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1,4,7-Trimethyloxatriquinane: S_N2 Reaction at Tertiary Carbon

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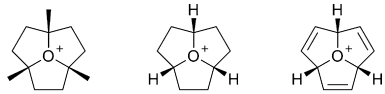
Abstract: The synthesis of 1,4,7-trimethyloxatriquinane (**1**), a 3-fold tertiary alkyl oxonium salt, is described. Compound **1** is inert to solvolysis with alcohols, even at elevated temperatures, but undergoes facile substitution with the strongly nucleophilic azide anion. Since an S_N1 pathway is excluded, the only reasonable mechanistic interpretation for the reaction between **1** and N_3^- is S_N2, despite the fact that substitution is occurring at a tertiary carbon center. This finding is supported by computational modeling and a study of the reaction kinetics, and is also consistent with observed solvent and salt effects.

It is a matter of convention in the field of organic chemistry that alkyl oxonium salts are exceptionally reactive toward nucleophiles and are counted among the most powerful alkylating agents known. Tertiary (3°) representatives of the species would be expected to be potent S_N1 electrophiles. Another fundamental principle, taught in undergraduate organic chemistry textbooks, is that bimolecular nucleophilic substitution (S_N2) reactions do not occur at tertiary carbon centers. In this paper, we present 1,4,7-trimethyloxatriquinane **1**, a molecule that challenges both of the above paradigms. It is a 3-fold tertiary alkyl oxonium ion and yet shows extraordinary stability toward nucleophiles that would rapidly cleave typical R_3O^+ salts. More remarkably, when it does undergo substitution, it appears to do so via an S_N2 mechanism.

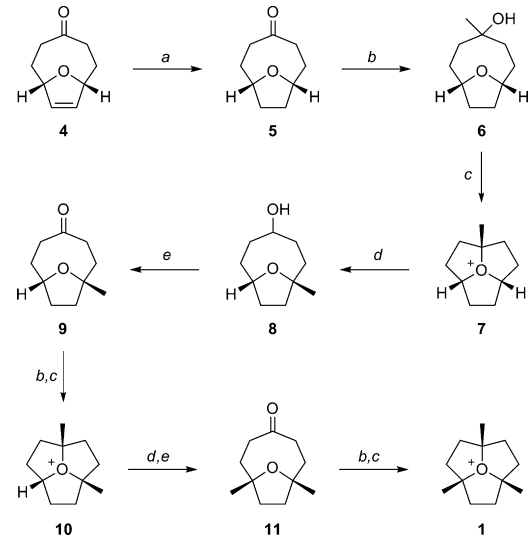


1 **2** **3**

In 2008, we reported the synthesis of oxatriquinane **2** and oxatriquinacene **3**, which themselves were shown to possess unheard of stability for alkyl oxonium salts.[1,2] For example, oxatriquinane salts could be chromatographed on silica gel and even heated at reflux in water or ethanol. Although much less robust than **2**, oxatriquinacene **3**, a triply bis-allylic oxonium ion, was stable in acetonitrile, which would be alkylated to the nitrilium salt by Meerwein reagents. Both **2** and **3**, however, quickly reacted with strong nucleophiles such as CN^-, OH^-, and N_3^- to give the expected substitution products. Embarking on the path toward the "indestructible" alkyl oxonium ion, we decided to look first at the triply α-substituted analogue of **2**, i.e. **1**, fully aware that alternative reaction paths were being opened up, in particular S_N1/E1 as well as possible E2 elimination from the methyl group.

1,4,7-Trimethyloxatriquinane **1** was synthesized as shown in Scheme 1. Thus, starting with bicyclic enone **4**, an intermediate in the synthesis of oxatriquinacene **3**,[1] hydrogenation gave ketone **5** which was cycled through a series of MeMgBr additions, ring closures, ring openings with hydroxide, and oxidations to finally give **1**, which could be isolated as a crystalline PF_6 salt.

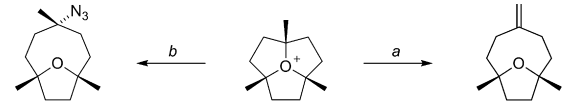
Scheme 1[a]



4 **5** **6** **7** **8** **9** **10** **11** **1**

[a] Reagents and conditions: (*a*) H_2, Pd/C, MeOH, 88%; (*b*) MeMgBr, THF; (*c*) conc. aq. HCl, sat. aq. KPF_6, 62% from **5**; (*d*) aq. NaOH, acetone; (*e*) CrO_3, pyr, 61% from **7**; repeat steps *b* and *c*, 63% from **9**; repeat steps *d* and *e*, 61% from **10**; repeat steps *b* and *c*, 57% from **11**.

