ELSEVIER

Journal of Fluorine Chemistry 90 (1998) 63–66

JOURNAL OF FLUORINE CHEMISTRY

Artificial neural system prediction of aryl fluoride yields in nucleophilic fluorinations

Jingke Zhu *, Dezhao Chen, Fenghua Pan, Youshou Luo

Department of Chemical Engineering, Zhejiang University, Hangzhow 310027, China

Received 11 July 1997; accepted 29 January 1998

Abstract

Multilayered Feed-Forward Networks were employed to model on halogen-exchange fluorination reactions and predict the aryl fluoride product yields.

Keywords: Halogen-exchange fluorination; Aryl fluoride; Neural system

1. Introduction

Fluoronitroaromatics are useful as intermediates in the synthesis of agrochemicals and pharmaceuticals. Among various synthetic methods, the halogen-exchange fluorination technique is one of the most important procedures for the preparation of fluoronitroaromatics. However, the yield of desired aryl fluoride varies greatly with the chloronitroaromatic employed. The combined effect of electronic and steric factors [1], as well as solvent and reaction temperature, made it difficult to predict yields. Artificial Neural Networks (ANN), having characteristic ability to process information, have been developing quickly during the past 20 years. We find it is possible to model the reaction conditions and predict yields by means of ANN.

2. ANN input pattern

To be suitable for ANN computing, the factors that affect halogen-exchange fluorination reaction need to be represented in a numeric way. In our work, a ten-dimensional vector was used as the ANN input signal, and a real number output represented the yield of the desired product. Table 1 lists the 16 compounds used for ANN training and the two for ANN model testing. It shows how to turn reactant and reaction conditions into the input signals.

* Corresponding author.

0022-1139/98/$19.00
PII S0022-1139(98)00158-4

3. Multilayered feed-forward (MLF) network

The ANN employed is a MLF network [2] that consists of 10 nodes in the input layer, 8 in the hidden layer, and 1 in the output layer. The network structure is illustrated by Fig. 1.

Each node in the network contains three functions:

input function $$i_j = \sum_k w_{jk} r_{jk} + \theta_j$$

processing function $$a_j = \frac{1}{1+\exp(-\lambda_j i_j)}$$

output function $$o_j = a_j$$

where r_{jk}, i_j and o_j are inputs, total input and output of node j respectively. The parameters w_{jk}, θ_j and λ_j are weight connecting nodes j and k, threshold and temperature coefficient, respectively. These three kinds of ANN parameters are determined through ANN training [3].

4. Model building

With 16 samples and error back propagation (BP) algorithm [4], the MLF network was trained by updating the network parameters, which were initialized randomly between −1 and 1. Once the average absolute error between the target (yield reported [5]) and network output (yield computed) decreased below 0.005, the network parameters were settled. In this way, models were set up. Table 2 lists both the network outputs computed by one of the MLF net-

Table 1
Compounds and their input patterns (–NO_2 as reference groups)

Pattern no. sample	Substituted $C_6H_5NO_2$[a]	Temperature (°C)	Solvent[b]	Number of NO_2	Position of other NO_2[c]	Number of *o*-Cl	Number of *p*-Cl	Number of *m*-Cl	Pos. of replaced Cl[d]	Number of replaced Cl	Number of Cl adjacent to replaced Cl
1	***2,4***-Cl_2–	170	3	1	0	1	1	0	2	2	0
2	***2***-Cl–	185	2	1	0	1	0	0	0	1	0
3	***4***-Cl,3-NO_2	100	2	2	1	1	1	0	2	1	0
4	***2***,3-Cl_2–	150	1	1	0	1	0	1	0	1	1
5	***4***-Cl–	240	3	1	0	0	1	0	1	1	0
6	***4***-Cl,3-NO_2	100	1	2	1	1	1	0	2	1	0
7	***4***-Cl,3-NO_2	140	4	2	1	1	1	0	2	1	0
8	***2***-Cl–	170	1	1	0	1	0	0	0	1	0
9	***2***-Cl–	230	3	1	0	1	0	0	0	1	0
10	***4***-Cl,3-NO_2	220	0	2	1	1	1	0	2	1	0
11	3,***4***,5-Cl_3–	150	1	1	0	0	1	2	1	1	2
12	***2,4***-Cl_2–	180	2	1	0	1	1	0	2	2	0
13	***2***,3,***4***-Cl_3–	190	2	1	0	1	1	1	2	2	2
14	***4***-Cl,3-NO_2	150	1	2	1	1	1	0	2	1	0
15	***4***-Cl–	190	2	1	0	0	1	0	1	1	0
16	***2,4***-Cl_2,5-NO_2	180	0	2	1	2	2	0	2	2	0
Model test											
17	***2***,5-Cl_2–	190	2	1	0	1	0	1	0	1	0
18	3,***4***-Cl_2–	190	2	1	0	0	1	1	1	1	1

[a]Group replaced by F^- is set in italic and bold type.
[b]0: no solvent; 1: DMF; 2: DMSO; 3: $DMSO_2$; 4: $(CH_2CH_2CN)_2$.
[c]0: no other NO_2; 1: *meta*-NO_2.
[d]0: *ortho*-Cl; 1: *para*-Cl; 2: both 0 and 1.

