Tetrahedron 65 (2009) 10945–10949

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Intrinsic barrier for protonation of radical anions

Esther Rozental, Shmaryahu Hoz *

Department of Chemistry, Bar Ilan University, Ramat Gan 52900, Israel

ARTICLE INFO

Article history:
Received 25 June 2009
Received in revised form
30 September 2009
Accepted 22 October 2009
Available online 31 October 2009

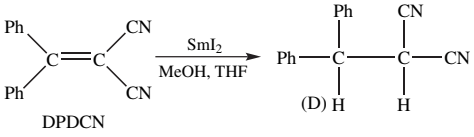
Keywords:
Radical anion
Protonation
Intrinsic barrier
Marcus equation

ABSTRACT

Ab initio calculations on radical anions show that, counterintuitively, protonation on the radicaloid carbon is favored. In the case of radical anions derived from acrylonitrile and acrylaldehyde, protonation on the heteroatom is less favored than protonation on the radicaloid carbon. However, in nitroethylene, the preferred protonation site is on the nitro oxygen in accordance with experimental observation.

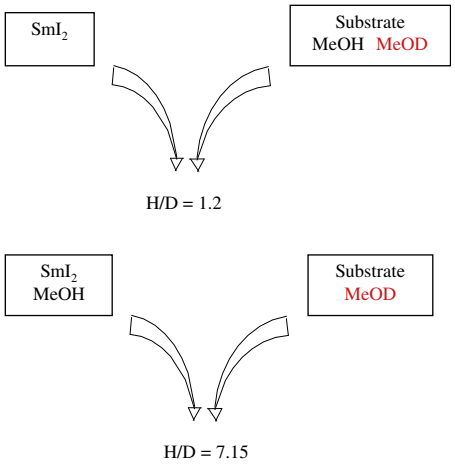
1. Introduction

In our first work on the chemistry of SmI_2, we have studied the reduction of 1.1-diphenyl-2.2-dicyanoethylene (DPDCN—Eq. 1).[1]



(1)

Incorporation isotope effect was one of the mechanistic exploration tools used in of this study. The experiment was conducted in two different manners. In the first one, a THF solution of the substrate containing MeOH and MeOD was reacted with a THF solution of SmI_2. In the second one, MeOH was introduced into the SmI_2 solution while MeOD was added to the substrate solution. The analysis of the *H*/*D* incorporation into the benzylic carbon, performed by NMR, yielded different results for the two modes of mixing as is schematically shown in Scheme 1. In the first mode, the



Scheme 1.

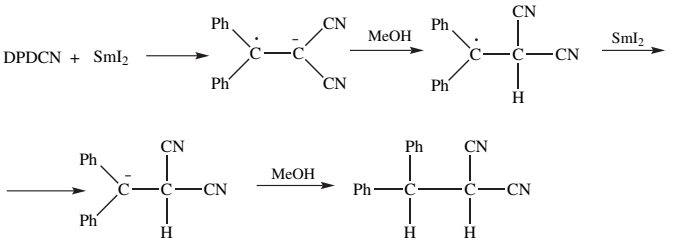
H/*D* ratio was 1.2 whereas in the second it went up to 7.15. This dramatic increase implies that the proton source, MeOH, forms a complex with SmI_2.

If one assumes that the mechanism of reduction is the one shown in Eq. 2, this result is surprising since protonation on the β carbon occurs only after three events have taken place: electron transfer, proton transfer and a second electron transfer.

Throughout the whole course of these steps the identity of the MeOH molecule initially complexed to SmI_2 would have to be

* Corresponding author.
E-mail address: shoz@mail.biu.ac.il (S. Hoz).

0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.10.092

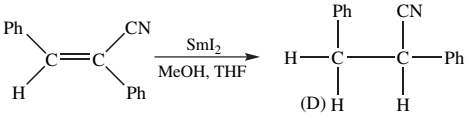


(2)

retained. Thus, in spite of the fact that both ligand exchange and proton exchanges are relatively very fast processes, all three reaction steps described above would have to occur before any significant ligand exchange or *H*/*D* scrambling takes place.

