Detection of Electrophilic Aromatic Substitution by Addition–Elimination using Natural Abundance Deuterium NMR: a Pyrrole Example

Michael De Rosa,*[b] Robert G. Shadle[b] and Natalie Foster[b]

[a] *The Pennsylvania State University, Delaware Country Campus, Department of Chemistry, 25 Yearsley Mill Road, Media, PA 19063, USA*

[b] *Lehigh University, Department of Chemistry, Seeley G. Mudd Building 6, Bethlehem, PA 18015-3172, USA*

Natural abundance ^2H NMR has been used to demonstrate that the reaction of 1-methylpyrrole with *N*-chloroimides occurs by addition–elimination and this method can be applied to other reactions.

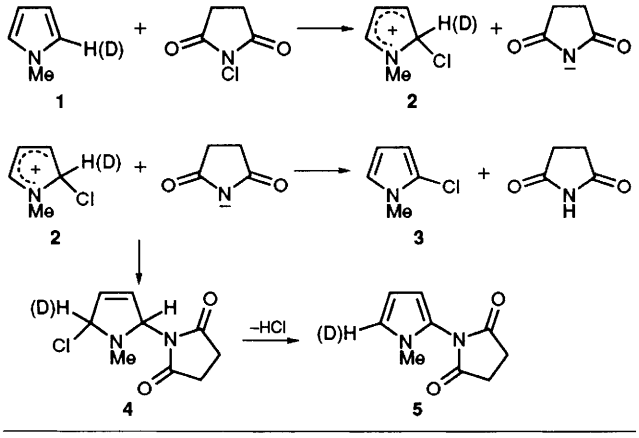
Electrophilic aromatic substitution typically occurs by an S_E2 mechanism in aromatic[1] and heteroaromatic[2] systems. This is not the only pathway and occasionally substitution by addition–elimination[3] (σ-substitution[4]) occurs. It is often difficult in these examples to determine if in fact substitution has occurred by addition–elimination and not another pathway.[5]

Electrophilic aromatic substitution by addition–elimination occurs because the reaction of the initially formed σ-complex with a nucleophile becomes competitive with its deprotonation to form the expected substitution product.[5,6] It can be seen that any factor which further slows down deprotonation will favour substitution by addition–elimination. Therefore, substitution of deuterium for hydrogen should favour the addition–elimination reaction and an isotope effect should be observed. It should be emphasized that in such a system an isotope effect would be observed irrespective of whether deprotonation occurs in the rate-determining step or a fast step. In the latter case it would be an example of a 'hidden' isotope effect,[7] which effects the *product distribution*[8] but not the kinetics.

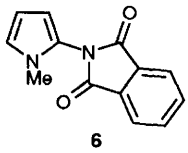
Martin and Martin have observed dramatic differences in the natural deuterium distribution in the same molecule but from different sources.[9] One of the consequences of this discovery has been the use of ^2H NMR to determine primary[10,11] and secondary[11] kinetic isotope effects. In this communication, we illustrate how isotope effects, determined by natural abundance ^2H NMR, can be used to demonstrate if electrophilic aromatic substitution has occurred by addition–elimination.

The reaction of 1-substituted pyrroles with *N*-chloroimides gave a product in which an imidyl group became attached to the pyrrole ring.[12] It was proposed that this reaction occurred by a process of addition–elimination.[12] Scheme 1 illustrates what happens to the naturally occurring deuterium at C-2(5) of the pyrrole ring in the reaction of 1-methylpyrrole **1** with *N*-chlorosuccinimide. In the chlorination process the proton (deuterium) at the position initially attacked by the electrophile is lost. But in the addition–elimination reaction the proton (deuterium) is retained at the position initially attacked by the electrophile. The presence of deuterium at C-2(5) would favour addition–elimination over substitution and the deuterium content at C-2(5) of the product **5** would be expected to be greater than in the starting pyrrole.

Pyrrole **5** was prepared[12] and its ^2H natural abundance NMR spectrum was recorded at room temperature.† The deuterium isotope effect was calculated using eqn. (1)[10,13]



† A 63.2 mg sample was dissolved in 3.00 ml of $CHCl_3$. The natural abundance ^2H NMR was obtained at a frequency of 76.774 MHz on a Bruker AM500 FT-NMR using a 10 mm broad band probe. Typically 4096 transients were collected in 8 K channels with a spectral width of 1000 Hz, 2.05 s acquisition time and a 90° pulse length of 6.0 μs.