Table 2
Target and network outputs of the samples

Pattern no.[a]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Target output (%)	69.5	61.0	78.0	53.0	90.0	77.0	81.0	40.0	60.0	68.0	83.0	68.0	23.0	77.0	80.0	87.0
Network output (%)	69.4	60.9	78.4	52.8	89.7	78.1	79.8	39.7	60.4	67.0	83.0	68.1	23.0	77.9	80.5	85.7

[a]Corresponding to that in .
Target output (i.e., yield reported) is based on the complete conversion. Three significant figures are given for the network outputs.

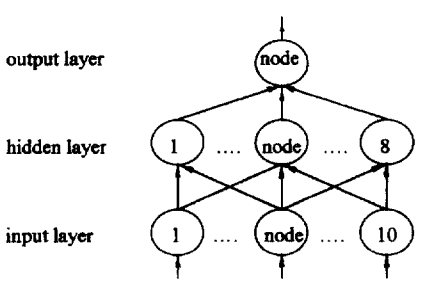

Fig. 1. Network structure.

works (models) and the target outputs for the samples. As can be seen from Table 2, the outputs of the MLF network coincide with the target outputs to a high degree.

5. Predicting method

In principle, the network is ready to make prediction once it is set up. The problem is that the parameters of a trained network are not uniquely determined even if the same average

Table 3
Predictions made by MLF networks with different parameters

Network No.	Training time (min)	Error[a]	Yield predicted (%)	
			17[b]	18[b]
1	6	0.0019	66.7	80.0
2	8	0.0038	42.4	80.4
3	9	0.0034	42.3	36.1
4	15	0.0044	51.8	83.2
5	12	0.0047	58.2	83.0
6	14	0.0049	40.5	83.6
7	10	0.0042	58.2	81.8
8	8	0.0024	56.1	84.5
9	16	0.0046	74.5	83.6
10	14	0.0042	61.1	87.9
11	20	0.0047	67.8	83.2
12	19	0.0049	68.8	85.8
13	14	0.0044	63.1	82.3
14	9	0.0040	53.6	88.0
15	8	0.0038	23.1	48.6
16	10	0.0043	55.3	93.0
17	5	0.0039	56.2	82.5
Mean			55.3 ± 32.2	79.3 ± 43.3
Mean omitting Nos. 3 and 15			58.3 ± 17.8	84.0 ± 9.00
Yield reported [5]			58.0	84.0

[a]Average absolute error of the network output for samples.
[b]Pattern no. corresponding to that in .

Table 4
Experimental results of replacement of aromatic-Cl by –F

Pattern no.	Reactant[a] substituted $C_6H_5NO_2$	Solvent	Reaction time (hr)	Temp. (°C)	Dried KF (equivalent)	Conversion (%)	Yield of fluoro analog (%)	Mean (%)
17	***2***,5-Cl_2–	DMSO	3	190	1.5	98.2	52.1, 48.6	50.3, 1.8
18	3,***4***-Cl_2–	DMSO	1	190	1.5	99.0	75.2, 78.1	76.6, 1.5

[a]Group replaced is set in italic and bold type.

absolute error is reached because network training is a random process. Naturally, the predictions would vary with networks having the same structure but different parameters. It is important to know the variability of the predictions. For this purpose, two halogen-exchange fluorination reactions were modeled by a number of networks trained from different initial parameters. The results are shown in Table 3. We can see that most of the predictions, though distributive, are around 55% for pattern 17 and 79% for pattern 18. It is suggested that the average value be used as the final prediction.

6. Experiment comparison

Two halogen-exchange reactions were carried out. The reaction conditions and results are shown in Table 4.

Comparing the results with those predicted in Table 3, we can see that the experimental results are 9% lower for pattern 17 and 3% for 18. These facts suggest that the predictions made by the MLF networks are in reasonable accord with the experiment.

7. Discussion

If some of the networks in Table 3 are omitted on a statistical base (i.e., more than a required number of standard deviation for 17 results), e.g., 3 and 15, then the average yield increases to 58.3% and 84.0% which is the 'yield reported' column. In this way, the prediction quality would be improved.

8. Conclusion

By using a set of discrete and continuous numeric data as inputs that contain information on reactant structure and other reaction conditions, the trained MLF networks (models) can model halogen-exchange fluorination reactions and predict yields with ease and quickness.

References

[1] J.H. Clark, D.K. Smith, Tetrahedron Lett. 26 (1985) 223.
[2] J.W. Barry, Chemometr. Intell. Lab. Syst. 18 (1993) 115.
[3] C. Yaqiu, C. Dezhao, Proceedings of the Second Asian Control Conference, Seoul, Vol. 3, 22-25 July 1997, pp. 819–822.
[4] D.E. Rumelhart, G.E. Hinton, R.J. Williams, in: D.E. Rumelhart, J.L. McClelland (Eds.), Parallel Distributed Processing: Explorations in Microstructures of Cognition, Vol. 1: Foundations, MIT Press, Cambridge, MA, 1986, pp. 318–362.
[5] L. Fu, Technical advance on preparation of aryl fluorides—fluorination with metal fluorides, Youji Fu Gongye 3 (1992) 7 (The summary with 10 refs. covers the factors that affect fluorination reactions and the applications of the fluorination).