This baffling result forced us to reexamine the experimental observation as well as our basic assumptions. The experimental fact, i.e., the incorporation isotope effect, was tested and confirmed by three generations of graduate students. The assumption that proton exchange rates on heteroatoms are fast is well established.[2] However, the rate of ligand exchange on SmI_2, to the best of our knowledge, has never been determined. Using the stopped flow technique, we have carried our three different experiments relying on the fact that the spectra of SmI_2 in THF, its complexes with MeOH and with HMPA differ significantly from each other. In the first experiment we mixed SmI_2 in THF with MeOH in THF. The replacement of the THF molecules by the MeOH molecules in the coordination sphere of SmI_2 occurred in the dead time of the instrument (0.1 ms) and the spectrum of the MeOH complex appeared immediately. Starting with SmI_2 MeOH complex and displacing this ligand by HMPA and vice versa gave the same result. Namely, ligand exchange on SmI_2 is indeed very rapid.[3]

The last hypothesis to be examined is the mechanism shown in Eq. 2; specifically, the claim that the first protonation occurs at the 'carbanionic' position α to the two cyano groups. The test study was performed[4] on another substrate, 1.2-diphenyl-2-cyanoethylene (Eq. 3).



(3)

The study showed that, counterintuitively, the first protonation occurs on the 'radicaloid' carbon β to the cyano group.[5]

In the present paper we explore computationally the preferred protonation site of various radical anions, the equilibria and the kinetics associated with the process.

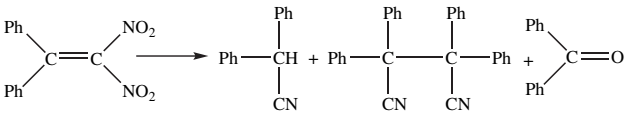
2. Results and discussion

2.1. Methodology

Calculations were performed using the Gaussian 03 suit of programs at the B3LYP/6-31+G* level.[6] Transition states were confirmed by frequency analyses. Archives are given in Supplementary Data Section.

In a previous work we have shown that the protonation site of the radical anion coincides with the thermodynamic stability.[4] Namely, protonation occurs on the site that generate the more stable radical. Therefore, in the first stage we first examined the thermodynamic stability of a series of radicals obtained by protonation of the radical anions. The compounds are acrylonitrile, acrylaldehyde, their nitro analog, and the above three systems with a phenyl ring at the other end of the double bond, balancing the effect of the activating group. To these we have added the theme compound DPDCN and benzophenone. The results are given in Table 1. In addition to the energy of protonation, the spin densities on the relevant atoms are also given in the table. In all three parent compounds, the largest spin density is, in accordance with the VB notation, on C1. This would imply preferred protonation on C2. Yet, protonation on C1 is found to be favored over that on C2 by 9–15 kcal/mol. Addition of a phenyl ring at the other terminus of the double bond resulted in an attenuating or reversal of the effect. For acrylonitrile, the addition of the phenyl ring made C2 the preferred site of protonation by 2.3 kcal/mol. Interestingly, 'doubling' the system (two phenyl rings and two cyano groups as in DPDCN) still results in preference for protonation on C1 by 3.0 kcal/mol. Thus, most likely, in the presence of a large amount of MeOH, protonation by a MeOH molecule coordinated to the SmI_2 occurs at C1, within the ion pair, immediately or concomitant with the electron transfer step and not after three steps as we hypothesized before. This probably unveils the mystery around the incorporation isotope effects mentioned in the introductory section. It should be pointed out that this study is meant to be only indicative and not a fully quantitative one. For the latter, higher level calculations including ZPE and solvent effects should be performed. Thus, in the case of DPDCN it would seem that most of the reaction proceeds via first protonation on C1 and with the high kinetic isotope effect observed.

We turn now to protonation at the terminal atom of the activating group. The thermodynamic data in Table 1 shows that the protonation on the nitrogen atom of acrylonitrile is less favored than protonation on C1 by 23 kcal/mol and that on the oxygen of acrylaldehyde by 10 kcal/mol. It is important to note that protonations on heteroatoms, for even slightly exothermic reactions, may reach the diffusion control limit. Thus, depending on the relative acidity of the proton donor, protonation on these heteroatoms may be faster but, being reversible, the proton will usually end up on C1. The situation is different with nitroethylene. This substrate was included in the study because of our previous finding[7] that in the reduction of the nitroolefin (Eq. 4), the nitro group is reduced first.