Scheme 2[a]



13 **1** **12**

[a] Reagents and conditions: (*a*) $Et_4N^+AcO^-$, MeCN; (*b*) $Bu_4N^+N_3^-$, $CHCl_3$.

We first subjected **1** to classic solvolysis conditions (refluxing ethanol) and found no trace of reaction, even after several hours. Hence, it quickly became clear that **1** was not going to traverse a reaction pathway involving a unimolecular mechanism, whether substitution or elimination. Reaction with basic nucleophiles, such as methoxide, cyanide, or acetate, led to the anticipated elimination product **12** (Scheme 2). However, it turned out that **1**, like **2**, was rapidly opened by tetrabutylammonium azide in $CHCl_3$ to give bicyclic azide **13** as the sole product. When the reaction was carried out in methanol, a protic solvent, the rate significantly decreased, but the product was the same. The addition of a salt ($LiBF_4$) was found to further reduce the reaction rate.

Thus, the reaction of **1** with azide had the appearance of a bimolecular substitution, despite the fact that the center of attack is a 3° carbon. In order to demonstrate unequivocally that the kinetics were second order, we determined the concentration dependence with respect to the nucleophile. Reactions were conducted in a solution of 0.003 M **1** and 0.2 M $LiBF_4$ in CD_3OD. The role of the lithium salt was to slow the reaction rate so that

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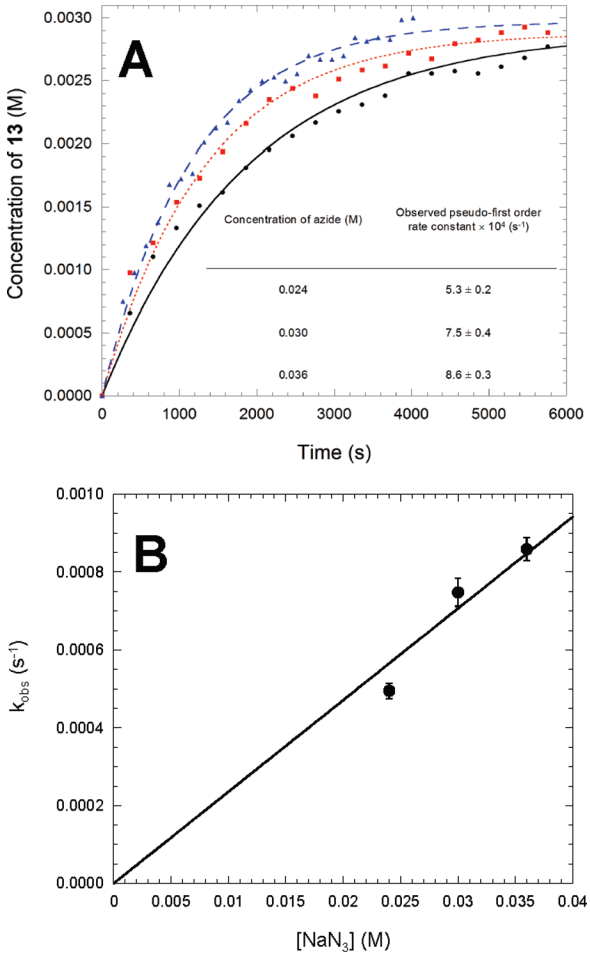

Figure 1. (A) Plot of [**13**] versus time for the reaction of 0.003 M **1** and NaN_3 at three different concentrations (black, 0.024 M; red, 0.030 M; and blue 0.036 M), with observed pseudo-first-order rate constants (inset). (B) Plot of k_{obs} versus NaN_3 concentration.

NMR data could be collected over a reasonable period of time. The appearance of **13** was monitored by ^{1}H NMR at three different concentrations of NaN_3 (0.024, 0.030, and 0.036 M). Figure 1A presents the fits of the NMR integration data to a single exponential equation. These conditions give good pseudo-first-order behavior, as evidenced by the good fit of the kinetic data (NMR integration values for the methyl group vicinal to the azido group in **13**) to the equation. Figure 1B is a plot of the observed pseudo-first-order rate constants vs azide concentration. The results presented in Figure 1B can be interpreted in no other way than describing a second-order reaction mechanism. The slope of the fitted line in Figure 1 provides the value of the second-order rate constant of 0.0235 ± 0.0011 M^{-1} s^{-1} for this reaction.

