

## CAN THE INHIBITION OF GRIGNARD REACTION CONSIST IN THE CAPTURE OF FREE RADICALS? THE AM1 CALCULATION OF FUKUI'S REACTIVITY INDICES FOR POTENTIAL RADICAL SCAVENGERS

Ants TUULMETS and Mati KARELSON

Tartu Ülikooli keemiaosakond (Department of Chemistry, University of Tartu), Jakobi 2, EE-2400 Tartu, Eesti (Estonia)

Presented by K. Lääts

Received December 27, 1993; accepted February 2, 1994

**Abstract.** Water and methanol do not inhibit Grignard reaction by the capture of free radicals, but ethers do in the case of radical diffusion into the solution.

**Key words:** Grignard reagent, free radicals, quantum chemical calculations.

Under ordinary conditions, the reaction between metallic magnesium and organic halides does not start immediately but only after some induction period. The duration of the latter may vary considerably owing to the action of different activators and inhibitors [1]. The formation of Grignard reagent proceeds presumably via the formation of free radicals and therefore it is reasonable to assume that the inhibitor may attack these free radicals.

Recently we were able to show that (1) the critical phase of the induction period is the cleansing of magnesium surface from the oxidic film by Grignard reagent formed in the beginning of the reaction, (2) during the induction period the well-known Grignard inhibitors (water, alcohols, etc.) react only with the Grignard reagent steadily entering into solution, and (3) at least in the case of *n*-butyl bromide no free radicals can be detected in the solution during the induction period [2].

The behaviour of classical Grignard inhibitors in the actual presence of free radicals in the solution remains, however, unclear. Therefore we have chosen Fukui's reactivity indices [3] for the quantitative comparison of the reactivity of possible radical scavengers in their interaction with the free radicals. For a radical reaction of some reagent the reactivity index  $S_r$ , as approximated by the frontier MO term only, is defined as follows [3]:

$$S_r = \frac{C_{\text{HOMO}}^2}{\alpha - \varepsilon_{\text{HOMO}}} (-\beta) + \frac{C_{\text{LUMO}}^2}{\varepsilon_{\text{LUMO}} - \alpha} (-\beta),$$

where  $\alpha$  is the ionization potential of the radical,  $C$  and  $\varepsilon$  denote MO coefficients and the orbital energies of the reagent reaction centre, respectively, and  $\beta$  is the value of the resonance integral. For simplicity, we assume  $\beta = -1$  everywhere (cf. [4]).

The MO coefficients of reagent compounds were calculated using the semiempirical AM1 method [5,6]. In order to model the effect of the

condensed medium (solution), the self-consistent reaction field method [7-9] was applied. This method accounts for the solvent polarization effects in the field of the solute molecule. As follows from the discussion below, these effects are not negligible in the calculation of Fukui's coefficients for the compounds of the present study.

The common inhibitors of Grignard reaction are water and methanol. Dimethyl ether, which is experimentally involved as a solvent, was also modelled in the calculations. So, the calculations were carried out for two model media, corresponding to the macroscopic dielectric permittivity of ether ( $D=4.0$ ) and water ( $D=80.0$ ). In the latter case the methanol molecule was treated as nucleophilically solvated by one water molecule. The obtained reactivity indices were also multiplied by the statistical factors equal to the number of the equivalent hydrogen atoms in the molecule in order to obtain scaled relative reactivities of the reagents towards the variation of free radicals (see the Table).

The results of the calculations for methanol in aqueous solution can be taken as a proof of the validity of the theoretical method applied by the present authors. Namely, the results obtained are fully consistent with the experimental fact that in water alcohols interact with the free radicals only through methylenic hydrogen atoms [10, 11]. The same appears to be valid for methanol in ether, and thus water and alcohols should interfere the Grignard reagent formation quite differently, i.e. if the inhibitors act as radical scavengers, aliphatic alcohols should behave as strong inhibitors whereas water should exhibit a weak activity if any at all. However, this is not the case when *n*-butyl bromide reacts with magnesium in diethyl ether because both water and alcohols have a rather similar inhibiting activity [2]. Hence, the calculated reactivity indices also support our conclusion that the inhibition of the Grignard reaction does not consist in the capture of free radicals [2].