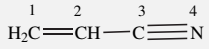
(4)

The data in Table 1 seems to corroborate this fact since the protonation on the nitro oxygen is thermodynamically favored over that on C1 by 2.4 kcal/mol.

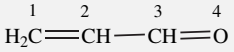
Since we conducted few studies on benzophenones in the past,[8] we also included in the present study the protonation of the radical anion of benzaldehyde as a model. In this case, we have also examined ring protonation at the *para* position. Much to our surprise, protonation at the *para* position and on the oxygen atom are largely favored over protonation at the benzylic carbon.

It should be noted that coupling between SmI_2 and the radical anion may change the spin densities as well as the charge distribution. However, this will not affect the site selectivity because, a) we have shown that product stability dictates the site selectivity, and since the SmI_2 is not paired to the product radical, it will not affect the selectivity; b) If the SmI_2 is not covalently bound to one of the carbon atoms, the rapid thermal motion within the ion pair will equilibrate all the spin—charge distributions at a rate around 10^{-12} to 10^{-13} s^{-1}. Therefore, according to the Curtin Hammett principle, their relative populations will not affect the product distribution.

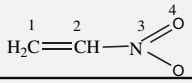
Table 1
Spin densities of the radical anions and the energies of the corresponding radicals



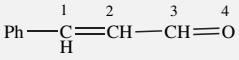
Position	1	2	3	4
Spin density	0.73	0.15	−0.02	0.22
Energy of Protonated radical anion (a.u.)	−171.42426	−171.40245	−171.39615	−171.38837
Relative stability of the radical (kcal/mol)	0	13.69	17.64	22.53



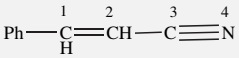
Position	1	2	3	4
Spin density	0.62	−0.01	0.25	0.22
Energy of Protonated radical anion (a.u.)	−192.50696	−192.48347	−192.45654	−192.49047
Relative stability of the radical (kcal/mol)	0	14.74	31.64	10.35



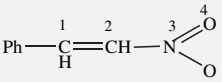
Position	1	2	3	4
Spin density	0.53	−0.13	0.23	0.23
Energy of Protonated radical anion (a.u.)	−283.68483	−283.67085	−283.60141	−283.68868
Relative stability of the radical (kcal/mol)	0	8.77	52.34	−2.42



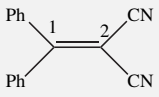
Position	1	2	3	4
Spin density	0.26	0.11	0.14	0.16
Energy of Protonated radical anion (a.u.)	−423.56497	−423.56422	−423.52475	−423.56480
Relative stability of the radical (kcal/mol)	0	0.47	25.24	0.10



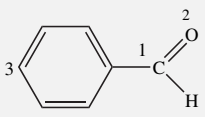
Position	1	2	3	4
Spin density	0.21	0.30	−0.04	0.16
Energy of Protonated radical anion (a.u.)	−402.48138	−402.48498	−402.46601	−402.46479
Relative stability of the radical (kcal/mol)	0	−2.26	9.64	10.41



Position	1	2	3	4
Spin density	0.36	0.01	0.14	0.18
Energy of Protonated radical anion (a.u.)	−514.74248	−514.75353		−514.76044
Relative stability of the radical (kcal/mol)	0	−6.94		−11.27



Position	1	2
Spin density	0.41	0.16
Energy of Protonated radical anion (a.u.)	−725.77786	−725.77304
Relative stability of the radical (kcal/mol)	0	3.03



Position	1	2	3
Spin density	0.48	0.18	−0.02
Energy of Protonated radical anion (a.u.)	−346.12229	−346.14824	−346.14244
Relative stability of the radical (kcal/mol)	0	−16.28	−12.65

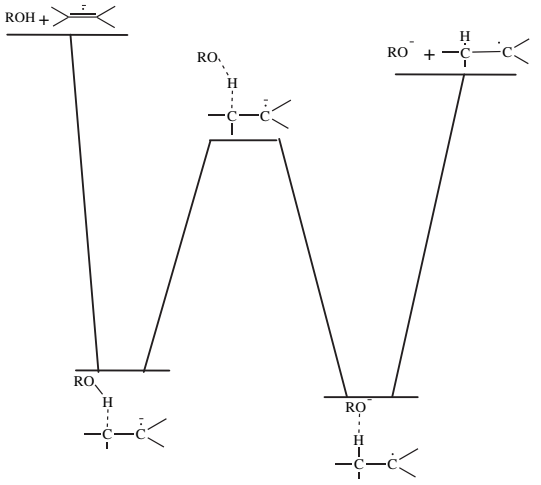


Figure 1. Schematic presentation of the gas phase reaction profile for protonation of radical anion.

