rickson, D. N. *Inorg. Chem.* **1980**, *19*, 1170.
18. Lauffer, R. B.; Heistand, R. H.; Que, L. Jr. *Inorg. Chem.* **1983**, *22*, 50.
19. Lloret, F.; Julve, M.; Mollar, M.; Castro, I.; Latorre, J.; Faus, J.; Solans, X.; Morgenstern-Badaran, I. *J. Chem. Soc., Dalton Trans.* **1989**, 729.
20. Masaki, Y.; Koji, A.; Shinsaku, S. *J. Chem. Soc. Perkin Trans.*. **1990**, *1*, 2687.
21. Araki, K.; Kuboki, T.; Otohata, M.; Kishimoto, N.; Yamada, M.; Shiraishi, S. *J. Chem. Soc., Dalton Trans.* **1993**, *21*, 3647.
22. Ashmawy, F. M.; Issa, R. M.; Amer, S. A.; McAuliffe, C. A.; Parish, R. V. *J. Chem. Soc., Dalton Trans.* **1986**, 421.
23. McAuliffe, C. A.; Parish, R. V.; Ashmawy, F. M.; Issa, R. M.; Amer, S. A. *J. Chem. Soc., Dalton Trans.* **1987**, 2009.
24. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon Press: Oxford, U. K., 1988.
25. Boucher, L. J. *Inorg. Chem.* **1976**, *15*, 1334.
26. Dilworth, J. R.; McAuliffe, C. A.; Sayle, B. J. *J. Chem. Soc., Dalton Trans.* **1977**, 849.
27. Ueno, K.; Martell, A. E. *J. Phys. Chem.* **1956**, *60*, 1270.
28. Nakamoto, K.; Martell, A. E. *J. Chem. Phys.* **1960**, *32*, 588.
29. Coleman, W. M.; Boggess, R. K.; Hughes, J. W.; Taylor, L. T. *Inorg. Chem.* **1971**, *10*, 2195.
30. Sacconi, L.; Bertini, I. *J. Am. Chem. Soc.* **1966**, *88*, 5180.
31. Sarama, B. D.; Ray, K. R.; Sievers, R. E.; Bailar, J. *J. Am. Chem. Soc.* **1964**, *86*, 14.
32. Coleman, W. M.; Goehring, R. R.; Taylor. L. T.; Mason, J. G.; Boggess, R. K. *J. Am. Chem. Soc.* **1979**, *101*, 2311.
33. Bard, A. J.; Faulkner, L. R. *Electrochemical Methodes*; John Wiley & Sons: New York, 1980.

Hydrodediazoniation of Arenediazonium Tetrafluoroborate with Triethylamine

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Received October 20, 1995

Hydrodediazoniation product (**3a-d**) was found to be the major product in the reaction of arenediazonium tetrafluoroborate (**1a-d**) with triethylamine (**2**) in methanol under nitrogen at room temperature. A quantitative study on the title reaction was investigated in detail and two remarks were noteworthy. One was the linear increase in the yield of **3a-d** by increasing the molar concentration of **2** until equimolar concentration was reached between **1a-d** and **2**. The other was the suppression of the formation of **3a-d** in the presence of oxygen. Based on these results, the title reaction was better understood by 1 : 1 electron transfer reaction between reactants (**1a-d** and **2**) rather than by radical chain mechanism proposed in the reaction of arenediazonium tetrafluoroborate and triphenylphosphine.

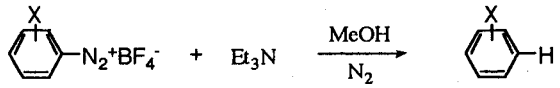
Introduction

Hydrodediazoniation of arenediazonium salt is chiefly achieved by using various inorganic and organic reductants[1] such as hypophosphorous acid,[2] hot ethanol,[2,3] triphenylphosphine,[4] *N,N*-dimethylformamide,[5,6] *N*-benzylpiperidine,[7] and ferrocene[8] etc.. In spite of many dediazoniation methods, there are problems in each method. For instances, a substrate bearing electron-donating substituent in the para position, such as methoxy and methyl as in *p*-anisidine and *p*-toluidine does not give the expected arene but tarry materials.[5] On the other hand, some inorganic reductants are not effective in organic solvent.[8] Herein, we report that triethylamine, a common and cheap compound, is an efficient reductant in reaction with arenediazonium tetrafluoroborate under nitrogen atmosphere to give corresponding arene. To the best of our knowledge, this quantitative study on the reaction of arenediazonium tetrafluoroborate with triethylamine is a first report[9] though derivatives of piperidine and pyrrolidine are documented in the literature.[7]