The high reactivity index for dimethyl ether suggests that the free radicals should have been trapped by ether if they had entered the solution during the Grignard reagent formation and therefore the process should have been totally suppressed even in the absence of the inhibitors. This makes the idea that all radicals produced in the Grignard reagent formation leave the surface and diffuse freely in solution at all times questionable.\*

It is very likely that only the radicals of low reactivity can flow into solution and, being not scavenged by the solvent, return to the metal surface to give rise to a customary high yield of the Grignard reagent. Indeed, radical attack on solvent is rarely observed in the reactions of common organic halides with magnesium [14, 15]. However, 1-adamantyl radical, the least reactive among the radicals considered above (Table), exhibits a substantial attack to the solvent [15, 16]. Assuming that the reactivity of radicals towards an ether parallels that in the Grignard reagent formation, it follows unavoidably that the transformation of the radicals into the corresponding Grignard reagent and their departure from the surface are competitive processes, the latter leading mainly to products resulting from the solvent attack.

Our results suggest that the Fukui index approach is fruitful for the prediction of radical reactivities and therefore can give further information on the detailed mechanism of the Grignard reaction in solution, e.g. the quantitative data on the possible competition between the Grignard reagent formation process and the reaction with a solvent.

\* For a recent discussion whether the radicals leave the surface of magnesium and flow permanently into solution or not, see [12, 13] and papers cited therein.

Calculated Fukui's reactivity indices for the reaction of various free radicals with water, methanol, and dimethyl ether

Reagents	Reactivity indices <sup>a</sup>				
	Me <sup>c</sup>	Ph <sup>c</sup>	<i>n</i> -Bu <sup>c</sup>	<i>t</i> -Bu <sup>c</sup>	1-Ad <sup>b</sup>
Dimethyl ether <sup>c</sup> (C—H)	0.744	0.552	0.192	0.133	0.121
Methanol <sup>c</sup> (C—H)	0.327	0.255	0.138	0.107	0.094
Methanol <sup>c</sup> (O—H)	0.018	0.019	0.021	0.023	0.025
Water <sup>c</sup> (O—H)	0.042	0.043	0.048	0.052	0.055
Methanol <sup>d</sup> (C—H)	0.441	0.270	0.156	0.115	0.106
Methanol <sup>d</sup> (O—H)	0.014	0.015	0.016	0.018	0.019
Ionization potential of the free radical, eV [ <sup>17</sup> ]	9.84 <sup>e</sup>	9.25	8.02	6.70	6.21

<sup>a</sup> Multiplied by a statistical factor, equal to the number of the equivalent hydrogen atoms.

<sup>b</sup> 1-Adamantyl.

<sup>c</sup> In the ether medium.

<sup>d</sup> In water, reagent nucleophilically solvated by a water molecule.

<sup>e</sup> Our AM1 UHF calculations gave an ionization potential value 9.88 eV.

## REFERENCES

1. Kharash, M. S., Reinmuth, O. Grignard Reactions of Nonmetallic Substances. Prentice-Hall, Inc., New York, 1954.
2. Tuulmets, A., Heinoja, K. Influence of inhibitors on initiation of the Grignard reaction. Nature of induction period. — Organic Reactivity (Tartu), 1990, 27, 27—41.
3. Fukui, K. Theory of Orientation and Stereoselection. Springer, Berlin, 1975.
4. Fleming, I. Frontier Orbitals and Organic Chemical Reactions. J. Wiley & Sons, London, 1976.
5. Dewar, M. J. S., Zoebisch, E. G., Healy, E. F., Stewart, J. J. P. AM1: A new general purpose quantum mechanical molecular model. — J. Am. Chem. Soc., 1985, 107, 3902—3909.
6. Stewart, J. J. P. MOPAC Program Package 3.0. QCPE, 1983, No. 455.
7. Tapia, O., Goscinsky, O. Self-consistent reaction field theory of solvent effects. — Mol. Phys., 1975, 29, 1653—1660.
8. Karelson, M. *Ab initio* self-consistent reaction field calculations I: Method. — Organic Reactivity (Tartu), 1980, 17, 357—364.
9. Karelson, M., Tamm, T., Katritzky, A. R., Cato, S. J., Zerner, M. C. M.O. calculations applicable to condensed phases. The combination of self-consistent reaction field theory with semi-empirical quantum chemical methods. — Tetrahedron Comput. Methodol., 1989, 2, 295—304.
10. De Tar, D. F., Turetzky, M. N. The mechanisms of diazonium salt reactions. The products of the reactions of benzene diazonium salts with methanol. — J. Am. Chem. Soc., 1955, 77, 1745—1752.
11. Packer, J. E., House, D. B., Rasburn, E. J. The radical reactions of arenediazonium ions in aqueous solution. — J. Chem. Soc., 1971B, 1574—1580.
12. Garst, J. F., Ungvary, F., Batlani, R., Lawrence, K. E. Solvent attack in Grignard reagent formation from bromocyclopropane and 1-bromohexane in diethyl ether. — J. Am. Chem. Soc., 1991, 113, 5392—5397.
13. Walborsky, H. M., Zimmerman, C. The surface nature of Grignard reagent formation. Cyclopropyl magnesium. — J. Am. Chem. Soc., 1992, 114, 4996—5000.