We now turn from the thermodynamics to the kinetics and examine protonation rates on the two substrates, acrylonitrile and acrylaldehyde radical anions. Due to the differences in the acidity between the corresponding two radical anions and the acidity differences between the two sites (C1 and C2) within each of them, we chose to use the fictitious alcohol–FCH_2OH, whose acidity was found suitable for the four different protonation sites. A schematic reaction profile is shown in Figure 1.[9]

This scheme is usually drawn for gas phase S_N2 reactions but can be utilized here as well. Upon encounter of a charged species with a neutral one, an ion–dipole complex (IDC) is formed. Usually this is accompanied by a large decrease in energy due to polarization and charge dispersal phenomena. The IDC in our case, in addition to the aforementioned effects, includes also a hydrogen bond between the proton donor and the radical anion. In the present study we were able to locate the IDC where the hydrogen bond is directed specifically either to C1 or to C2 (IDC1 and IDC2). The proton transfer then takes place within the encounter complex to give the IDC of the product. In Figure 1 this is marked with the letter 'p' to distinguish it from the IDC of the reactants, which is marked by 'r'. The last step in this series of events is the dissociation of the IDCp to the products—the protonated radical anion and the conjugated base of the proton donor.

We were able to identify for both radical anions, the ion–dipole complexes with hydrogen bonds to C1 and to C2 as well as the corresponding transition states. The data are given in Table 2.

The data show that there is indeed clear preference for protonation on C1 over C2. The preference is less pronounced for acrylonitrile than for acrylaldehyde.[10] This could be explained on the basis of a selectivity reactivity argument since the radical anion of acrylonitrile is more basic and therefore more reactive than acrylaldehyde. A more refined analysis rests on the Hammond postulate.[11] Since acrylonitrile is expected to be more reactive than acrylaldehyde, the transition state for its protonation will be earlier, sensing to a lesser degree the difference between the stabilities of the radical generated by the protonation. Therefore, the thermodynamic differences will affect more the later transition states in the protonation of acrylaldehyde, resulting in a larger difference between the activation energies for the protonation at the two sites. The position of the transition states along the reaction coordinate is also reflected in the C–H bond lengths at the respective transition states. In acrylonitrile it is 1.474 Å for C1 and 1.348 Å for C2 whereas for acrylaldehyde these are 1.377 Å for C1 and 1.260 Å for C2.

Table 2
Activation energies for protonation on C1 and C2 of acrylonitrile and acrylaldehyde radical anions in kcal/mol

	C1	C2
Acrylonitrile	0.53	4.87
Acrylaldehyde	2.30	15.30

Table 3
Energies associated with the Marcus equation

Position	IDCr[a]	IDCp[a]	TS[a]	Ea[b]	ΔE_0[b]	Ea_{int}[b]
$H_2C{=}CH{-}C{\equiv}N$						
1	−385.84999	−385.86035	−385.84914	0.53	−6.50	2.85
2	−385.84214	−385.83890	−385.83438	4.87	2.03	3.78
$H_2C{=}CH{-}CH{=}O$						
1	−406.94021	−406.94174	−406.93655	2.30	−0.95	2.76
2	−406.93715	−406.91535	−406.91278	15.30	13.68	6.72

[a] In a.u.
[b] In kcal/mol.

An important question is: in the absence of a thermodynamic bias, will our intuition fail us again or will protonation take place at the carbanionic center? The simplest way to approach this issue is by using the Marcus equation[12] (Eq. 5). According to Marcus theory, the barrier height depends on two parameters, the intrinsic barrier (Ea_{int}) and the thermodynamics of the reaction (ΔE_0). The intrinsic barrier is the barrier when the reactants and products are of the same energy. Endothermic reactions will increase the barrier height and exothermic ones will lower it.

$$Ea = Ea_{int} + \Delta E_0/2 + E_0^2/16Ea_{int} \quad (5)$$

For this purpose we had to calculate also the IDCs of the products of the proton transfer steps. The Marcus intrinsic barriers are given in Table 3. It can be seen from the table that even after neutralizing the thermodynamic effect, protonation is preferred on C1 in both systems.

