

Accelerated Oxygen-Dependent Stability: A Case Study with Chlorpromazine

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Introduction

- An oxygen- and moisture-modified Arrhenius equation has been proposed to model oxidative degradant growth.

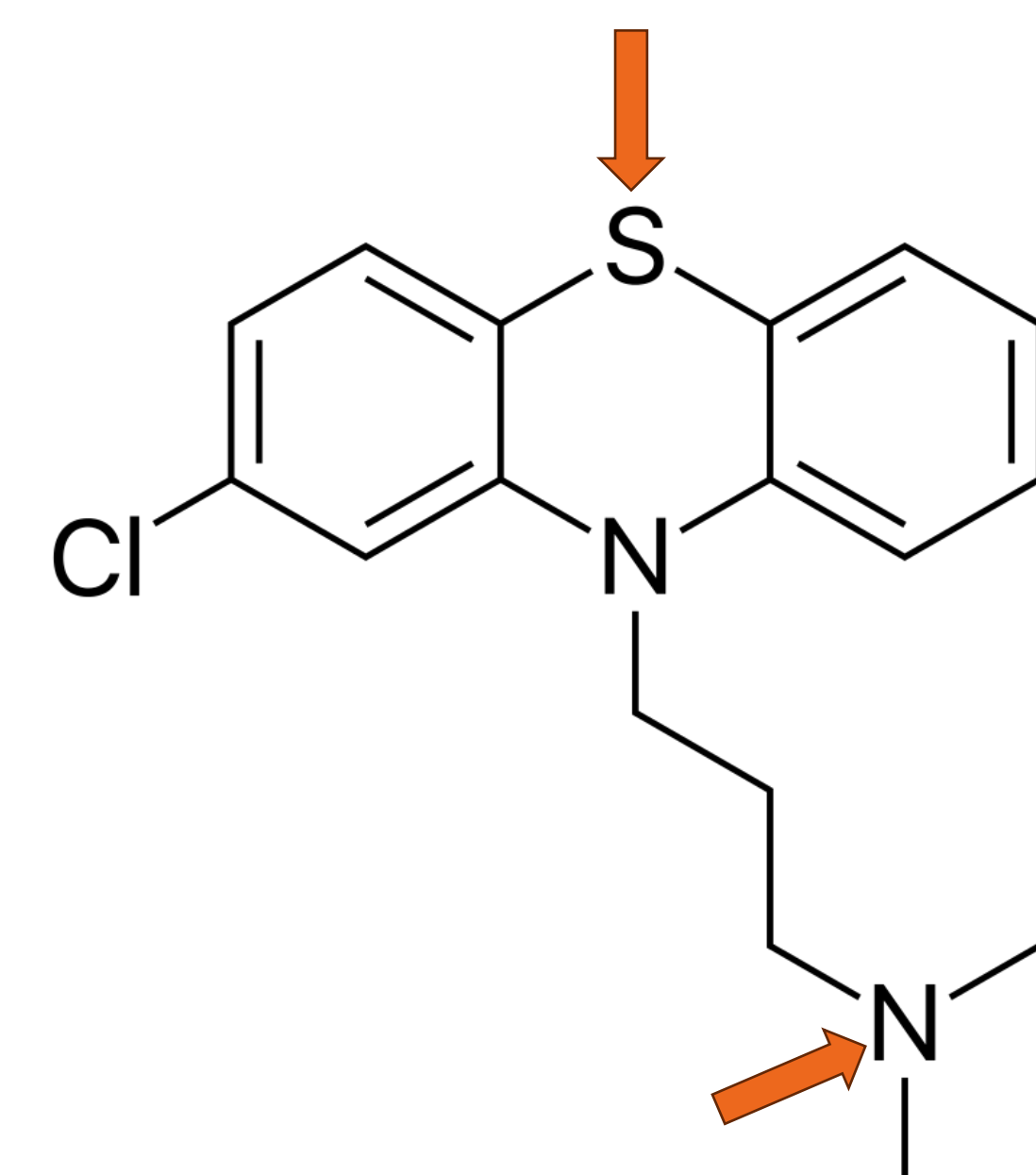
Oxygen- and Moisture-modified Arrhenius Equation

$$\ln(k) = \ln A - \frac{E_a}{RT} + B(RH) + C \ln \frac{[O_2]}{21\%}$$

- Chlorpromazine (CPZ) tablets were used as a case study to experimentally validate this equation and confirm its ability to use highly accelerated conditions to accurately model long-term growth of oxidative degradants in a drug product.

