Experimental observation and quantum chemical investigation of thallium(i) (Z)-methanediazotate: synthesis of a long sought and highly reactive species†‡

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For the first time, successful synthesis and characterisation of the missing (Z)-isomer of thallium(i) methanediazotate has been accomplished, utilising low-temperature NMR monitoring analysis. The title compound was synthesised from N-methyl-N-nitrosourea and thallium(i) propoxide, under sub-ambient temperatures, as a highly moisture sensitive entity. Quantum chemical calculations, performed at the CCSD(T) level, depict excellent conformity to experimental results. Indeed, compared to its (E) counterpart, the formation of the title compound is thermodynamically less favoured, but preferred by means of kinetic control owing to a hindered isomerisation.

Alkane diazotates1,2 have long been discussed as highly reactive species, generated in the in vivo metabolism of N-nitrosoureas, and are responsible for the alkylation of DNA, thereby, acting as potent carcinogens.3 Fixation of nitrous oxide (N2O) by frustrated Lewis-pairs (FLPs)4 and N-heterocyclic carbenes5 also leads to the formation of diazotates. The high moisture sensitivity, exhibited by these entities, makes them extremely difficult to isolate and handle at room temperature. In spite of that, certain diazotates, such as 1, 2 and 4–6, have been isolated and characterised by the XRD technique,6 for example, potassium(i) (Z)-methanediazotate (4) (Scheme 1a). It is long known that configurational isomerism exists in the diazotates owing to the restricted rotation about the N–N bond, and that (Z)-isomers are highly reactive when compared to the corresponding (E)-isomers.

Particularly noteworthy are thallium(i) methanediazotates,7 of which heretofore only the (E)-isomer 1 was isolated and characterised by single crystal X-ray analysis, by Keefer et al. Molecule 1 was synthesised by the nitrosation of methylhydrazine in the presence of thallium(i) ethoxide (TIOEt) (Scheme 1b), as a highly crystalline material stable to hydrolysis, a property which is highly contrasting to other similar diazotates and explained by the possible covalent nature of the thallium(i) cation. The configuration was assigned by analogy with the very few (Z)-isomers, obtained by utilising the base induced decomposition of N-alkyl-nitroso-N-acyl derivatives (Scheme 1b). However, the exact mechanism detailing the preference of a particular configurational isomer remains speculative, since contrasting theoretical reports exist about the type of the conformation of N-nitrosourea 7 in solvents, and furthermore, no consideration of the solvent was taken into account in determination of the anti/syn existence. Keefer and coworkers,7 however, could not directly characterise thallium(i) (Z)-methanediazotate (3), citing its highly reactive nature, and that still remains a gap in the field of thallium diazotates as well as in the larger case of covalent metal diazotates.

We became interested in the synthesis of (Z)-methanediazotate 3 and also in the theoretical basis for the formation of this diazotate along with the possibility of (Z)-(E) isomerisation under solvation. Thallium(i) alkoxides7–9 are unique bases owing to their covalent character and solubility in a range of organic solvents, even at low-temperatures, which is quintessential for monitoring reactions by low-temperature NMR analysis. Therefore, 15N-labelled N-methyl-N-nitrosourea (7) was synthesised and reacted with TIOEt at −40 °C in CD3Cl2, under constant monitoring by low-temperature NMR spectroscopy.10 In this case, we could only observe the doublet for CH2N15N at δ = 3.34 with 3J(15N,1H) = 1.1 Hz in the 1H NMR spectrum and a signal at δ = 14.17 in the corresponding 15N NMR spectrum. The identity of 15N-labelled diazomethane was further confirmed by 15N,1H gHMBCAD and by comparison with literature known values.11 This result is in complete agreement with the known methods for the synthesis of diazotates and the observed secondary products in the absence of electrophiles (Scheme 2).11
However, owing to our previous experience with thallium(I) alkoxides, it is known that TlOEt and thallium(I) propoxide (TlOPr) react differently, probably because of their varying association nature. Therefore, to a solution of TlOPr (1.1 eq.) in CD$_2$Cl$_2$, maintained at $-60\,^\circ$C, was added N-nitrosourea (10 mg), and the reaction was analysed by sub-ambient temperature $^1$H and $^{15}$N NMR monitoring technique. To our pleasant surprise, along with the signals of CH$_2$N$_{15}$N, we also obtained well-defined signals for thallium(I)(Z)-methanediazotate in 14% yield ($^1$H NMR), with a doublet at $\delta = 3.17$ with $^3J(^{15}$N,$^1$H) = 4.0 Hz in the $^1$H NMR spectrum (Fig. 1), and a singlet at $\delta = 104.5$ for the $^{15}$NOTl unit. The structure was further confirmed by $^{15}$N,$^1$H gHMBCAD 2D-NMR technique (Fig. 2). Compound 3 was stable for only a few hours at $-60\,^\circ$C, and decomposed completely to CH$_2$N$_{15}$N (confirmed by NMR as mentioned before), which led to an increase of the total diazomethane yield from 31% to 43%. Since the $^1$H NMR data and high stability of the corresponding (E)-diazotate 1 ($\delta = 3.43$), stable at RT, contrasts significantly with the properties of the aforementioned species and because of the additional evidence obtained through $^{15}$N NMR as well as 2D-NMR experiments, the structure of the highly elusive (Z)-diazotate 3 is now confirmed.