Experimental

Synthesis of Diazonium Tetrafluoroborates. Nine substrates (**1a-d**) were prepared according to the known procedure.[10] The diazonium salt was dried overnight in a vacuum dessiccator. IR spectrum showed the complete removal of water in the starting diazonium salt which was used directly for the reaction.

Quantitative Determination of Reaction Products (Standard Procedure). For the nine subtrates employed in this work, similar procedure was followed for the determination of the reaction products. The typical procedure in the case of m-nitrobenzenediazonium tetrafluoroborate ($\mathbf{1a_m}$) is as follows; In a two-necked round bottomed flask was introduced a solution of methanol (10 mL) containing tridecane (20 mM) as an internal standard. To this solution was added $\mathbf{1a_m}$ (1 mmol) and nitrogen was passed through the solution for 10 min. After then appropriate amount of triethylamine (0.5-1.5 eq) in methanol (3 mL) kept in addition funnel was run in dropwise. Immediately reaction took place



1a-d **2** **3a-d**

1 and 3

a : $\mathbf{a}_o$; X = o-NO_2 $\mathbf{a}_m$; X = m-NO_2 $\mathbf{a}_p$; X = p-NO_2
b : X = H **c** : $\mathbf{c}_m$;X = m-Me $\mathbf{c}_p$; X = p-Me
d : $\mathbf{d}_o$; X = o-OMe $\mathbf{d}_m$; X = m-OMe $\mathbf{d}_p$; X = p-OMe

Scheme 1.

Table 1. Reaction of $\mathbf{1a}_o$ with Triethylamine **2**.[a]

Atmosphere	**2** : $\mathbf{1a}_o$[b]	Product	Yield (%)[c]
N_2	0.5	**3a**	65
N_2	0.7	**3a**	78
N_2	0.9	**3a**	84
N_2	1.0	**3a**	83
N_2	1.5	**3a**	85
O_2	1.0	**3a**	52

[a]In methanol at ambient temperature (~15 ℃) and tridecane as an internal standard. [b]Molar ratio of **2** to $\mathbf{1a}_o$. [c]GC yield.

Table 2. Reaction of $\mathbf{1a}_m$ with Triethylamine **2**.[a]

Atmosphere	**2** : $\mathbf{1a}_m$	[b]Product	Yield (%)[c]
N_2	0.5	**3a**	23
N_2	0.7	**3a**	58
N_2	0.9	**3a**	66[d]
N_2	1.0	**3a**	72
N_2	1.5	**3a**	75
O_2	1.0	**3a**	33

[a]In methanol at ambient temperature (~15 ℃) and tridecane as an internal standard. [b]Molar ratio of **2** to $\mathbf{1a}_m$. [c]GC yield. [d]Small amount of 3,3′-dinitrobiphenyl was formed.

by evolution of nitrogen. After stirring for 30 min, the reaction mixture was analyzed by gas chromatograph (GC) and a gas chromatograph-mass spectrometer (GC/MS). When the substrate was either **1b** or **1c,d**, nonane or decane were used as an internal standard respectively.

Results and Discussion

Treatment of diazonium tetrafluoroborates (**1a-d**) in methanol with triethylamine at room temperature gave a corresponding arene (**3a-d**), hydrodediazoniation product, as a major compound (Scheme 1).

The results from the reaction of $\mathbf{1a}_o$, $\mathbf{1a}_m$, and $\mathbf{1a}_p$ with triethylamine are shown in Table 1-3 respectively.