To provide a context for the above result, we looked to the literature for examples of S_N2 reactions at 3° carbon. Whereas mechanistic ambiguity can be argued under some circumstances at arylated C(sp^3) centers,[3] literature claims for bimolecular reactions at a 3° alkyl carbon have been infrequent. In one of the earliest papers dealing with this subject, Ingold and co-workers concluded that halide exchange at *tert*-butyl centers in acetone was, to a considerable extent, a bimolecular process.[4] This finding was criticized by Winstein and co-workers, who elucidated an elimination−addition pathway for the reaction.[5a] Later, Cook and Parker published a detailed analysis of halide exchange with *tert*-butyl bromide and tetraethylammonium chloride in the presence of tetraethylammonium perchlorate, which provided evidence for ~5% of the reaction occurring by the S_N2 mechanism while the remaining 95% occurred via E2 elimination to isobutene.[5b]

The small fraction of S_N2 at the *tert*-butyl center can be enhanced by replacing the methyl groups with more electron-withdrawing substituents. For example, Miotti and Fava studied the halide exchange reaction of triphenylmethyl chlorides with either two or three rings substituted with a *p*-nitro group, which strongly destabilizes positive charge at the reaction center.[6] This disfavoring of the S_N1 pathway, with its carbocation intermediate, forces the reaction to occur through the S_N2 mechanism. Similarly, tertiary α-bromolactones and α-bromoketones are substituted through the S_N2 pathway.[7] Examples of intramolecular substitution at tertiary centers have also been proposed as concerted, nonsynchronous reactions at the S_N1-S_N2 borderline.[8]

The question arises as to whether it is possible that **1** might exist in equilibrium with a ring-opened, carbocationic intermediate, the formation of which is not rate-determining. This intermediate could undergo reversible reaction with solvent but irreversible, apparent S_N2 reaction with azide. To investigate this possibility, we attempted to model a bicyclic species of general structure **14** using DFT computational methods.[9] However, no minimum energy structure, or stationary point of any description, was located for **14** starting from a range of reasonable initial geometries. In each case, the oxygen and α-carbon simply reunite to give back **1**. It could, however, be argued that this would be a solvent-assisted process and that such an intermediate may not be observable in a continuum solvent model. But the experimental observation is that the substitution reaction is much faster in chloroform than it is in methanol, and if a discrete intermediate like **14** existed, its preferred formation in chloroform is difficult to rationalize. The observed solvent effect and the fact that the reaction is decelerated in the presence of an inert salt ($LiBF_4$)[10,11] speak strongly in favor of the proposed S_N2 mechanism.

1 **14**

In conclusion, we describe the synthesis of 1,4,7-trimethyloxatriquinane **1**, a 3-fold tertiary alkyl oxonium salt.[12] Like its predecessor oxatriquinane **2**, it is impervious to solvolysis by alcohols and yet undergoes facile substitution with the strongly nucleophilic azide anion. Since an S_N1 pathway is excluded, the only reasonable mechanistic interpretation for the reaction between **1** and N_3^- is S_N2, despite the fact that substitution is occurring at a tertiary carbon center. This finding is supported by a study of the reaction kinetics and is consistent with the observed solvent and salt effects. With the exception of unusual cases in which carbocation formation is electronically disfavored, there are no previous examples to our knowledge of substitution reactions at tertiary alkyl centers that proceed exclusively with second-order kinetics. We believe that we report the first such reaction here, and look forward to further probing the chemistry of these remarkable oxonium polycycles.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra and experimental details for the preparation of compounds **1** and **5**−**13**, and complete ref 9a. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) We note that **1** is not the only example of a tertiary oxonium ion. Gargiulo and Tarbell in 1969 described 1,2,2,5-tetramethyltetrahydrofuran, which was stable enough to be isolated. It did, however, show reactivity that would be expected of a 3° oxonium salt, solvolyzing with ethanol by exclusive attack at the 2-position: Gargiulo, R. J.; Tarbell, D. S. *Proc. Natl. Acad. Sci. U.S.A.* **1969**, *62*, 52.

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