Partial Vapor Pressure, Activity, Activity Coefficient and Henry's Law Vaporization Constant at 25 °C of Nicotine from Binary Mixtures with Glycerin and with Propylene Glycol

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Introduction

- E-liquids composed primarily of humectants
  - Glycerin and/or Propylene glycol (PG) typically > weight 90%
  - Nicotine typically (0 to 5) weight %
- No quantitative information on nicotine vapor behavior with these humectants in the literature
- **Objective: Measure equilibrium headspace concentration of nicotine for binary mixtures with glycerin and PG near 25 ^{o}C**
  - Concentration converted to partial pressure using Ideal Gas Law
  - Activity = partial pressure / undiluted vapor pressure
  - Activity coefficient = activity / solution mole fraction

Introduction

- Henry's law vaporization constant (H_V^{px}) = initial slope of partial pressure (p) vs mole fraction (x): $H_V^{px} = \lim_{x \to 0} \frac{p}{x}$
  - Initial data points of partial pressure vs mole fraction fit to quadratic equation to allow multiple points to be used
    - $p = bx + cx^2$ with constant set to zero to avoid offset of slope
    - And the constant was not statistically significant as well (p-value > 0.8)
  - Slope (dp/dx) = b + 2cx, **@ x = 0** gives **Initial Slope = b**
- Slight temperature correction to 25 °C using Clausius-Clapeyron equation
  - $p_2/p_1 = \exp[(-\Delta_l^g H/ R) * (1/T_2 - 1/T_1)]$ where:

    p = pressure (Pa), $\Delta_l^g H$ = enthalpy of vaporization (J/mol at 298.15 K), R = gas constant = 8.31446 J/(K mol), T = Temperature (K)
  - $\Delta_l^g H$ = 65.0 ± 0.83 kJ/mol from mean of 8 values from the literature

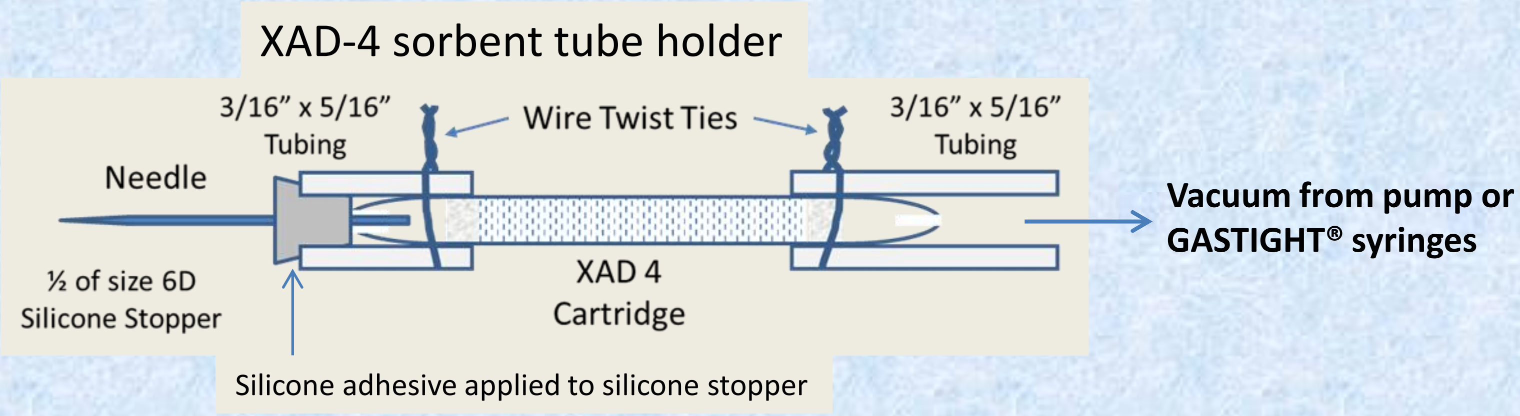
Experimental

Sample preparation

- Binary mixtures stored in aluminum-foil lined flexible bags filled with N_2[a]
- Headspace sampled through PTFE lined septum using non-coring needles[a]
  - Sampled using (6 mm diameter x 70 mm long) sorbent sampling tubes containing 120 mg of XAD-4 resin (SKC Inc., Eighty Four, PA)
  - Measured volumes sampled using peristaltic pump with output bubbled into calibrated (200 to 1000) mL volumetric flasks or GASTIGHT® syringes
  - In-syringe sampling used to check undiluted nicotine headspace sampling [a]
- Experiments conducted sequentially
  - First experiment : Nicotine in binary mixture with Glycerin
    - Samples in a room with stable temperature control (23.1 to 24.7 ^{o}C)
    - 12 mixtures, (0.0015 to 1.0) mole fraction nicotine
  - Second experiment : Nicotine in binary mixture with PG
    - Samples in environmental chamber (24.8 to 25.1 ^{o}C)
    - 8 mixtures, (0.0050 to 1.0) mole fraction nicotine

