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The Selective Functionalization of Saturated Hydrocarbons. Part 46.[1] An Investigation of Udenfriend's System under Gif Conditions.

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Abstract: Under Gif conditions using ascorbic acid as reductant and oxygen as oxidant in pyridine, the selectivity for secondary hydrogen functionalization is exceptional. EDTA (ethylenediamine-tetra-acetic acid) is *not* needed as a ligand for iron.

Introduction.

Gif chemistry requires the presence of a suitable carboxylic acid, for example picolinic acid, and a suitable pyridine base.[2] Most of the pyridine that we have used in the past can be replaced by the inert acetonitrile.[3] The recent recognition of two different manifolds in Gif-type oxidation has clarified many observations.[4]

In 1954,[5] Udenfriend proposed that a system based on Fe^{II} and EDTA in the presence of ascorbic acid and oxygen would serve for the biomimitic hydroxylation of organic substrates. Later work by Hamilton[6] concluded that oxygen, and not hydrogen peroxide, was the oxidant and that hydroxyl radicals were not involved. However, the yields in these heterogeneous oxidations of cyclohexane were small. Quite recently, a further study of the Udenfriend system concluded that hydroxyl radicals were indeed involved.[7]

The Udenfriend investigations[5] showed that maximal hydroxylation was attained with an Fe^{II} to ascorbic acid ratio of 1 to 9.5 and an Fe^{II} to ethylenediamine-tetra-acetic acid (EDTA) ratio of 1 to 5.3 at pH 5.5 in water. There was no reaction in the absence of Fe^{II} or ascorbic acid.

Since pyridine has such a remarkable effect in Gif chemistry, we decided to examine the Udenfriend system in this solvent. A further advantage is that saturated hydrocarbons are readily soluble and thus, this modification gives homogeneous solutions.

In initial experiments summarized in Table 1, we were surprised to find that the presence, or absence, of EDTA had no effect on the yields of cyclohexanone and cyclohexanol. The same conclusion was reached (Table 2) when H_2O_2 under argon was used as the oxidant. Here the oxidation products were minimal, but the presence of cyclohexyl radicals, as expected in the Fe^{II}-Fe^{IV} manifold,[4] was evident from the coupling to pyridine. Since EDTA had no effect on the yield or speed of the reaction, it was not used in the subsequent investigations.

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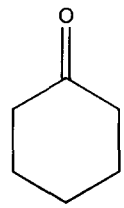
Table 1.

EDTA	1	2	Fe^{II}
0	0.60	0.06	21%
0.25	0.67	0.08	8.5%
2.5	0.63	0.09	21%

$FeCl_2\,4H_2O$ (0.5mmol), Ascorbic Acid (4.5mmol) and cyclohexane (20mmol) were dissolved in Pyridine (27mL). Then EDTA (x mmol) in solution in 3mL of water was added. The reaction mixture was cooled down to 0°C before bubbling oxygen through the solution. All data in mmol.



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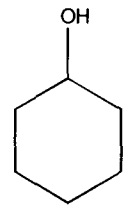

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Table 2.

EDTA	1	2	Dicyclohexyl	Pyridine Coupling	Fe^{II}
0	0.06	0.04	0.02	0.44	84
0.25	0.11	0.06	0.02	0.46	58
0.5	0.11	0.09	0.03	0.40	63.2
1	0.08	0.05	0.03	0.39	62
2	0.09	0.04	0.03	0.44	57.5

$FeCl_2\,4H_2O$ (0.5mmol), Ascorbic Acid (4.5mmol) and cyclohexane (20mmol) were dissolved in Pyridine (27mL). Then EDTA (x mmol) in solution in 3mL of water was added. The reaction mixture was cooled down to 0°C before bubbling argon through the solution during 20min. H_2O_2 (4mmol) was added under an argon stream. All data in mmol.

As expected (Table 3) in the absence of Fe^{II}, there was no oxidation. The addition of only 0.1mmol of $Fe^{II}Cl_2\,4H_2O$ gave significant oxidation which was not increased by increasing the Fe^{II} concentration fivefold or even tenfold.

Table 3.

Fe^{II}	1	2	Fe^{II}
0	0	0	0
0.1	0.69	0.1	0
0.5	0.57	0.06	15.5%
1	0.6	0.05	20%

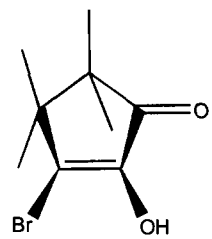
Conditions as in Table 1 except for variation in Fe^{II}.