Table 1: Formulation of 3.6 mg CPZ tablets

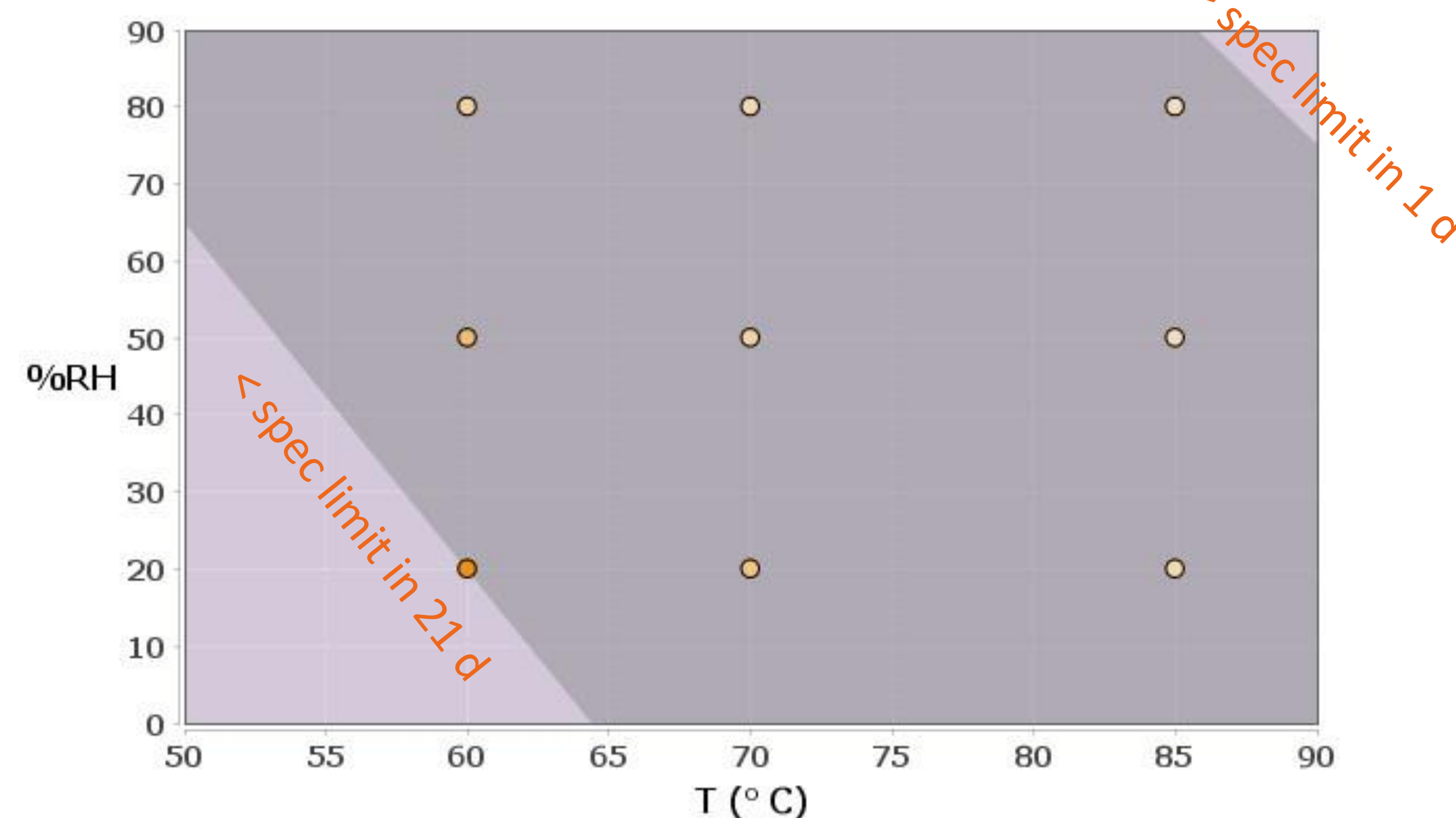
Component	% w/w
Chlorpromazine HCl	2
Microcrystalline cellulose	60
Lactose spray-dried	30
Croscopvidone	7
Magnesium stearate	1
Total	100



Structure of Chlorpromazine

ASAP Study Design

- Tablets were stressed at varying oxygen levels - 2, 5, 10, 21% - at each of the temperatures and relative humidities shown below.
- Multiple time points were taken at each condition.



