Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 931–934
Tetrahedron Letters

Application of electrospray ionization mass spectrometry for studies of anionic σ-adducts of aromatic nitrocompounds

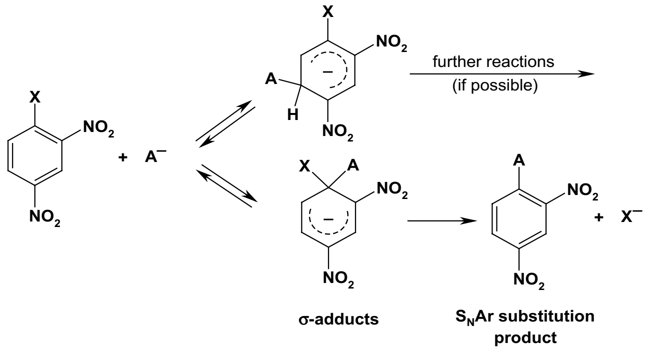
Witold Danikiewicz,* Tomasz Bieńkowski and Krzysztof Wojciechowski

Institute of Organic Chemistry, Polish Academy of Sciences, ul. Kasprzaka 44/52, 01-224 Warszawa, Poland

Received 24 October 2003; revised 12 November 2003; accepted 21 November 2003

Abstract—It has been found that anionic σ-adducts formed in the reactions of highly electrophilic nitroarenes with selected carbanions, alkoxide anions and amines can be transferred to the gas phase using an electrospray ion source and the resulting ions can be studied using various mass spectrometry techniques in the solvent-free environment. This method can also be used for estimating the relative equilibrium constants of the σ-adduct formation reactions in a liquid phase.

Anionic σ-adducts (known also as Meisenheimer or Jackson–Meisenheimer complexes), formed by addition of various nucleophiles to aromatic nitrocompounds, are very important intermediates in aromatic nucleophilic substitution reactions (Scheme 1).[1–3] These adducts are also interesting from a biochemical point of view because their formation is responsible for the biological activity of polynitroarenes.[4] On the other hand, chemical and physicochemical properties of polynitroarenes and related compounds possessing several nitro groups in their structures are the subject of continuous interest because the majority of modern explosives belong to this group of chemicals.[5] Nitrated aromatic compounds can also be found in environmental samples, where they are formed by nitration of aromatic hydrocarbons with nitrogen oxides in the atmosphere.[6,7]



Scheme 1. Formation of anionic σ-adducts of 1,3-dinitrobenzene derivatives with substituent X in position 4. Depending on X, the σ-adduct formed at position 4 can undergo elimination of X^- yielding the S_NAr substitution product.

The properties of anionic σ-adducts, including their structure, rates of formation, and equilibrium constants have been studied using many methods, mainly UV–vis and NMR spectrometry.[1] Mass spectrometry has not been used for these purposes. The only paper published on this subject describes MS properties of the previously synthesized, very stable hydride anion adduct of 2,4,6-trinitrotoluene.[8]

Electrospray ionization (ESI) is a versatile and powerful method for transferring ions from liquid to the gas phase making it possible to study them using various mass spectrometric techniques.[9,10] In our laboratory we tested the applicability of ESI-MS for liquid- and gas-phase studies of anionic σ-adducts. As model aromatic nitro compounds, we selected 1,3-dinitrobenzene (*m*DNB) and 1,3,5-trinitrobenzene (TNB). *m*DNB is known to form relatively stable adducts with reactive nucleophiles such as enolate anions of ketones. TNB is a much stronger electrophile and reacts with almost all types of nucleophiles, including neutral nucleophiles like amines.

All experiments were performed using an API 365 triple quadrupole mass spectrometer (Applied Biosystems) equipped with a TurboIonSpray™ electrospray ion

---

Keywords: Anionic σ-adducts; Aromatic nitro compounds; Carbanions; Electrospray mass spectrometry; Mass spectrometry fragmentation.

* Corresponding author. Tel.: +48-22-632-3221; fax: +48-22-632-6681; e-mail: witold@icho.edu.pl

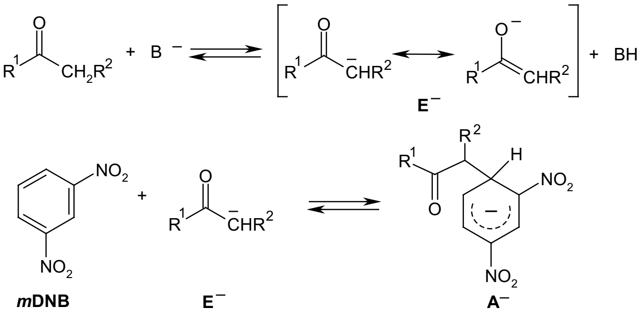
0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.11.094

source. This source was operated in the standard ESI mode, that is without additional drying gas. All reagents and solvents (HPLC grade) were commercially available and were used without further purification.