Finally, we would like to raise the basic question: why does the simple intuition fail us regarding the protonation site of radical anions? To answer this question we analyzed the ion–dipole complexes generated with acrylonitrile and FCH_2OH as precursors for protonation at C1 and C2. Table 4 summarizes the spin densities for these complexes.

The data in this table show unequivocally that the slight perturbation induced by having the alcoholic proton ca. 2 Å away from the said carbon atom is sufficient to induce a significant shift in spin density and therefore in the atomic charges. The outcome is that, although there is justification to place the negative charge on C2 (in the acrylonitrile model) as representing the major VB contributing configuration, the charge/spin localization is extremely sensitive to perturbations. Namely, the high degree of mobility of the added electron across the molecule enables a significant change in the coefficients of the SOMO on the various atoms by the

Table 4
IDCr data for acrylonitrile and acrylaldehyde radical anions

	C1	C2	C1	C2
	FCH_2-OH		HO-CH_2F	
	$H_2C^{1}{=}CH^{2}{-}CN$		$H_2C^{1}{=}CH^{2}{-}CN$	
Spin density	0.40	0.38	0.78	0.16
	FCH_2-OH		HO-CH_2F	
	$H_2C^{1}{=}CH^{2}{-}CHO$		$H_2C^{1}{=}CH^{2}{-}CHO$	
Spin density	0.43	0.15	0.68	−0.05

approaching electrophile. This enables the molecule to react with the approaching electrophile at a site different from the one suggested by the unperturbed structure. Thus, due to the high polarizability of the SOMO, factors such as charge and orbital control may be less important in determining the regiospecificity of the reaction. Factors such as product stability and intervention of protonation on the activating group via the Eigen mechanism[13] may determine the site of attack.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.10.092.

References and notes

1. Yacovan, A.; Bilkis, I.; Hoz, S. *J. Am. Chem. Soc.* **1996**, *118*, 261–262.
2. Bell, R. P. *The Proton in Chemistry*, 2nd ed.; Chapman & Hall: London, 1973.
3. Amiel-Levy, M. Ph.D. thesis, Bar Ilan University, 2008.
4. Amiel-Levy, M.; Hoz, S. *J. Am. Chem. Soc.* **2009**, *131*, 8280–8284.
5. Such a protonation was discovered also in frozen matrix and solution: (a) Madhavan, V.; Lichtin, N. N.; Hayon, E. *J. Org. Chem.* **1976**, *41*, 2320–2326; (b) Wojnárovits, L.; Takács, E.; Dajka, K.; D'Angelantonio, M.; Emmi, S. S. *Radiat. Phys. Chem.* **2001**, *60*, 337–343; (c) Madhavan, V.; Lichtin, N. N.; Hayon, E. *J. Am. Chem. Soc.* **1975**, *97*, 2989–2995.
6. Gaussian 03, Revision B.04 Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A.; Gaussian,: Pittsburgh PA, 2003.
7. Yacovan, A.; Hoz, S. *J. Org. Chem.* **1997**, *62*, 771–772.
8. (a) Kleiner, G.; Tarnopolsky, A.; Hoz, S. *Org. Lett.* **2005**, *7*, 4197–4200; (b) Farran, H.; Hoz, S. *Org. Lett.* **2008**, *10*, 865–867; (c) Farran, H.; Hoz, S. *Org. Lett.* **2008**, *10*, 4875–4877.
9. (a) Lieder, C. A.; Brauman, J. I. *J. Am. Chem. Soc.* **1974**, *96*, 4028–4030; (b) Wilbur, J. L.; Brauman, J. I. *J. Am. Chem. Sot.* **1991**, *113*, 9699–9701.
10. At the suggestion of a referee, we calculated the activation energies in THF. For acrylaldehyde using the SCRF procedure the preference for the attack at C2 decreased slightly from 13 to 11.6 kcal/mol and for acrylonitrile it decreased from 4.3 to 4.2 kcal/mol. Because of the similarity of the GS and TS for the 1 and 2 positions, the nearly identical ΔEa in the gas phase and in THF is not unexpected.
11. Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334–338.
12. Marcus, R. A. *Annu. Rev. Phys. Chem.* **1964**, *15*, 155–196.
13. Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1–19.