Stressing

- CPZ tablets and a saturated salt solution were sealed in a canning jar in a controlled oxygen environment.
- Jars and salts were sized to provide oxygen and moisture in excess of what may be sorbed or reacted away so that conditions over study length were effectively constant.



Methods

Analysis

- Relative growth of CPZ's primary oxidative degradants, CPZ sulfoxide and CPZ N-oxide, was quantified by high performance liquid chromatography (HPLC) analysis of tablets after stressing.

Modeling

- ASAPprime® determines the time to reach a specification limit (isoconversion time) for each degradant at each condition, which can then be fit to the Arrhenius equation.
- The proposed oxygen sensitivity term was incorporated into the ASAPprime® models by fitting calculated isoconversion times to the oxygen- and moisture-modified Arrhenius equation in a modified software version.
- In combination with the tablets' oxygen consumption rate and the primary packaging oxygen transmission rate, long-term drug-product shelf life can be predicted.

Results

Example Isoconversion Plots for CPZ Sulfoxide Growth at 85°C/23% RH

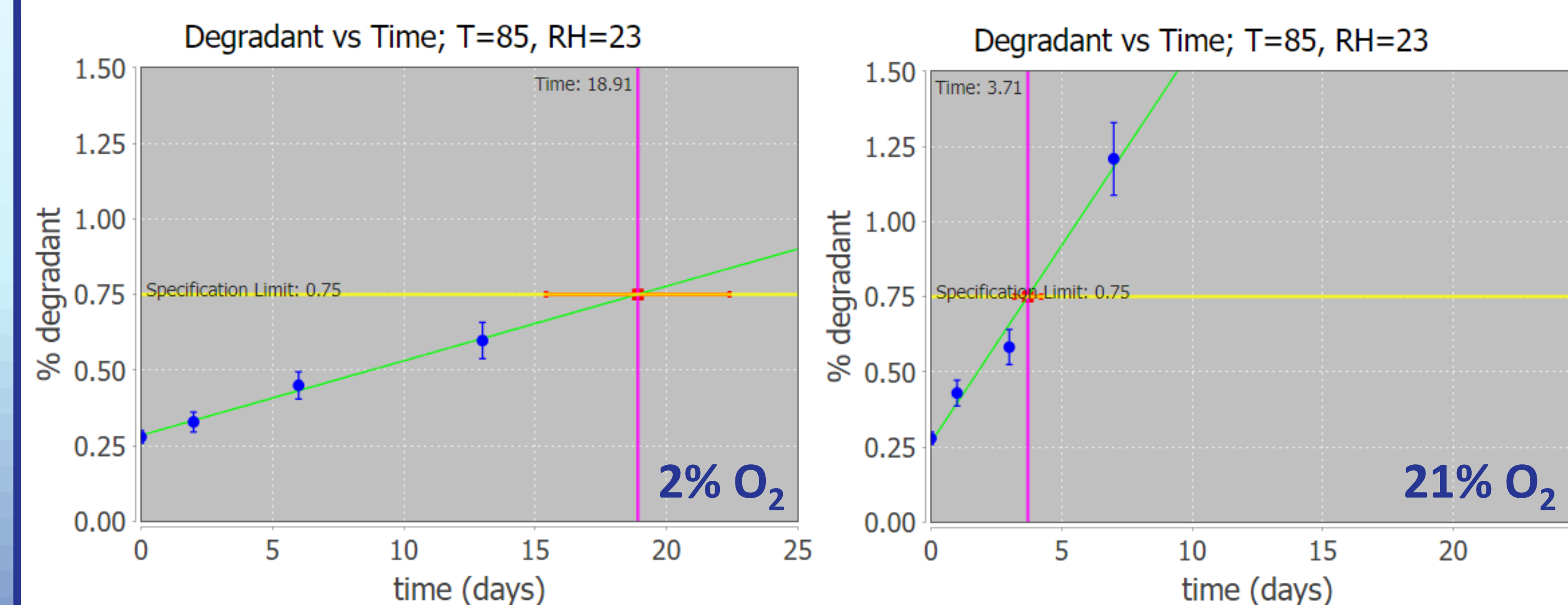
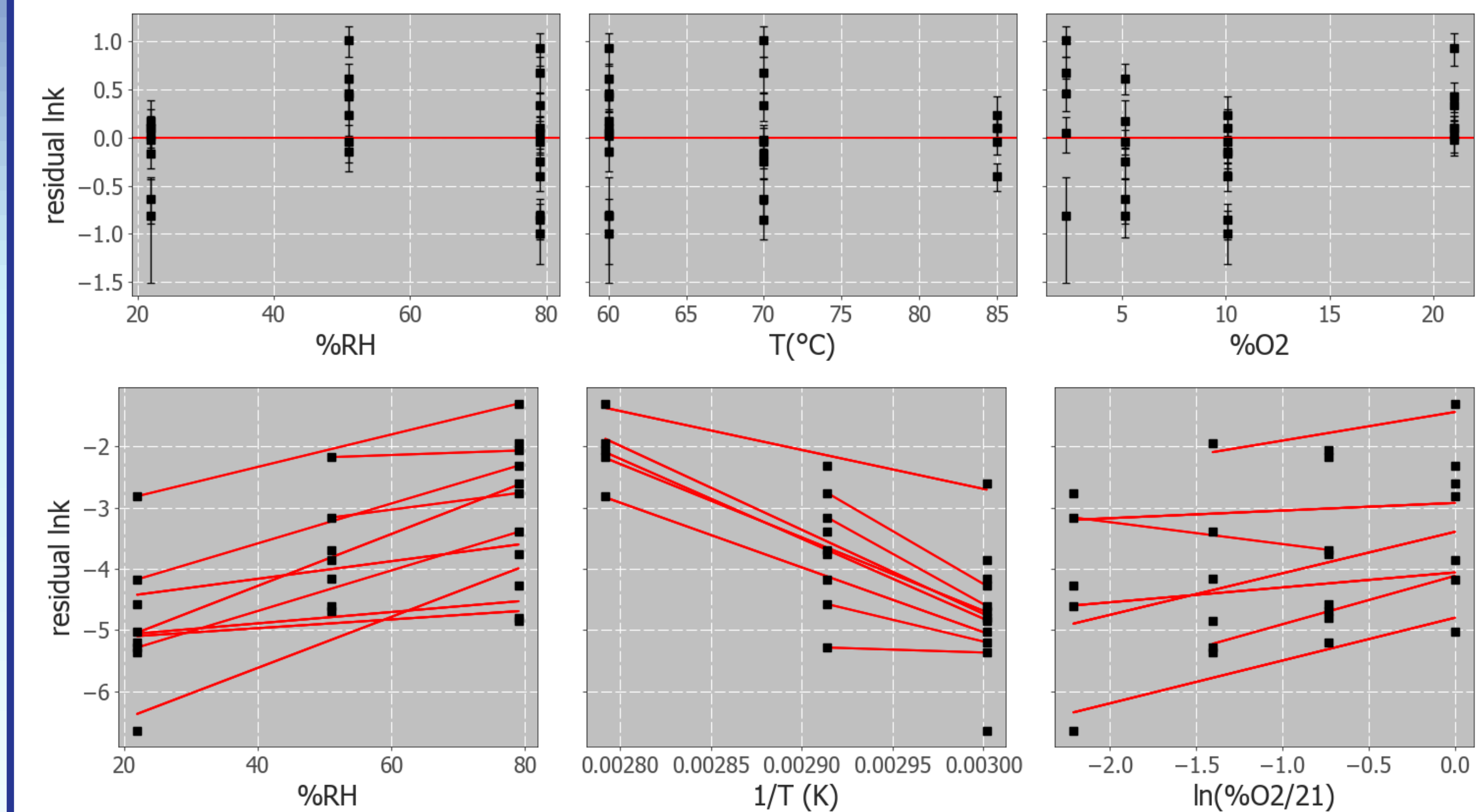