From the results in Table 1-3, two remarks are noteworthy. One is the dependency of the yield% on the amount of triethylamine until **2/1a** reaches 1. This indicates that

Table 3. Reaction of $\mathbf{1a}_p$ with Triethylamine **2** in methanol.[a]

Atmosphere	**2** : $\mathbf{1a}_p$[b]	Product	Yield (%)[c]
N_2	0.3	**3a**	41
N_2	0.5	**3a**	58
N_2	0.7	**3a**	68
N_2	0.8	**3a**	74
N_2	0.9	**3a**	88
N_2	1.0	**3a**	85
N_2	1.5	**3a**	87
O_2	0.9	**3a**	23

[a]In methanol at ambient temperature (~15 ℃) and tridecane as an internal standard. [b]Molar ratio of **2** to $\mathbf{1a}_p$. [c]GC yield.

Table 4. Reaction of **1b** with Triethylamine **2**.[a]

Atmosphere	**2** : **1**[b]	Product	Yield (%)[c]
N_2	0.5	**3b**	35[d]
N_2	1.0	**3b**	74[e]
O_2	1.0	**3b**	7

[a]In methanol at ambient temperature (~15 ℃) and nonane as an internal standard. [b]Molar ratio of **2** to **1b**. [c]GC yield. [d]Major product was anisole. [e]Anisole was a minor product.

Table 5. Reaction of $\mathbf{1c}_m$ with Triethylamine **2**.[a]

Atmosphere	**2** : **1**[b]	Product	Yield (%)[c]
N_2	0.5	**3c**	15[d]
N_2	1.0	**3c**	49[d]
N_2	1.5	**3c**	58[d]
O_2	1.0	**3c**	5

[a]In methanol at ambient temperature (~15 ℃) and decane as an internal standard. [b]Molar ratio of **2** to $\mathbf{1c}_m$. [c]GC yield. [d]Unidentified product was formed.

the reaction of substrate and the triethylamine might be a 1 : 1 reaction. The other is inhibition of the reaction by oxygen. Based on these observations one might conceive triethylamine as an electron-transfer agent. Then nitrophenyl radical would be formed as an intermediate. Support for the intermediacy of nitrophenyl radical was observed in our reaction. *i.e.* 3,3′-dinitrobiphenyl was obtained from the reaction of $\mathbf{1a}_m$ with **2** (Table 2). When there was no other substituent in the benzene ring such as in **1b** (Table 4), similar results were obtained as was in the case of **1a**, except the much increased inhibition of the reaction in the presence of oxygen.

One particular thing in the reaction of **1b** with triethylamine (Table 4) was the formation of anisole as a major product when the value of **2/1b** was 0.5. However when the amount of triethylamine was increased, the formation of anisole was suppressed to a negligible amount.

In order to see the substituent effect in the hydrodediazoniation of arenediazonium tetrafluoroborate with triethylamine, arenediazonium salts bearing weakly electron donating methyl group were employed. Thus the results obtained

Table 6. Reaction of **1c**$_p$ with Triethylamine **2**.[a]

Atmosphere	**2** : **1c**$_p$[b]	Product	Yield (%)[c]
N_2	0.5	**3c**	43
N_2	1.0	**3c**	79
O_2	1.0	**3c**	11

[a]In methanol at ambient temperature (~15 ℃) and decane as an internal standard. [b]Molar ratio of **2** to **1c**$_p$. [c]GC yield.

Table 7. Reaction of **1d**$_o$ with Triethylamine **2**.[a]

Atmosphere	**2** : **1d**$_o$[b]	Product	Yield (%)[c]
N_2	0.5	**3d**	49
N_2	1.0	**3d**	84
O_2	1.0	**3d**	18

[a]In methanol at ambient temperature (~15 ℃) and decane as an internal standard. [b]Molar ratio of **2** to **1d**$_o$. [c]GC yield.

Table 8. Reaction of **1d**$_m$ with Triethylamine **2**.[a]

Atmosphere	**2** : **1d**$_m$[b]	Product	Yield (%)[c]
N_2	0.5	**3d**	10[d]
N_2	1.0	**3d**	49[e]
O_2	1.0	**3d**	6

[a]In methanol at ambient temperature (~15 ℃) and decane as an internal standard. [b]Molar ratio of **2** to **1d**$_m$. [c]GC yield. [d]Unidentified product was a major. [e]Small amount of 3,3'-dimethoxybiphenyl was also obtained.