6

$$k_H/k_D = \frac{R_{YHn-1}/R_0}{(1 - R_{YHn-1}/R_0)(n-1)} \quad (1)$$

where R_0 = initial deuterium content of reactant; R_{YHn-1} = deuterium content of product; n = number of equivalent hydrogens.

The 1-methyl deuterium resonance was used as the integration standard in both compounds and its integral was set at 3.00 arbitrary units. In 1-methylpyrrole **1** the C-2(5) hydrogens had 3.09 units (R_0)‡ of deuterium and in the product **5** there were 2.32 units (R_{YHn-1}) of deuterium at C-5. Clearly, there was an increase in the deuterium content at C-5 and an isotope effect of 3.0 was obtained using eqn. (1).

The same process was carried out for the addition–elimination product **6** formed from the reaction of **1** and *N*-chlorophthalimide.[12] In this case an isotope effect of 7.0 was observed.§ As noted above any factor that slows deprotonation would favour the addition–elimination process and it is likely that the larger isotope effect observed during the formation of **6** reflects steric hindrance to deprotonation when the bulkier *N*-chlorophthalimide is used. Studies have shown that steric hindrance can lead to the observation of an isotope effect during electrophilic aromatic substitution.[7,14]

The results of this study confirm our original mechanistic suggestion that this reaction occurs by addition-elimination[5] and not by a radical[15] or electron-transfer mechanism.[16]

The ^{2}H NMR method described in this study can be used in suspected addition–elimination reactions in which the hydrogen at the carbon initially attacked by the electrophile is retained in the final product. This occurs in cases such as the pyrrole example above where an unexpected group becomes attached to the ring or when addition–elimination results in an unexpected isomer *e.g. meta* instead of *ortho/para*.[4] Given the simplicity of this procedure it should become the method of choice for determining if electrophilic aromatic substitution has occurred by addition–elimination in these types of reactions.

This work was funded through grant CHEM 9007784 from the National Science Foundation.

Received, 15th June 1993; Com. 3/03457G

‡ The CH_3/C-2(5) natural abundance deuterium ratio at these positions was *ca.* 1 : 1 in the commercial (Aldrich) product.

§ The NMR sample was prepared by dissolving 47.5 mg of **6** in 3.00 ml of $CHCl_3$.

References

1 R. Taylor, *Electrophilic Aromatic Substitution*, Wiley, New York, 1990.
2 A. R. Katritzky, *Handbook of Heterocyclic Chemistry*, Pergamon, Oxford, 1985.
3 P. D. B. de la Mare and R. Bolton, *Electrophilic Additions to Unsaturated Systems*, 2nd. edn., Elsevier, Amsterdam, 1982, pp. 345–353.
4 P. Kovacic and J. A. Levisky, *J. Am. Chem. Soc.*, 1966, **88**, 1000 and references cited therein.
5 M. De Rosa and I. Brillembourg, *J. Chem. Soc., Chem. Commun.*, 1986, 1585.
6 J. A. Joule and G. F. Smith, *Heterocyclic Chemistry*, Van Nostrand Reinhold, London, 1972, pp. 189–190.
7 L. Melander and W. H. Saunders, Jr., *Reaction Rates of Isotopic Molecules*, Wiley, New York, 1980, pp. 162–167.
8 P. C. Myhre, M. Beug and L. L. James, *J. Am. Chem. Soc.*, 1968, **90**, 2105.
9 G. J. Martin and M. L. Martin, *Tetrahedron Lett.*, 1981, **22**, 3525.
10 R. A. Pascal, Jr., M. W. Baum, C. K. Wagner, L. R. Rodgers and D. S. Huang, *J. Am. Chem. Soc.*, 1986, **108**, 6477.
11 B. L. Zhang, *Magn. Reson. Chem.*, 1988, **26**, 955 and references cited therein.
12 M. De Rosa, G. Cabrera Nieto and F. Ferrer Gago, *J. Org. Chem.*, 1989, **54**, 5347.
13 Ref. 7, pp. 91–111.
14 H. Zollinger, *Helv. Chim. Acta*, 1955, **38**, 1623 and references cited therein.
15 P. S. Skell and J. C. Day, *Acc. Chem. Res.*, 1978, **11**, 381.
16 F. Effenberger, *Acc. Chem. Res.*, 1989, **22**, 27.