[a] *St.Charles & Moldoveanu, Beitr. Tabakforsch. Int. 27 (2016) 11-19*

Sample preparation



Sample preparation

- XAD-4 resin and glass plugs transferred to 4 mL vial
- 3 mL Extraction Solution + 60 µL Internal Standard (I.S.) added & shaken for 25 minutes
  - Extraction solution = ethyl acetate + 5000 ppm triethylamine (to prevent nicotine adsorption to glass)
  - I.S.= 10.9 µg/mL (+/-) deuterated nicotine (methyl-d3) in extraction solution
  - Aliquot of extract pipetted to 1.5 mL GC vials for analysis
- In-syringe sampling used a 10 mL GASTIGHT® syringe with conical point needle and shutoff valve
  - 1.5 mL extraction solution added to syringe
  - Headspace aspirated through solution until desired volume
  - Valve closed and syringe shaken manually for 5 minutes
  - Extract transferred to 1.5 mL GC vials for analysis

GC/MS/MS Analysis of Nicotine

- Agilent 7890B/7810B system in multiple reaction monitoring (MRM) mode
- DB-Waxetr 30 m x 0.25 mm i.d. column with a 0.25 µm film
- Nicotine concentration vs (peak area nicotine / peak area I.S.) calibration
- Signal/noise, S/N = 632 for 3.0 ng nicotine/mL (glycerin experiment) and S/N = 2391 for 24.7 ng nicotine/mL (PG experiment)

Conditions for the GC/MS/MS analysis of nicotine.

Parameter	Description	Parameter	Description
Initial oven temperature	50°C	Aux. temperature	250°C
Initial time	1.0 min	Solvent delay	3.75 min
Oven ramp rate	10°C/min	Gain factor	10
Oven temperature 1	240°C	Electron energy	45 V
Final time	10 min	MS source temperature	230°C
Total run time	30.0 min	Acquisition mode	MRM
Inlet temperature	280°C	d3-Nicotine precursor ion	165.1
Inlet mode	Splitless	d3 Nicotine product ion	87.1
Purge time	1.0 min	MS1 resolution	Unit
Purge flow to split vent	15.0 mL/min	Dwell time	120 ms
Carrier gas	Helium	CE	11 V
Injection volume	1.0 µL	Nicotine precursor ion	162.1
Flow mode	Constant flow	Nicotine product ion	84.1
Flow rate	1.0 mL/min	MS1 resolution	Unit
Nominal initial pressure	7.65 psi	Dwell time	120 ms
GC outlet	MS/MS	CE	11 V

Results

Nicotine in Glycerin *(0.02 mole fraction = 3.5 weight %)*

Mean Nicotine data ± Expanded Uncertainty[a,b] for Nicotine (1) + Glycerin (2) at 25 ºC

No. of Measurements N, Mole Fraction x, Partial Pressure $\bar{p}$, Activity $\bar{a}$, Activity Coeff. $\bar{\Upsilon}$

N	x_1	$\bar{p}_1$/Pa	$\bar{a}_1$	$\bar{\Upsilon}_1$
3	0.0015 ± 0.00010	0.069 ± 0.019	0.0168 ± 0.0062	11.2 ± 4.4
4	0.00499 ± 0.000081	0.223 ± 0.039	0.054 ± 0.013	10.8 ± 2.7
4	0.00927 ± 0.000077	0.432 ± 0.034	0.104 ± 0.020	11.2 ± 2.2
5	0.0121 ± 0.00023	0.584 ± 0.025	0.141 ± 0.023	11.6 ± 1.9
6	0.02002 ± 0.000073	0.87 ± 0.15	0.210 ± 0.048	10.5 ± 2.4
5	0.0235 ± 0.00043	0.986 ± 0.051	0.238 ± 0.039	10.1 ± 1.7
6	0.0501 ± 0.00010	1.58 ± 0.36	0.38 ± 0.10	7.6 ± 2.0
5	0.093 ± 0.0017	2.253 ± 0.097	0.544 ± 0.088	5.83 ± 0.96
6	0.2533 ± 0.00089	2.96 ± 0.49	0.71 ± 0.16	2.82 ± 0.62
6	0.461 ± 0.0091	3.60 ± 0.36	0.87 ± 0.15	1.89 ± 0.33
6	0.741 ± 0.0032	4.35 ± 0.56	1.05 ± 0.20	1.42 ± 0.27
14	0.998 ± 0.0016	4.14 ± 0.50	1.00 ± 0.17	1.00 ± 0.17

[a] k=2 for *x*, [b] 95.45% confidence interval for N-1 degrees of freedom from Student's t distribution for others

Nicotine in PG (0.02 mole fraction = 4.2 weight %)

Mean Nicotine data ± Expanded Uncertainty[a,b] for Nicotine (1) + PG (2) at 25 °C