In the first series of experiments we recorded ESI mass spectra of anionic σ-adducts of the enolate anions of selected ketones with *m*DNB (Scheme 2). The solutions of σ-adducts were prepared by addition of potassium methoxide to the solution of ketone and *m*DNB (approx. 10:1 molar ratio) in THF or acetonitrile (MeCN). After 10 min the deeply colored solution was infused into the ion source using a syringe pump and a series of negative ion spectra were recorded. The representative examples, obtained for acetone, cyclohexanone, and acetophenone are presented in Figure 1.

In all cases the dominant signal in the spectrum corresponds to the respective anionic σ-adduct. Other peaks observed in the spectra were due to the enolate anions and the *m*DNB anion (*m*/*z* 167) or radical anion (*m*/*z* 168). Very similar results were also obtained for some other ketones, such as 2-butanone and cyclopentanone. These results prove that it is possible to transfer anionic σ-adducts from the liquid phase to the gas phase using a standard electrospray ion source.

Gas-phase σ-adducts can be studied using typical mass spectrometry techniques. In Figure 2 we present collision-induced dissociation (CID) spectra of the σ-adducts shown in Figure 1. It is noteworthy that all three adducts show significantly different fragmentation patterns, however some similarities also exist. In all cases the dominating fragment is the enolate anion resulting from the simple reversal of the σ-adduct formation reaction. The second common fragment is the [M − 47] peak resulting from elimination of a HNO_2 molecule, but the intensity of this peak is very low. The other fragments are different. The σ-adduct with acetone (and also with 2-butanone) fragments yielding, in addition to the above mentioned ions, the nitrite anion (NO_2^-, *m*/*z* 46), and the anion of *m*DNB (*m*/*z* 167; Fig. 2a). The nitrite anion is also a product of the fragmentation of the σ-adduct with cyclohexanone (and cyclopentanone) but, instead of the *m*DNB anion, a *m*DNB radical anion peak (*m*/*z* 168) is observed with very high intensity (Fig. 2b). The adduct with acetophenone shows the simplest fragmentation pattern dominated by the enolate anion peak (Fig. 2c).



Scheme 2. Formation of the anionic σ-adduct of *m*DNB with enolate anions of ketones.

In this short communication it is not possible to give full rationalization for the observed differences in the fragmentation patterns, however some results can be explained briefly. For example, comparison of the proton affinities of the enolate anions used in this study (369.6, 366.4, and 361.3 kcal/mol for acetone, cyclohexanone, and acetophenone, respectively) show that the acetophenone anion is the most stable.[11] This explains why the fragmentation of its adduct with *m*DNB requires the lowest energy and results in the formation of this anion as practically the only product. Formation of the radical anion of *m*DNB during fragmentation of the adduct with the cyclohexanone enolate anion can be rationalized by comparison of the electron affinities of the respective enolate radicals.[11] These values (2.06, 1.76, and 1.53 eV for acetophenone, acetone, and cyclohexanone, respectively) show that the cyclohexanone enolate anion can detach an electron most easily, therefore facilitating homolytic C–C bond cleavage between the aromatic ring and cyclohexanone ring carbon atoms in the adduct.

At the present stage of our work, we were able to observe ESI mass spectra of anionic σ-adducts for enolate anions of ketones only. Attempts to observe adducts with less basic and, consequently, less reactive nucleophiles failed, indicating, that the equilibrium constants