We also examined iso-ascorbic acid, which is one third of the price of ascorbic acid. The results are given in Table 4 along with data for two analogues **3** and **4**. Ascorbic acid and its isomer gave the same results, but the bromo-compound **3** was inactive and **4** showed only slight activity. We attribute this steric hindrance to complex formation.

Table 4.

	1	2	Fe^{II}
Ascorbic Acid	0.20	0.00	21%
Iso-ascorbic Acid	0.20	0.00	20%
3	0.00	0.00	76%
4	0.03	0.02	41.4%

$FeCl_2\,4H_2O$ (0.25mmol), Analogues (1mmol), cyclohexane (20mmol) in solution in pyridine (13.5mL). 1.5mL of water are added. Stirring under oxygen from 0°C to RT.



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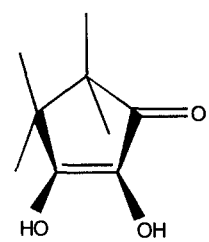

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The amount of oxidation was proportional to the amount of ascorbic acid added (Table 5). Since ascorbic acid is a good trap for radicals, especially hydroxyl radicals, it seemed unlikely that the mechanism of oxidation could be radical based. Indeed, we found no evidence of chloride formation on addition of excess chloride ion. In the Fe^{II}-Fe^{IV} manifold, chloride formation[4] is often seen from the reaction of a carbon radical with Fe^{III}-Cl. Trapping by pyridine and by Tempo were also not observed.

Table 5.

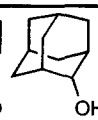
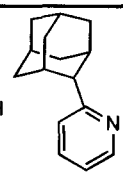
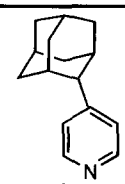
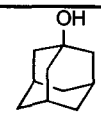
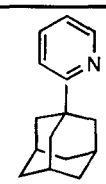
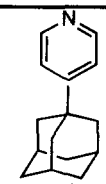
Ascorbic Acid	1	2	Ascorbic Acid/Ketone	Fe^{II}
0	0	0		0%
0.5	0.08	0	6.37	74.8%
1	0.145	0	6.89	66.4%
2	0.31	0.02	6.49	31.3%
4.5	0.67	0.09	6.71	21%

$FeCl_2\,4H_2O$ (0.5mmol), Ascorbic Acid (x mmol) and cyclohexane (20mmol) were dissolved in Pyridine (27mL). Then 3mL of water were added. The reaction mixture was cooled down to 0°C before bubbling oxygen through the solution.

Adamantane reactivity was studied next (Table 6) using the customary reaction conditions.[8] The usual normalized selectivity for adamantane (secondary/tertiary products) for Gif Chemistry is 0.3, whilst radical

chemistry, in our hands, is about 0.1. The observed value of about 0.7 shows that the Udenfriend system in pyridine is exceptionally selective. The lack of coupling of the secondary position to pyridine (not radicals) is normal, but the absence of the tertiary alcohol **7** has not been observed before. Of course, the selectivity will be a reflection of the ligands bonded to the iron. Clearly ascorbic acid binds in such a way as to imitate picolinic acid. The increased selectivity with adamantane could be explained by the ligand reducing any radicals by hydrogen atom transfer before they could escape from the influence of the bound ascorbic acid.

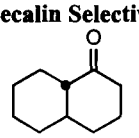
Table 6--Selectivity C_2/C_3.

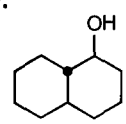
Conditions	 **5**	 **6**	 **8**	 **9**	 **7**	 **10**	 **11**	C_2/C_3 normalized
Fe^{II} Asc. Acid (4.5mmol) O_2	0.21	0.025	0.00	0.00	0.00	0.06	0.04	**0.75**
Fe^{II} Asc. Acid (10mmol) O_2	0.35	0.04	0.00	0.00	0.00	0.11	0.075	**0.68**

Fe^{II} Asc. Acid O_2: Adamantane (5mmol), $FeCl_2$ $4H_2O$ (0.5mmol), Ascorbic Acid (x mmol), Pyridine 27mL, H_2O (3mL) under oxygen.