Table 9. Reaction of **1d**$_p$ with Triethylamine **2**.[a]

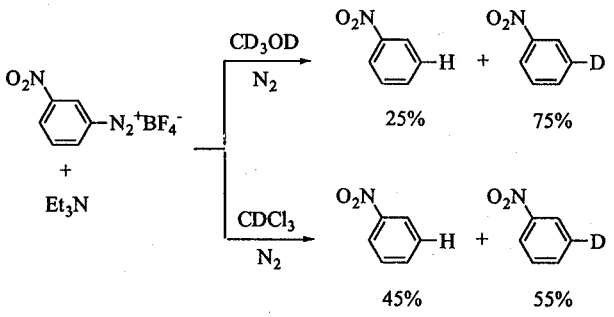
Atmosphere	**2** : **1d**$_p$[b]	Product	Yield (%)[c]
N_2	0.5	**3d**	52
N_2	1.0	**3d**	87
O_2	1.0	**3d**	20

[a]In methanol at ambient temperature (~15 ℃) and decane as an internal standard. [b]Molar ratio of **2** to **1d**$_p$. [c]GC yield.

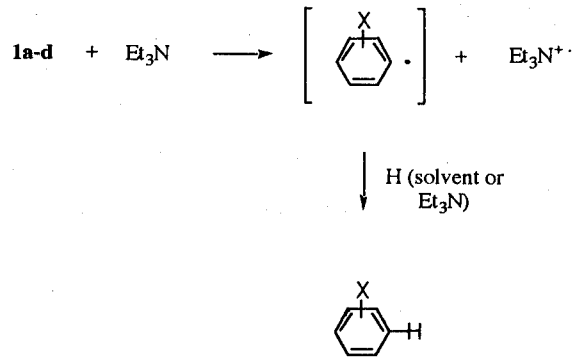
using *m*-methylbenzenediazonium tetrafluoroborate (**1c**$_m$, Table 5), and *p*-methylbenzenediazonium tetrafluoroborate (**1c**$_p$, Table 6) are shown in Table 5 and 6.

As can be seen in Table 5 and 6, the dediazoniation of *m*-methylbenzenediazonium tetrafluoroborate (**1c**$_m$, Table 5), and *p*-methylbenzenediazonium tetrafluoroborate (**1c**$_p$, Table 6) were similar to those of previous subtrates such as **1a** and **1b**. One thing to note was the relatively low yield% of **1c**$_m$ compared with **1c**$_p$ (Table 6). At present it is not clear why a substrate having substituent in the meta position give lower yield than that having subtituent in the ortho or para position. The similar observation was obtained for other substrates having meta sustituent such as in the case of **1a**$_m$ (Table 2) and **1d**$_m$ (Table 8).

Substrates **1d** bearing strongly electron-donating methoxy substituent also gave hydrodediazoniation product readily by



Scheme 2.



Scheme 3.

triethylamine (Table 7-9).

Again dediazoniation of **1d**$_m$ with triethylamine gave 3,3'-dimethoxybiphenyl, a intermolecularly coupled product (Table 8) similarly as **1a**$_m$ (Table 2).

In order to have more knowledge about the hydrogen source of the product, arene, the control experiments were carried out in deuterated solvents such as methanol-d_4 (99.95%) and chloroform-d (99.8%). The results are shown in Scheme 2, where 3-deuterionitrobenzene and undeuterated nitrobenzene was obtained in 75% and 25% respectively.

As can be seen in Scheme 2, one might conceive that appreciable amount of undeuterated nitrobenzene must come from other compound considering the high deuterium% of methanol-d_4. A strong candidate for the source of hydrogen might be triethylamine. This assumption was confirmed again with the use of chloroform-d (Scheme 2) which gave deuterated nitrobenzene and undeuterated nitobenzene in 55% and 45% respectively. The much increased relative proportion of undeuterated nitrobenzene (45%) in chloroform-d compared to that obtained in methanol-d_4 might be understood in terms of the different bond strength of C-D in the two reagents.

Overally we believe that the first step of the reaction of Scheme 1 would be an electron-transfer from the triethylamine to the substrate, producing cation radical of triethylamine and aryl radical which would then abstract hydrogen from either triethylamine or solvent to make arene, a hydrodediazoniation product (Scheme 3).