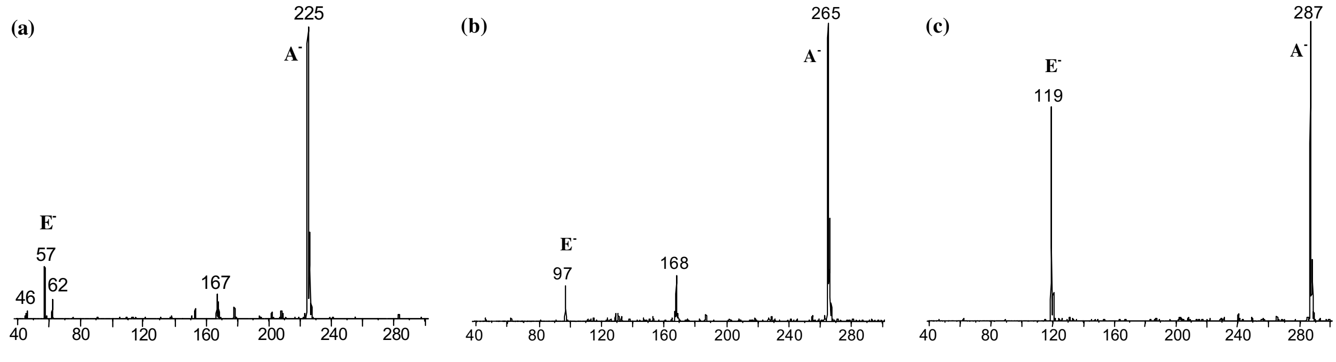


Figure 1. ESI mass spectra of the MeCN solutions of σ-adducts formed in the reactions of *m*DNB with: (a) acetone, (b) cyclohexanone, and (c) acetophenone in the presence of MeOK. Labeled peaks correspond to the following ions: **A**−—σ-adduct, **E**−—enolate anion.

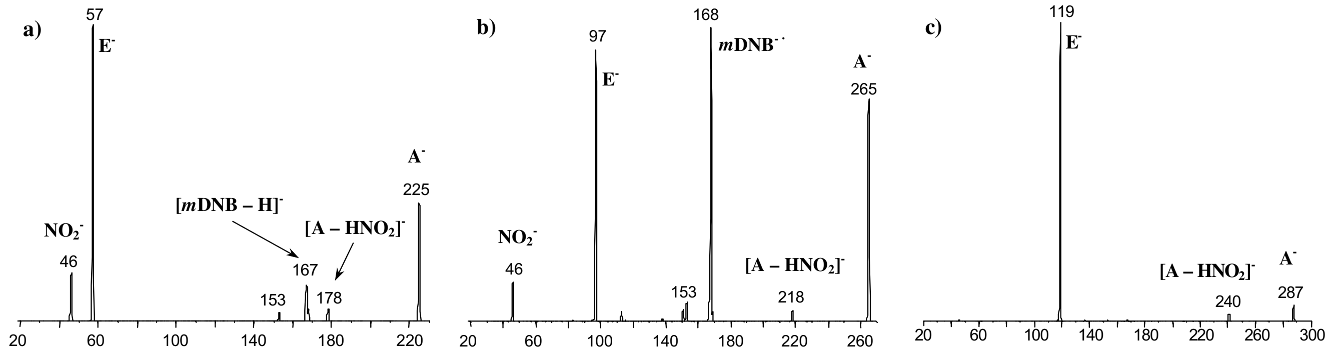
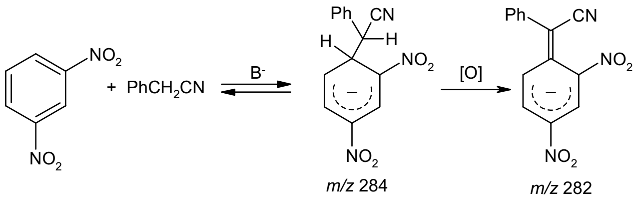


Figure 2. CID spectra of the σ-adduct anions presented in Figure 1: (a) with acetone, (b) with cyclohexanone, and (c) with acetophenone. Labeled peaks correspond to the following ions: $\mathbf{A}^-$—σ-adduct, $\mathbf{E}^-$—enolate anion, [***m*****DNB–H**]$^-$—mDNB anion, ***m*****DNB**$^{\cdot-}$—mDNB radical anion, [**A–HNO**$_2$]$^-$—anion formed by HNO_2 elimination from $\mathbf{A}^-$.

of these reactions were not high enough to provide measurable concentrations of the σ-adducts or that the σ-adduct formed rapidly underwent further transformations. The latter was observed in reactions with phenylacetonitrile and nitromethane in THF solution using MeOK as base, in which intense peaks with m/z values two mass units lower than the expected σ-adducts have been recorded. This observation can be rationalized by the assumption that under the reaction conditions rapid oxidation of the anionic σ-adduct takes place yielding an anion of the hydrogen substitution product:



The oxidation step of these reactions is irreversible, so a measurable concentration of the product can be achieved. Such reactions are often observed for anionic σ-adducts.[1,2] More investigations are required in order to identify the oxidizing agent, which is responsible for this reaction under the conditions used in our experiments.

