ELSEVIER

Journal of Pharmaceutical and Biomedical Analysis
17 (1998) 375–378

JOURNAL OF
PHARMACEUTICAL
AND BIOMEDICAL
ANALYSIS

Determination of relative acidities of some α,ω-bis(3-alkyl(aryl)-4,5-dihydro-1H-1,2,4-triazol-5-on-4-yl) alkanes

Serdar Karaböcek, Ömer Dalman, Sinan Nohut, Mehmet Tüfekçi, Kemal Sancak, Saadettin Güner

Karadeniz Technical University, Department of Chemistry, 61080 Trabzon, Turkey

Received 4 August 1997

Abstract

The solutions of nine α,ω-bis(3-alkyl(aryl)-4,5-dihydro-1H-1,2,4-triazol-5-on-4-yl) alkanes were titrated with tetrabutylammoniumhydroxide (TBAH) in methanol, using potentiometric method. The half neutralization potentials values were found for all cases. Potentiometric titration curves of compounds in methanol with 0.03 M TBAH are similar to those of weak acids obtained in aqueous media with strong bases. Methanol is found to be a suitable medium for the weakly acidic compounds titrated since they are poorly dissolved in other organic solvents. A comparison among the compounds having the same alkyl chains between the two ring systems has shown that basicity increases and acidity decreases as the size of alkyl chains increases. However, the compound with a substituted phenyl group was found to be the most acidic one among the examined compounds indicating that phenyl group donates ring electrons less effectively to the system. This can be attributed to the stability of the benzene ring.

Keywords: Tetrabutylammoniumhydroxide (TBAH); Potentiometric titrations; Acidity

1. Introduction

There have been a number of systematic studies of the basicity and acidity in different media using different techniques [1–13], but unfortunately very few have dealt with substituted triazole–alkanes. It is well known that two major factors influence the basicity or acidity of a molecule [14–17], namely, structural and solvent effects. In most molecules there are two or more structural effects and it is usually very difficult to assess how much each effect contributes to the basicity or acidity of a molecule. Moreover, it is sometimes extremely difficult to differentiate between structural and solvent effects.

The considerable biological importance of triazoles has stimulated much work on this heterocycle [18–22]. Some naturally occurring substances of pharmacological interest have been found to possess a triazole ring in their structure [23–25]. The exact role of this heterocycle in the mode of action as antibiotic or antitumor drugs remains obscure [26].

0731-7085/98/$19.00
PII S0731-7085(97)00210-0

An acceptable representation of the structure of a 1,2,4-triazole must take into consideration its amphoteric nature; the mobility of the imino hydrogen atom; the great stability, aromatic character, and substitution pattern of the nucleus; and the physical evidence that suggests its considerably polar nature. 1,2,4-triazole is readily soluble in polar solvents and only slightly soluble in nonpolar solvents, the solubility in the latter being increased by substitution on the nitrogen atom.

In this paper, we tried to investigate structural and solvent effects of several substituents on the basicity or acidity of the model acid, bis(3-alkyl-(aryl)-4,5-dihydro-1H-1,2,4-triazol-5-on-4-yl)-alkane. The 1,2,4-triazol derivatives was titrated potentiometrically as acids with tetrabutylammonium hydroxide (TBAH) in methanol.

2. Experimental

2.1. Apparatus

2.1.1. Potentiometer and accessory

An Orion (Orion Research) Model 601A digital pH meter equipped with glass and calomel electrodes (Ingold, The Orion 90-20-00 double, junction reference electrode contained) was used throughout this work. The saturated KCl solution of the calomel electrode was removed and the electrode washed several times with anhydrous methanol. After drying, the electrode was then filled with saturated KCl solution in non-aqueous methanol. A pressure of 20 mmHg was applied to the solution in the calomel electrode in order to prevent the diffusion of the solution into the electrode. After each titration the electrode was washed twice with anhydrous methanol to remove impurities from the surface of the electrodes. Pure anhydrous methanol dries easily without leaving any stains. Before using again, electrodes were dipped into pure methanol solvent to remove any traces of impurities. All titrations were performed in a jacketed cell having a nitrogen inlet and an outlet. The cell was connected to a water-circulating thermostat at 25 ± 1°C during the titrations.

In titrations, a microburette having 1.0 ml capacity and 0.01 ml grids was used. The reservoir of microburette was isolated from humidity and carbon dioxide using a tube filled with pelleted solid sodium hydroxide, and the titrations were carried out in a 50-ml beaker wound with copper wire on a magnetic stirrer (IKA-Werke, Staufen, Germany). The copper wire and all other electrical equipments were earthed.