In conclusion, hydrodediazoniation of arenediazonium tetrafluoroborate by triethylamine proceeded quite efficiently in mild conditions. Our results demonstrated that the use of triethylamine in hydrodediazoniation of arenediazonium tetrafluoroborate can be used as a general synthetic method.

Acknowledgment. Financial support from OCRC sponsored by the KOSEF (1995) and the Basic Science Research Program, Ministry of Education (1995) is gratefully acknowledged.

References

1. Galli, C. *Chem. Rev.* **1988**, *88*, 765-792.
2. Kornblum, N. *Org. React.* **1957**, *2*, 262-340.
3. Blatt, A. H. *Organic Syntheses Coll. Vol. II* **1950**, 592-594.
4. Yasui, S.; Fujii, M.; Kawano, C.; Nishimura, Y.; Shioji, K.; Ohno, A. *J. Chem. Soc. Perkin Trans. 2* **1994**, 177-183.
5. Threadgill, M. D.; Gledhill, A. P. *J. Chem. Soc. Perkin Trans. 1* **1986**, 873-876.
6. Wassmundt, F. W.; Kiesman, W. F. *J. Org. Chem.* **1995**, *60*, 1713-1719.
7. Meerwein, H.; Allendoerfer, H.; Beekmann, P.; Kunert, Fr.; Morschel, H.; Pawellek, F.; Wunderlich, Kl. *Angew. Chem.* **1958**, *70*, 211-215.
8. Wassmundt, F. W.; Kiesman, W. F. *J. Org. Chem.* **1995**, *60*, 196-201.
9. Following paper describes the use of triethylamine with arenediazonium chloride in aqueous solution. And they report very low yield usually less than 20% for the formation of hydrodediazoniation product. Horner, L.; Stoehr, H. *Chem. Ber.* **1953**, *86*, 1066-1071.
10. Roe, A. *Org. React.* **1952**, *5*, 193-223.

Pharmacophore Modeling of Angiotensin-II from Study of Its Nonpeptidic Antagonists

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Received October 25, 1995

Early attempts to identify plausible conformations of a linear octapeptide hormone, angiotensin-II (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe), using various theoretical and experimental methods, have led to various conformational models. So far, no consensus has been made about the solution phase structure and the receptor binding structure of angiotensin-II. The ultimate goal for the conformation study of the peptide hormone is to develop a new potent drug. Therefore, we have devised a strategy for designing the pharmacophore by studying thermodynamically possible conformations of various kinds of angiotensin-II antagonists and angiotensin-II.

Introduction

Human angiotensin-II (A-II), a linear octapeptide hormone of sequence Asp-Arg-Val-Tyr-Ile-His-Pro-Phe, is a major active component of the renin-angiotensin system (RAS)[1] which plays a central role in the regulation of blood pressure. It is generally believed that the biological activity of a hormone is closely related to its three dimensional (3D) conformation.

The conformation of A-II has been studied with a variety of methods.[2~14] On the basis of these studies, various conformational models of A-II in aqueous solution have been proposed. These are α-helix,[2] random coil,[3] β-turn,[4] γ-turn,[4] cross β-structure,[5] S-shape,[6] and more complex models.[7~9] However, no consensus has been reached yet about the 3D conformation of A-II in aqueous solution. These various models suggest that it is unlikely that only one or a few conformations are present in solution for such a relatively small linear peptide. Thus, it is believed that the conformation of A-II is in rapid thermodynamic equilibrium in aqueous solution, and there exist a large number of conformational states.[9,15]

The purpose of the conformational study of A-II may be to develop a new potent drug which can be used as an inhibitor of A-II. The structure of a potential drug is related with the 3D conformation of A-II at the receptor binding site which is, unfortunately, not available. Alternatively, the conformation study on A-II analogues that are biologically active and are more rigid than A-II may give useful information for the development of the potent drug because these analogues should share some common 3D structural features with A-II.

There have been various kinds of well known A-II antagonists, e.g., saralasin ([Sar[1], Ala[8]]A-II)[12] and DUP-753 (brand-name losartan).[16] In this study, the conformation of A-II and its peptide analogues are investigated by molecular dynamics (MD) method, and the conformation of rather rigid organic antagonists are studied by a conventional conformation search method. From the results, we propose that A-II and its antagonists share common 3D structural features which would be important in the binding mode of A-II to the receptor.