In the second part of our work, we investigated anionic σ-adducts formed by 1,3,5-trinitrobenzene (TNB) with selected nucleophiles. It was found that almost all the nucleophiles studied—alkoxide anions, enolate anions, and primary and secondary aliphatic amines—form adducts in observable concentrations. Representative examples are shown in Figure 3.

ESI mass spectra recorded for the σ-adducts formed from TNB with the majority of nucleophiles are much more complex than those of mDNB. TNB is a much stronger electrophile and it is also a relatively strong C–H acid ($pK_a = 12.9$ in DMSO).[12] The electrophilic properties of TNB are so strong that even in solution in methanol the σ-adduct formed by CH_3O^- addition (m/z 244) is the most abundant ion as shown in Figure 3a. In this spectrum a peak due to the TNB radical anion (m/z 213) is not observed but its fragmentation product formed by NO loss (m/z 183) is quite abundant. An interesting peak appears at m/z 214. It most likely corresponds to the σ-adduct of the hydride anion of TNB, which, analogously to an adduct of trinitrotoluene,[8] should be quite stable. The source of H^- anions is not yet clear and additional experiments with deuterium-labeled reagents are necessary. It has to be noted that

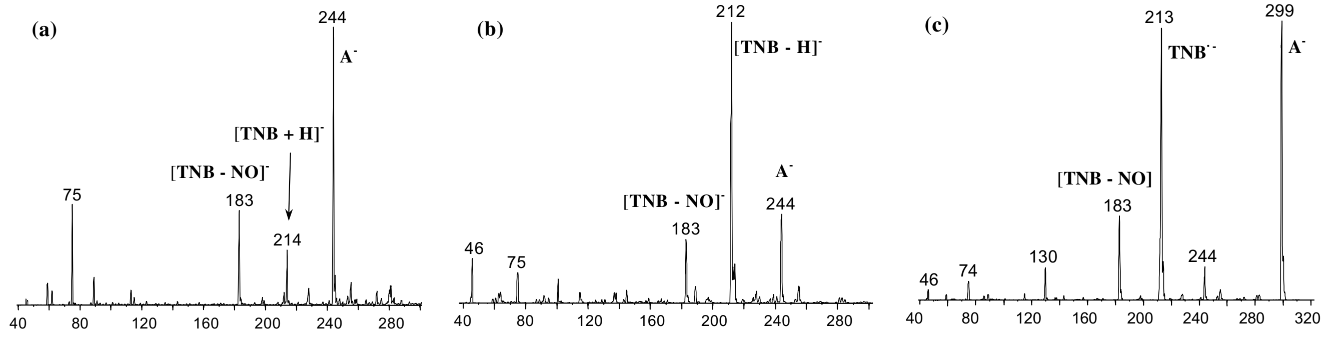
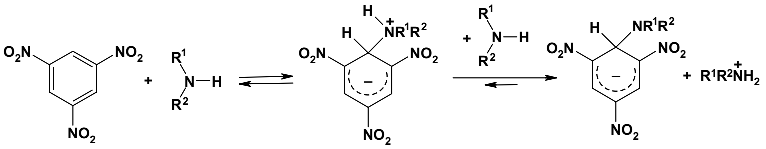


Figure 3. ESI mass spectra of: (a) MeOH solution of TNB, (b) MeOH solution of TNB in the presence of MeOK, (c) MeOH solution of TNB and morpholine. Labeled peaks correspond to the following ions: $\mathbf{A}^-$—σ-adduct, [**TNB–H**]$^-$—TNB anion, [**TNB+H**]$^-$—H^- adduct to TNB, **TNB**$^{\cdot-}$—TNB radical anion, [**TNB–NO**]$^-$—anion formed by NO elimination from the TNB radical anion.



Scheme 3. Two-step formation of anionic σ-adducts in the reaction of TNB with primary and secondary amines.

the reduction reactions are quite common under negative ion electrospray conditions because the negatively charged stainless steel capillary works as a cathode and electrolytic reduction is possible.[13] The elemental compositions of all the ions mentioned above have been confirmed by accurate mass measurements on a high resolution ESI-TOF mass spectrometer (Mariner, Applied Biosystems).