Moreover, due to the existence of hindered rotation about N–N bond in N-nitrosoureas like 7 in different solvents, thereby, giving rise to syn/anti rotational isomers, it becomes essential to define the preference of a particular rotamer in special solvents. This existence of rotational isomerism plays an important role about the outcome of the stereochemistry of the thallium diazotates 1/3. Therefore, we performed high-level quantum chemical calculations pertaining to the anti/syn conformational isomerism of N-nitrosourea 7 as well as the (Z)/(E) configurational isomerism of 3/1. Low-level theoretical calculations, without any consideration of solvent contributions, have been performed before, regarding to ionic diazotates, but they cannot be extended to covalent diazotates like 1/3. Furthermore, by comparing the isomerisation energetics to the mechanisms for the TlOPr induced formation of both diazotates from the corresponding conformers of 7 (Fig. 3), we explain the occurrence of the thermodynamically less stable (Z)-isomer.
The molecular geometries were optimised by TURBOMOLE V6.5, using RI-DFT** with the PW6B95 functional, the D3 dispersion correction, the TZVPP basis set (def2-TZVPP with corresponding ECP for Ti) as well as the COSMO solvation model ($\varepsilon = 8.9$ for CD$_2$Cl$_2$). Numerical frequency analyses were performed to characterise the stationary points and to obtain the zero point vibrational energy. The freemodule was used to calculate the Gibbs free energy contribution at the reaction temperature ($-60$ °C). We also performed CCSD(T)/cc-pVXZ ($X = T, Q$) calculations (with pseudopotential for Ti) and a subsequent CBS(34) extrapolation according to eqn (1) and (2) as well as CCSD(T)(F12)/cc-pVTZ-F12 (ref. 24) (aug-cc-pwCVTZ-PP basis for Ti) calculations to obtain highly accurate electronic energies. Additionally, we applied the focal-point method in eqn (3), using an MP2 increment to approach the CBS limit.

$$E_{HF}^{(XY)} = \frac{e^{-6.3\sqrt{Y}E_{HF}^{(X)} - e^{-6.3\sqrt{Y}E_{HF}^{(Y)}}}}{e^{-6.3\sqrt{Y}E_{HF}^{(X)} - e^{-6.3\sqrt{Y}E_{HF}^{(Y)}}}}$$  
(1)

$$E_{corr}^{(XY)} = \frac{X^3 E_{corr}^{(X)} - Y^3 E_{corr}^{(Y)}}{X^3 - Y^3}$$  
(2)

$$E_{fo/TZ} = E_{cc-pVXZ}^{CCSD(T)} + (E_{mp2/cc-pVTZ-F12}^{CCSD(T)} - E_{mp2/cc-pVTZ})$$  
(3)

With the single-point energy $E_M$ obtained by method $M$, and a Gibbs free energy contribution $G_{-60}$, as well as a COSMO solvation correction $\Delta E_{solv}$, both at the PW6B95-D3/TZVPP level, the total Gibbs free energy of a structure is obtained as:

$$G = E_M + G_{-60} + \Delta E_{solv}$$  
(4)

$$\Delta E_{solv} = E_{COSMO} - E_{noCOSMO}$$  
(5)

As shown in Table 1, the reaction energy ($\Delta G_{react}$) for the anti-syn isomerisation of 7 is positive, representing the higher stability of the anti-rotamer. In contrast, the (Z)-diazotate 3, which yields from the anti-rotamer, is less stable than the (E) form. Indeed, the experimental results show the formation of the (Z) isomer, which excludes a thermodynamic reaction control (Fig. 3).