Solutions of the substituted 1,2,4-triazol-5-on derivatives (25 ml, 10^{-3} M) were titrated with the standard solution of 0.03 M TBAH. During the titration, potential values and the volume of titrant added were recorded regularly.

2.2. Chemicals and standard solution

Methanol, pyridine, acetonitrile, benzene, aliphaticestherethoxycarbonylhydrazone, α,ω-diaminoalkane, petroleum ether, chloroform, ethanol, potassium hydroxide and other chemicals used in the study were purchased from Merck (Darmstadt, Germany).

The 0.1 M methanolic solution of TBAH was purchased from Merck and diluted to 0.03 M with methanol. This solution was used after standardization with benzoic acid. This standardized solution was kept in a colored bottle in cold under nitrogen atmosphere.

2.3. Synthesis of 1,2,4-triazol-5-on alkanes

α,ω-bis(3-alkyl(aryl)-4,5-dihydro-1H-1,2,4-triazol-5-on-4-yl) alkanes used in potentiometric titrations were synthesized according to the literature [18]. The formula of the 1,2,4-triazol-5-on derivatives are given in Fig. 1.

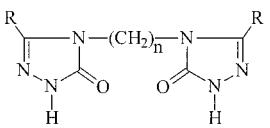
2.4. Stock solutions of 1,2,4-triazol-5-on alkanes

2.5×10^{-4} mol of each substituted 1,2,4-triazol-5-on derivatives was weighed accurately and dissolved in 250 ml methanol. These solutions were kept in a colored bottle in cold under nitrogen atmosphere.

3. Results and discussion

It is well known that N–H proton on 1,2,4-triazol-5-on ring system has weak acidic properties and therefore, these type compounds are dissolved in basic media as NaOH by releasing N–H proton [27]. Weak acidic properties of such triazole derivatives make them very suitable for substitution type reactions [28,29]. Therefore, it is of interest to know their acidic properties of these compounds.

In this study, the solutions of α,ω-bis(3-aryl-4,5-dihydro-1H-1,2,4-triazol-5-on-4-yl)alkanes (I–IX) prepared [18] were titrated with TBAH in methanol, using potentiometric method and a curve for each titration was obtained. All the substituted 1,2,4-triazole alkanes (I–IX) yielded *S* shaped regular titration curves. Curves for compounds I and IX are given in Fig. 2. The half neutralization potentials values for compounds I–IX are tabulated in Table 1. Nine substituted 1,2,4-triazol-5-on alkanes were titrated potentiometrically with TBAH at 25°C. Potentiometric titration curves of compounds in methanol with 0.03 M TBAH are similar to those of weak acids obtained in aqueous media with strong bases. Methanol is found to be a suitable medium for the weakly acidic compound titrated since they



Compound	R	n
I	$-CH_2CH_3$	4
II	CH_3CHCH_3	4
III	$-CH_2CH_2CH_3$	4
IV	$-CH_2CH_3$	6
V	CH_3CHCH_3	6
VI	$-CH_2CH_2CH_3$	6
VII	$-C_6H_5$	6
VIII	$-CH_2CH_3$	8
IX	$-CH_2CH_2CH_3$	8

Fig. 1. The general formula of α,ω-bis(3-aryl-4,5-dihydro-1H-1,2,4-triazol-5-on-4-yl) alkanes

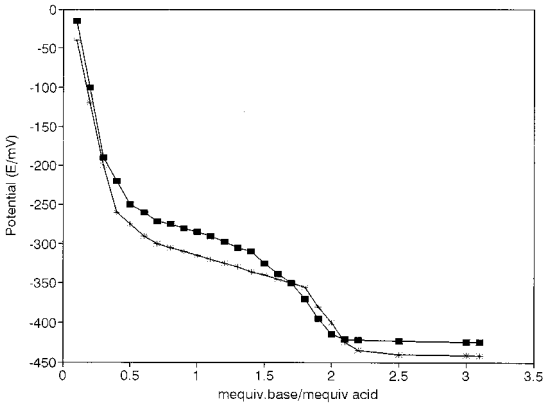


Fig. 2. The potentiometric titration curves for compounds I (■) and IX (✱).

are poorly dissolved in other organic solvents. A clear acidity order due to size of the alkyl chains between the two triazole ring system could not be deduced. However, when Table 1 is examined carefully, the following basicity order for these compounds can be deduced with regard to the size of *R* groups: IX > II > V > VI > IV > III > VIII > I > VII. Therefore, the decrease in acidity which possibly originated from inductive effect or hyperconjugation was observed with regard to increases in size of alkyl chain. A comparison among the compounds having the same alkyl chains between the two ring systems was made,