Addition of MeOK to the MeOH solution of TNB causes significant changes in the spectrum (Fig. 3b). The intensity of the peak corresponding to the TNB anion is strongly enhanced and the *m/z* 214 peak practically disappears. Correlation of the first effect with the pH change of the solution is obvious. The second effect most likely reflects the pH-induced changes in the appropriate redox potentials but more investigations are required to confirm this assumption.

Very interesting results were obtained in the reactions of TNB with primary and secondary aliphatic (e.g., CH_3NH_2, $C_2H_5NH_2$, *n*-$C_3H_7NH_2$, and *iso*-$C_3H_7NH_2$) and heterocyclic (pyrrolidine, piperidine, and morpholine) amines carried out in methanol or acetonitrile. In all cases intense peaks corresponding to the σ-adducts formed according to the reaction shown in Scheme 3 are observed.

The representative spectrum recorded for an MeOH solution of TNB with a 10-fold excess of morpholine is presented in Figure 3c. In this case, a peak at *m/z* 213, corresponding to the TNB radical anion is observed instead of at *m/z* 212. The CID spectrum shows that the $TNB^{\cdot -}$ ion is formed as the fragmentation product of the σ-adduct ion (*m/z* 299 in this case). Methanol is not the best solvent for these studies because it competes with the amine in the formation of σ-adduct ions (*m/z* 244). Our experiments show that acetonitrile is the solvent of choice in the case of amino σ-adducts. One of the possible applications of our methodology is the estimation of the relative equilibrium constants of the formation of TNB–amine σ-adducts, which is still a subject of interest.[14]

Our preliminary results presented in this paper show that ESI-MS is a very useful method for studying anionic σ-adducts in solution and in the gas phase. Comparing the two analytical techniques most frequently used in σ-adducts studies, that is UV and NMR spectrometry, electrospray mass spectrometry offers several advantages. Its sensitivity is comparable to that of UV but, in contrast to the latter method, it also gives important information about the molecular masses of ions studies making possible qualitative analysis of the reaction mixtures. On the other hand, NMR spectrometry gives much more structural information about the species studied but its sensitivity is rather low and the results are difficult to interpret in the case of multi-component mixtures. Mass spectrometry also offers the possibility of studying the properties of isolated σ-adducts ions in the gas phase. The results of such studies, when compared with the results obtained in the liquid phase, should give us a better understanding of the solvation effects in the chemistry of σ-adducts.

References and notes

1. Terrier, F. *Nucleophilic Aromatic Displacement: The Influence of the Nitro Group*; VCH: New York, 1991.
2. Artamkina, G. A.; Egorov, M. P.; Beletskaya, I. P. *Chem. Rev.* **1982**, *82*, 427–459.
3. Buncel, E.; Dust, J. M.; Terrier, F. *Chem. Rev.* **1995**, *95*, 2261–2280.
4. Liou, J.-Y.; Huang, T.-M.; Chang, G.-G. *J. Protein Chem.* **2000**, *19*, 615–620.
5. Casetta, B.; Garofolo, F. *Org. Mass Spectrom.* **1994**, *29*, 517–525.
6. Jacob, J.; Karcher, W.; Belliardo, J. J.; Dumler, R.; Boenke, A. *Fresenius' J. Anal. Chem.* **1991**, *340*, 755.
7. Williams, T. T. J.; Perreault, H. *Rapid Commun. Mass Spectrom.* **2000**, *14*, 1474–1481.
8. Yinon, J.; Johnson, J. V.; Bernier, U. R.; Yost, R. A.; Mayfield, H. T.; Mahone, W. C.; Vorbeck, C. *J. Mass Spectrom.* **1995**, *30*, 715–722.
9. *Electrospray Ionization Mass Spectrometry, Fundamentals, Instrumentation, and Applications*; Cole, R. B., Ed.; Wiley: New York, 1997.
10. *Applied Electrospray Mass Spectrometry*; Pramanik, B. N., Ganguly, A. K., Gross, M. L., Eds.; Marcel Dekker: New York, 2002.
11. *NIST Chemistry WebBook* (available at http://webbook.nist.gov/chemistry/).
12. Koppel, I. A.; Koppel, J.; Pihl, V.; Leito, I.; Mishima, M.; Vlasov, V. M.; Yagupolskii, L. M.; Taft, R. W. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1125–1133.
13. Ref. 9, Chapter 2.
14. Crampton, M. R.; Lord, S. D. *J. Chem. Soc., Perkin Trans. 2* **1997**, 369–376.