotates differing only in the configuration about the N=N bond. For example, only through parallel studies with the corresponding *Z* diazotates can the effect of stereochemistry be separated from that of solvation in dissecting onium diazotate reactivity as proposed above.

Accordingly, we have attempted on several occasions to prepare the *Z* isomer of **4** using variants of eq 3 in which thallium(I) ethoxide was used as base. While we have not yet succeeded in isolating the desired product, thallium(I) (*Z*)-methanediazotate (**14**), we have been able to confirm its existence as an intermediate in the reaction sequence shown in eq 7. Compound **14** was



14 15 (7)

prepared by stirring ether solutions of thallous ethoxide and *N*-methyl-*N*-nitrosourethane at 0 °C. The identity of the product was established by an analytical method similar to that employed in the qualitative identification of **4**, i.e., by trapping with a suitable electrophile and examining the NMR. Addition of iodomethane-d_3 to the initial reaction mixture of eq 7 led to isolation of a trideuteriated derivative of dimethylnitrosamine whose mass spectrum was identical with that of **11** and whose ^{1}H NMR spectrum also consisted of two peaks at the shifts expected for the methyl singlets of **9**; in this case, however, the higher field signal was by far the larger, confirming the identity of the methylation product as (*E*)-methyl(methyl-d_3)nitrosamine (**15**) and allowing the configuration of the intermediate diazotate to be assigned as *Z* (**14**).

It is hoped that further attempts to characterize and perhaps even isolate **14** may provide additional insight into the chemistry of the thallium(I) alkanediazotates as well as of other novel *N*-nitroso compounds whose preparations the thallium derivatives' availability will have made possible.

Conclusions and Significance

The unusual bonding and solubility characteristics of thallium(I) (*E*)-methanediazotate (**4**) have been of significant advantage in seeking to overcome some of the longstanding problems of work with diazotates. In addition to promising some very favorable synthetic implications, the high solubility of **4** in certain nonpolar solvents should permit straightforward kinetic studies of the diazotate's reactivity in homogeneous mixtures of widely varying polarity. The full range of mechanistic possibilities made available by the stabilizing and solubilizing influence of thallium is only beginning to be probed; we have found, for example, that **4** is rapidly converted to largely insoluble product(s) upon irradiation for a few minutes in chloroform-*d* solution in a quartz tube, suggesting that an interesting and potentially rich photochemistry of diazotates awaits exploration. Electrochemical and other fundamental chemical investigations of diazotates in solution should also be possible and may prove similarly rewarding. The direct biological significance of **4** and related materials is likely to be severely limited by the thallium compounds' notorious toxicity,[19] but important applications in biological research could nevertheless develop through their use as synthetic intermediates, e.g., via ion exchange to form other soluble diazotates.

Acknowledgment. We thank P. Roller for mass spectral determinations, G. Chmurny and B. Hilton for collecting some of the NMR data, J. Hrabie for invaluable consultations, and the National Cancer Institute Chemical Carcinogen Reference Standard Repository for providing azoxymethane. Work was supported in part by National Cancer Institute Grant CA 35733.

Supplementary Material Available: Full crystal structure analysis report, including atomic coordinates and anisotropic thermal parameters for non-hydrogen atoms in crystalline Tl(CH_3NNO), selected interatomic distances and angles, and mean plane calculations (14 pages); structure factor amplitude tables (4 pages). Ordering information is given on any current masthead page.

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