14. Bodewitz, H. W. H. J., Blomberg, C., Bickelhaupt, F. The formation of Grignard compounds. — *Tetrahedron*, 1978, **34**, 2523—2527.
15. Molle, G., Bauer, P., Dubois, J. E. Formation of cage-structure organomagnesium compounds. Influence of the degree of adsorption of the transient species at the metal surface. — *J. Org. Chem.*, 1982, **47**, 4120—4127.
16. Юраченко А. Т., Федоренко Т. В., Родионов В. Н. Синтез 1-адамантилмагний-бромиды. — *Ж. орг. хим.*, 1985, **21**, 1673—1677.
17. Lias, S. G., Bartness, J. E., Liebman, J. F., Holmes, J. L., Levin, R. D., Mallard, W. G. Gas-phase ion and neutral thermochemistry. — *J. Phys. Chem. Ref. Data*, 1988, **17**, suppl. 1.

## **KAS GRIGNARD'I REAKTSIOONI INHIBEERIMINE VÕIB SEISNEDA VABADE RADIKAALIDE PÜÜDMISES? FUKUI REAKTSIOONIINDEKSITE ARVUTAMINE AMI-MEETODIL POTENTSIAALSETE RADIKAALIPÜÜDJATE TARVIS**

Ants TUULMETS, Mati KARELSON

Kasutades poolempiirilist AMI-meetodit ning modelleerides keskkonna mõju kooskõlalise reaktsioonivälja meetodiga arvutati võimalike Grignard'i reaktsiooni inhibiitorite Fukui reaktsiooniindeksid mõningate tüüpiliste radikaalide puhul. Tulemused kinnitavad eksperimentaalselt tuvastatud fakti, et vesi ega alkoholid ei inhibeeri Grignard'i reaktsiooni vabade radikaalide püüdmisega, kuid eetrid võivad seda teha juhul, kui radikaalid difundeeruvad lahusesse.

## **ВОЗМОЖНО ЛИ ИНГИБИРОВАНИЕ РЕАКЦИИ ГРИНЬЯРА УЛАВЛИВАНИЕМ СВОБОДНЫХ РАДИКАЛОВ? ВЫЧИСЛЕНИЕ РЕАКЦИОННЫХ ИНДЕКСОВ ФУКУЯ ДЛЯ ПОТЕНЦИАЛЬНЫХ ЛОВУШЕК РАДИКАЛОВ МЕТОДОМ АМ1**

Антс ТУУЛМЕТС, Мати КАРЕЛСОН

С помощью полуэмпирического метода АМ1 и моделированием эффектов среды методом самосогласованного реакционного поля вычислены реакционные индексы Фукуя для потенциальных ингибиторов реакции Гриньяра относительно некоторых типичных радикалов. Результаты подтверждают экспериментально установленные факты, что вода и спирты не ингибируют реакцию Гриньяра улавливанием свободных радикалов, а простые эфиры способны к этому в случае диффузии радикалов в раствор.