The selectivity for *trans*- and *cis*-decalin oxidation gave normalized values for C^2/C^3 of about 2. This is in agreement with values recently communicated to us by Prof. Ulf Schuchardt (Campinas, Brazil)[9] and is more selective than the data that we had reported earlier.[10]

Table 7--Decalin Selectivity.


12-*trans*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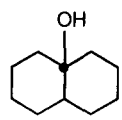
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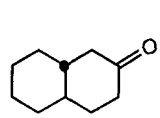
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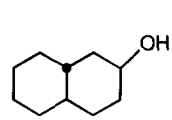
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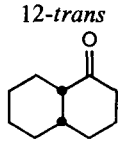
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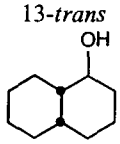
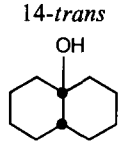
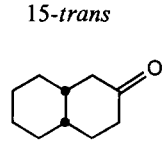
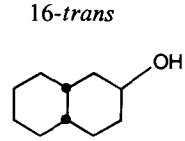

13-*cis*


14-*cis*


15-*cis*


16-*cis*

	12-trans	12-cis	13-trans	13-cis	15-trans	15-cis	16-trans	16-cis	14-trans	14-cis	C_2/C_3 normalized
A	0.19	0.00	0.00	0.01	0.23	0.00	0.01	0.00	0.04	0.01	2.2
B	0.41	0.00	0.03	0.01	0.51	0.00	0.03	0.00	0.10	0.03	1.8
C	0.09	0.29	0.00	0.01	0.00	0.39	0.03	0.07	0.04	0.05	2.6

Decalin (20mmol) $FeCl_2$ $4H_2O$ (0.5mmol), Ascorbic Acid (x mmol), Pyridine (27mL), H_2O (3mL) under oxygen. **A**: *trans*-decalin (20mmol), Ascorbic Acid (4.5mmol). **B**: *trans*-decalin (20mmol), Ascorbic Acid (10mmol). **C**: *cis*-decalin (20mmol), Ascorbic Acid (10mmol).

The Kinetic Isotope Effect for cyclohexanone formation using this new system was 2.03, but the value for alcohol formation was only 1.09. The conditions were $FeCl_2$ $4H_2O$ (0.5mmol), ascorbic acid (4.5mmol) and cyclohexane (20mmol) in pyridine (27mL) and water (3mL). After cooling to 0° oxygen was bubbled through the solution for 30 minutes.

In the systems where superoxide and Fe^{II} react to furnish Fe^{III}-OOH which then evolves into Gif Chemistry, the addition of triphenylphosphine does not affect the total oxidation, but it does change dramatically the ketone to alcohol ratio.[11] This is because the hydroperoxide intermediate is reduced by the triphenylphosphine to give alcohol.

When triphenylphosphine was added to the Fe^{II}-acsorbic acid system with bubbling of oxygen, the results (summarized in Table 8) were the maintenance of the total oxidation, but a marked decrease in the ratio of ketone to alcohol from 19 to 2. Thus, the hydroperoxide must be an intermediate.

Table 8--Influence of Triphenylphosphine.

PPh_3	1	2	1 + 2	Ketone/Alcohol
0	0.70	0.04	0.74	18.75
2	0.55	0.15	0.70	3.66
4	0.50	0.26	0.76	1.92

$FeCl_2$ $4H_2O$ (0.5mmol), Ascorbic Acid (4.5mmol) and cyclohexane (20mmol) were dissolved in pyridine. At 0° oxygen was bubbled for 30mins.

The similarity between this new system and the earlier Zn^0-Fe^{II} catalyzed procedure (Gif^{IV}) is striking. The ascorbic acid system is even more selective for the secondary positions in a saturated hydrocarbon. Clearly the ascorbic acid is not only a reducing agent to reduce Fe^{III} to Fe^{II}, but also a ligand for the Fe^{II} which can replace the picolinic acid normally effective in Gif Chemistry. Ascorbic acid could be a bridging ligand between two Fe^{II} species. In this case, the mechanism would be as previously adumbrated.[4] In conclusion, there is no evidence for hydroxyl radical participation in this chemistry.

Experimental.

For General Experimental see Barton and Launay.[12] All experiments were run for 30 minutes by which time all the ascorbic acid had been oxidized and further oxidation did not take place.

Acknowledgements.

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