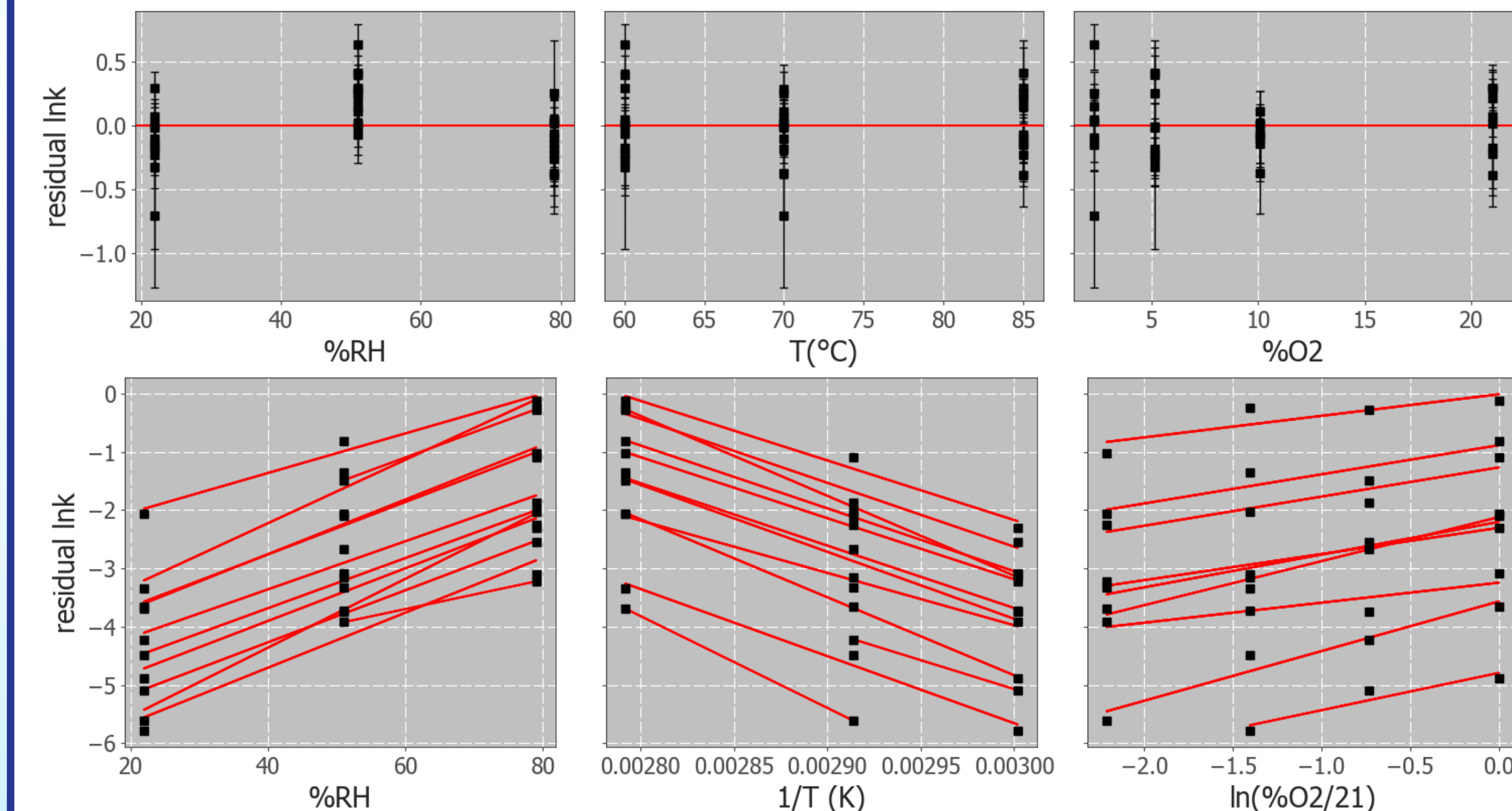
Table 2: Modeled Arrhenius Parameters for the Growth of CPZ N-oxide and CPZ Sulfoxide

Degradant	lnA	E _a (kcal/mol)	B	C	R ²	Q ²
N-oxide	24.9 ± 1.4	20.2 ± 1.0	0.026 ± 0.002	0.36 ± 0.07	0.83	0.79
Sulfoxide	27.9 ± 1.6	22.3 ± 1.2	0.046 ± 0.002	0.54 ± 0.05	0.97	0.96

Residual and Arrhenius Plots Demonstrating Model of CPZ N-oxide



Residual and Arrhenius Plots Demonstrating Model of CPZ Sulfoxide



Conclusions

- Data generated for oxidation of chlorpromazine tablets under designed accelerated stress conditions are consistent with the proposed oxygen- and moisture-modified Arrhenius equation
- All three variables (temperature, RH, and % oxygen) show independent behavior, with the oxygen dependence following a power law relationship

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