

PROJECT ADMINISTRATION DATA SHEET

ORIGINAL REVISION NO. _____

Project No./(Center No.) G-33-666 R6345-OA0 GTRC/GIT ~~XXXX~~ DATE 7 / 23 / 87

Project Director: Dr. Laren M. Tolbert School/Dept ~~XXXX~~ Chemistry

Sponsor: DHHS/PHS/NIH/National Cancer Institute

Agreement No.: Research Grant No. 1 R01 CA 43806-01A1

Award Period: From 7/1/87 To 6/30/88 (Performance) 9/30/88 Reports

Sponsor Amount: New With This Change Total to Date

Contract Value: \$ _____ \$ 134,610

Funded: \$ _____ \$ 134,610

Cost Sharing No./(Center No.) G-33-328/F6345-OA0 Cost Sharing: \$ 0

Title: Bio-Oxidation of Arylalkyl Hydrocarbons

ADMINISTRATIVE DATA

OCA Contact E. Faith Gleason

1) Sponsor Technical Contact:
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2) Sponsor Issuing Office:
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Grants Management Specialist
National Cancer Institute
National Institutes of Health
Bethesda, MD 20892

Military Security Classification: N/A
(or) Company/Industrial Proprietary: N/A

ONR Resident Rep. is ACO: Yes No
Defense Priority Rating: N/A

RESTRICTIONS

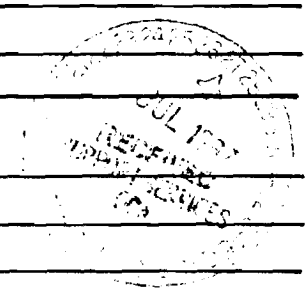
See Attached _____ Supplemental Information Sheet for Additional Requirements.

Travel: Foreign travel must have prior approval — Contact OCA in each case. Domestic travel requires sponsor approval where total will exceed greater of \$500 or 125% of approved proposal budget category.

Equipment: Title vests with GIT

COMMENTS:

First year of 3-year continuing grant.



COPIES TO: _____ SPONSOR'S I.D. NO. 02.108.001.87.008

Project Director
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Procurement/GTRI Supply Services
Research Security Services
Contract Support Div.(OCA)(2) F H.

GTRC
Library
Project File

PAT H.

SPONSORED PROJECT TERMINATION/CLOSEOUT SHEET

Date 7/6/88

Project No. G-33-666 School/Lab Chemistry

Includes Subproject No.(s) N/A

Project Director(s) L. M. Tolbert GTRC/~~GRI~~

Sponsor DHHS/PHS/NIH/National Cancer Institute

Title Bio-Oxidation of Arylalkyl Hydrocarbons

Effective Completion Date: 6/30/88 (Performance) 9/30/88 (Reports)

Grant/Contract Closeout Actions Remaining:

- None
- Final Invoice or Copy of Last Invoice Serving as Final
- Release and Assignment
- Final Report of Inventions and/or Subcontract:
Patent and Subcontract Questionnaire sent to Project Director
- Govt. Property Inventory & Related Certificate
- Classified Material Certificate
- Other _____

Continues Project No. _____ Continued by Project No. G-33-614

COPIES TO:

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G-33-666

SECTION IV PROGRESS REPORT SUMMARY		GRANT NUMBER CA43806-02	
PRINCIPAL INVESTIGATOR OR PROGRAM DIRECTOR L. M. Tolbert		PERIOD COVERED BY THIS REPORT	
APPLICANT ORGANIZATION Georgia Tech Research Corporation		FROM July 1, 1988	THROUGH June 30, 1989
TITLE OF PROJECT (Repeat title shown in item 1 on first page) Bio-oxidation of Arylalkyl Hydrocarbons			

(SEE INSTRUCTIONS)

1. Proposed Research. Minor changes in the scope of the originally proposed research are planned. In part, this reflects the increasingly apparent relationship between our ongoing studies in radical-cation deprotonations and recent data on radical-cation-mediated epoxidation by P450 mimics (Bruice et al, J. Amer. Chem. Soc., 1988, 110, 158). Thus we will add to our studies experiments with these P450 mimics, specifically, tetraphenylporphyrinatoiron(III) oxide. We will use the solvent dependence of the epoxidation/deprotonation to model oxygenase activity for olefins in the same way we have successfully modelled solvation/deprotonation activity in the anthracene series. This addition is well within the scope of our project, inasmuch as epoxidation of dimethylbenzanthracene is presumably the key feature in hydrocarbon activation and carcinogenesis. Also, to our list of mononuclear oxidation substrates for solvent studies, we will add p-cymene and p-ethyltoluene, as well as 1-ethyl-4-methylnaphthalene. These systems will yield complementary information on stereoelectronic effects to that obtained in the anthracene series.

2. Progress. Our novel observations on the dramatic solvent and stereoelectronic effects on deprotonation of 9,10-dialkylanthracenes have been reported (J. Amer. Chem. Soc., 1987, 109, 3477). In addition, we have recently completed DNA intercalation studies with dimethyl-, diethyl-, and ethylmethylantracene which indicate that the ethyl group has an insignificant effect on the binding constant. Thus the disparity between the ethyl- and methyl-substituted anthracene aromatics in carcinogenic behavior can be safely ascribed to the stereo-electronically controlled differential metabolism outlined in our Communication. Moreover, the binding constants we obtained allow us to conclude that the intercalation is unsymmetrical with respect to the anthracene nucleus.

Deuterium kinetic isotope studies have been completed and yield a primary kinetic isotope effect of ca. 1.8-2.0, depending upon substrate. This is in line with our prediction that primary isotope effects would be small for radical-cation deprotonations and is consistent with other enzymatic values with radical-cation intermediates. Thus other models based upon hydrogen atom abstraction are inappropriate.

Electrochemical studies on all anthracene derivatives are nearing completion. These studies indicate that radical-cation disappearance rates are structure independent, and indicate that the primary mechanism for radical-cation decay is nucleophilic attack. Thus despite a kinetic isotope effect of ca. 2.0 for product formation, disappearance of bis(trideuteromethyl)anthracene shows no isotope effect. In contrast, these rates are first order in water concentration. Again, this is consistent with our hypothesis.

SECTION IV PROGRESS REPORT SUMMARY(cont'd)		GRANT NUMBER CA43806-02	
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(SEE INSTRUCTIONS
(cont'd))

The syntheses of several cyanonaphthols have been completed. These show enhanced proton transfer efficiencies in nonaqueous solvents and will allow us to directly measure rates of proton transfer by fluorometric means. We will correlate these rates with rates of product formation in the electrochemical experiments.

5. Publications.

1. L. M. Tolbert and R. K. Khanna, "Dramatic Solvent and Stereoelectronic Effects a Biomimetic Oxidation: 9,10-Dialkylanthracenes. J. Amer. Chem. Soc., 1988, 109, 3477.
2. L. M. Tolbert, R. K. Khanna, and L. A. Bottomley, "Solvent and Isotope Effects on Radical Cation Deprotonations: 9,10-Dimethylanthracene", J. Amer. Chem. Soc., to be submitted.
3. L. M. Tolbert, R. K. Khanna, and L. Gelbaum, "Effect of Structure on DNA Intercalation of 9,10-Dialkylanthracene. The Ethyl Effect", J. Amer. Chem. Soc., to be submitted.