Table 1
The half neutralization potentials (HNP) obtained from titration curves of the studied α,ω-bis(3-aryl-4,5-dihydro-1H-1,2,4-triazol-5-on-4-yl)alkanes with TBAH in methanol (at 25 ± 1°C)[a]

Compound	HNP (mV)[b]
I	−280
II	−310
III	−286
IV	−290
V	−297
VI	−292
VII	−255
VIII	−285
IX	−315

[a] The cell was connected to a water-circulating thermostat at 25 ± 1°C during the titrations, under nitrogen atmosphere.
[b] Average of five measurements.

and an acidity order of I > III > II was established for $n = 4$, VII > IV > VI > V for $n = 6$, and VIII > IX for $n = 8$ (Table 1). These results clearly show that basicity increases and acidity decreases as the size of alkyl chains increases. However, compound VII having a substituted phenyl group is the most acidic one among the examined compounds indicating that phenyl group donates ring electrons less effectively to the system. This can be attributed to the stability of the benzene ring.

Acknowledgements

This work was supported by the Karadeniz Technical University Research Fund. Authors thank to Dr Esma Kılıç (Ankara Universty, Chemistry Department) for her helpful critics in the preparation of the manuscript.

References

[1] T. Gündüz, N. Gündüz, E. Kılıç, A. Kenar, Analyst 111 (1986) 1103.
[2] T. Gündüz, N. Gündüz, E. Kılıç, A. Kenar, Analyst 111 (1986) 1345.
[3] M.S. Munson, J. Am. Chem Soc. 87 (1965) 2332.
[4] J.S. Fritz, Anal. Chem. Soc. 25 (1953) 407.
[5] J.S. Fritz, C.A. Burgett, Anal. Chem. 44 (1972) 1673.
[6] N.V. Meurs, E.A. Dahmen, Anal. Chim. Acta 21 (1959) 193.
[7] A. Mucci, R. Domain, R.L. Benoit, Can. J. Chem. 58 (1980) 953.
[8] R.L. Benoit, M.J. Mackinon, L. Bergeron, Can. J. Chem. 59 (1981) 1501.
[9] T. Gündüz, N. Gündüz, E. Kılıç, P. Gürkan, Analyst 112 (1987) 1057.
[10] T. Gündüz, N. Gündüz, E. Kılıç, A. Kenar, G. Çetinel, Analyst 111 (1986) 1099.
[11] C.W. Pifer, E.G. Wollish, M. Schmall, Anal. Chem. 25 (1953) 310.
[12] S. Serin, Y. Gök, S. Karaböcek, N. Gültekin, Analyst 119 (1994) 1629.
[13] A. Kenar, T. Gündüz, E. Kılıç, Anal. Chim. Acta 324 (1996) 57.
[14] J.S. Fritz, Acid–Base Titrations in Non-aqueous Solvents, Allynn Bacon, Boston, MA, 1973.
[15] R.W. Taft, Prog. Phys. Org. Chem. 14 (1983) 247.
[16] J. Hine, Structural Effects on Equilibria in Organic Chemistry, Wiley, New York, 1975.
[17] J.W. Boyles, A.F. Taylor, J. Chem. Soc. (1961) 417.
[18] A.A. Ikizler, K. Sancak, Collect. Czech. Chem. Commun. 60 (1995) 903.
[19] J. Heeres, R. Hendrickx, J. van Custem, J. Med. Chem. 26 (1983) 611.
[20] J. Heeres, L.J.J. Backx, J. van Custem, J. Med. Chem. 27 (1984) 894.
[21] K. Richardson, P.J. Whittle, Eur. Pat. Appl. EP 126 (1984) 581.
[22] K. Richardson, P.J. Whittle, Chem. Abstr. 102 (1985) 149271w.
[23] P. Nusbaumer, G. Petranyi, A. Stutz, J. Med. Chem. 34 (1991) 65.
[24] T. Al Nakib, M.J. Meegan, A.M. Looney, M.L. Burke, Eur. J. Med. Chem. 27 (1992) 971.
[25] E. Drouhet, B. Dupont, Arzneim.-Forsch./Drug Res. 42 (1992) 705.
[26] J.M. Kane, B.M. Baron, M.W. Dudley, S.M. Sorensen, M.A. Staeger, F.P. Miller, J. Med. Chem. 33 (1990) 2772.
[27] J. Schmid, H. Gehlen, Z. Chem. 5 (1965) 304.
[28] C. Janiak, T.G. Scharmann, W. Günther, F. Girgsdies, H. Hemling, W. Hindrichs, D. Lentz, Chem. Eur. J. 9 (1995) 637.
[29] D.B. Reitz, M.A. Penick, M.B. Norton, E.J. Reinhard, Bioinorg. Med. Chem. Lett. 4 (1994) 105.