Furthermore, the activation barrier ($\Delta G_{act}$) for the formation of the syn-rotamer is around 90 kJ mol$^{-1}$ and therefore rather large, representing the hindered rotation. However, the direct isomerisation of 3 to 1 needs significantly more activation ($\geq$190 kJ mol$^{-1}$) and can thus be excluded. Also, the covalent nature of the Ti-X (X = O, N) bond is supported by the Ti-O bond length in (Z)-diazotate 3 (2.42 Å; Fig. 4), in accordance with published results.

Considering the different highly accurate CCSD(T) methods to approach the complete basis set (CBS) limit, the relative energies of all three (Table 1) are in perfect agreement. Hence, the most efficient of them, the focal-point method in eqn (3),

Table 1. Activation ($\Delta G_{act}$) and reaction ($\Delta G_{react}$) Gibbs free energies for the anti–syn isomerisation of 7 and the (Z)–(E) isomerisation from 3 to 1. All energies are in kJ mol$^{-1}$ and method (M) refers to the calculation of the electronic energy.

| Method | M | DFT$^a$ | fo/TZ$^b$ | CBS(34)$^c$ | TZ-F12$^d$ |
|--------|---|---------|---------|---------|---------|
| anti-7 → syn-7 | \(\Delta G_{act}\) | 103.2 | 89.8 | 91.5 | 90.8 |
| | \(\Delta G_{react}\) | 20.7 | 18.6 | 18.9 | 18.9 |
| 3 → 1 | \(\Delta G_{act}\) | 176.7 | 191.4 | 192.2 | 192.8 |
| | \(\Delta G_{react}\) | 17.8 | 14.0 | 16.7 | 15.1 |

$^a$ PW6B95-D3/TZVPP. $^b$ According to eqn (3), Ti: aug-cc-pwCVTZ-PP basis instead of cc-pVTZ-F12. $^c$ CBS(34) extrapolated CCSD(T)/cc-pVXZ according to eqn (1) and (2) with $X = 3, Y = 4$. $^d$ CCSD(T)(F12)/cc-pVTZ-F12, Ti: aug-cc-pwCVTZ-PP basis instead of cc-pVTZ-F12.

Fig. 3 Molecular structures, optimised with PW6B95-D3/TZVPP and COSMO ($\varepsilon = 8.9$), for the reactions anti-7 → 3 (top) and syn-7 → 1 (bottom). Bond lengths (Å) have been depicted and the asterisk (*) represents the n-propyl group, which has been omitted for clear representation. Atoms are H (white), C (grey), N (blue), O (red), Ti (brown).
The reaction proceeds via a 1,2-elimination mechanism with activation energies of about 58 kJ mol\(^{-1}\) for (Z)-diazotate 3. However, this second step is rate-determining as it provides a greater stability of the (Z)-isomer and slightly exothermic for (E). Furthermore, the anti-syn rotational isomerisation is hindered and features even a larger activation energy than the rate-determining step within the formation of title compound 3.

In summary, synthesis and characterisation of the elusive thallium(i) Z-diazotate 3 has been achieved for the first time. It was generated as a highly temperature and moisture sensitive entity by TiOPr induced decomposition of N-nitrosourea 7. The structure of the title compound has been confirmed unambiguously by \(^{1}\)H NMR, \(^{15}\)N NMR and \(^{15}\)N,\(^{1}\)H gHMBCAD NMR spectroscopic analytical technique. The decomposition of (Z)-diazotate 3 to CH\(_3\)N\(^{15}\)N also confirms the general rule about the decomposition of other known (Z)-diazotates to diazomethane, in the presence of a base. Quantum chemical calculations, performed at the CCSD(T) level, reveal a kinetic, rather than a thermodynamic control, for the mechanism of the (Z)-diazotate 3 formation. Indeed, the (Z)-diazotate is thermodynamically less stable than the (E) form, but generated from the more stable anti-conformer of nitrosourea 7. Furthermore, the anti/syn rotational isomerisation is hindered and features even a larger activation energy than the rate-determining step within the formation of title compound 3.

**N-Methyl-N-nitrosourea** is a highly potent carcinogen, therefore, great precautions should be taken while handling it. Thallium(i) propoxide is a toxic compound and should be handled in accordance with safety protocols. Thallium (E)-diazotate can also lead to spontaneous explosions, therefore great care must be exercised while handling the highly reactive (Z)-diazotate.

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