No. of Measurements N, Mole Fraction *x*, Partial Pressure $\bar{p}$, Activity $\bar{a}$, Activity Coeff. $\bar{\Upsilon}$

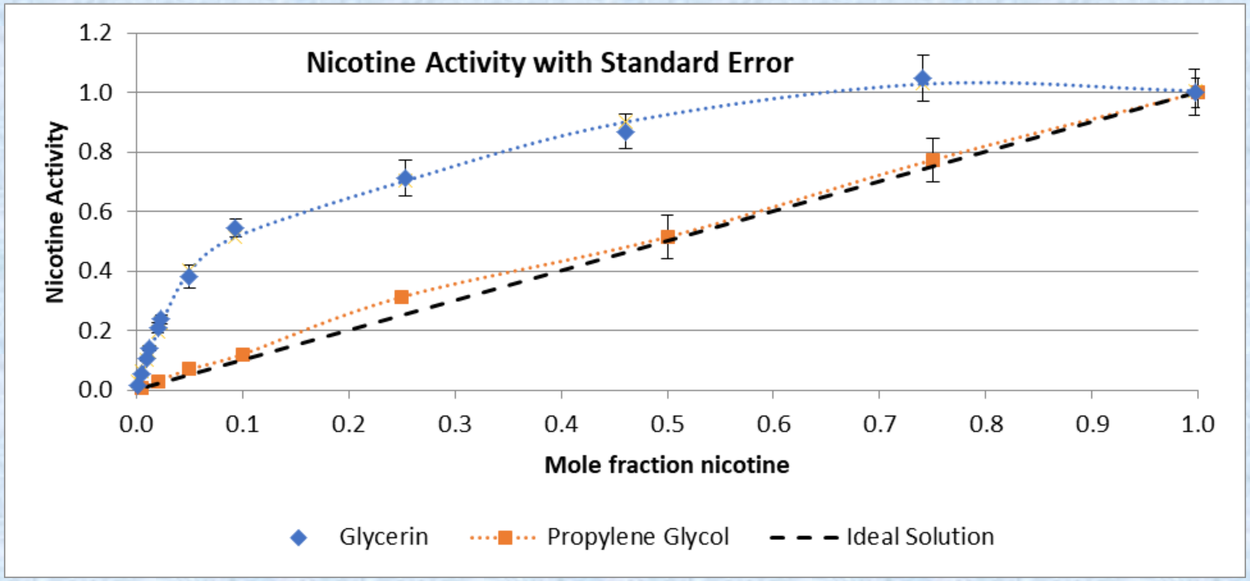
N	x_1	$\bar{p}_1$/Pa	$\bar{a}_1$	$\bar{\Upsilon}_1$
4	0.00506 ± 0.000019	0.0275 ± 0.0043	0.00744 ± 0.00086	1.49 ± 0.18
5	0.02015 ± 0.000075	0.1106 ± 0.0079	0.0298 ± 0.0030	1.49 ± 0.15
5	0.0504 ± 0.00019	0.261 ± 0.032	0.0704 ± 0.0074	1.41 ± 0.15
6	0.0999 ± 0.00034	0.448 ± 0.042	0.121 ± 0.012	1.21 ± 0.12
6	0.2486 ± 0.00091	1.164 ± 0.059	0.314 ± 0.034	1.25 ± 0.14
5	0.498 ± 0.0020	1.91 ± 0.40	0.51 ± 0.21	1.03 ± 0.43
5	0.747 ± 0.0028	2.87 ± 0.25	0.77 ± 0.21	1.03 ± 0.28
10	0.999 ± 0.0038	3.714 ± 0.081	1.00 ± 0.11	1.00 ± 0.11

[a] k=2 for *x*, [b] 95.45% confidence interval for N-1 degrees of freedom from Student's t distribution for others

Nicotine activity coefficient below 0.02 mole fraction

- Glycerin ~ 11 (implies partial pressure 11 times greater than Ideal Solution)
- PG ~ 1.5 (implies partial pressure 1.5 times greater than Ideal Solution)

Nicotine Activity vs Mole Fraction Nicotine



- Both mixtures show positive deviation from Ideal Solution
- Nicotine in Glycerin deviation much greater than in Nicotine in PG
- Nicotine in PG approaches Ideal Solution

Henry's Law Volatility Constant (H_V^{px})

- Initial slope of nicotine partial pressure vs mole fraction
- Nicotine in Glycerin ~ 10x greater than Nicotine in PG

Polynomial regression for H_V^{px}

Experiment	Glycerin	Propylene Glycol
No. of Points	7	6
Degrees of Freedom	5	4
R Squared	0.9998	0.9994
H_V^{px}/Pa (coefficient b)	**51.38**	**5.26**
u(H_V^{px})/Pa	0.69	0.19
U(H_V^{px})/Pa	1.8	0.52

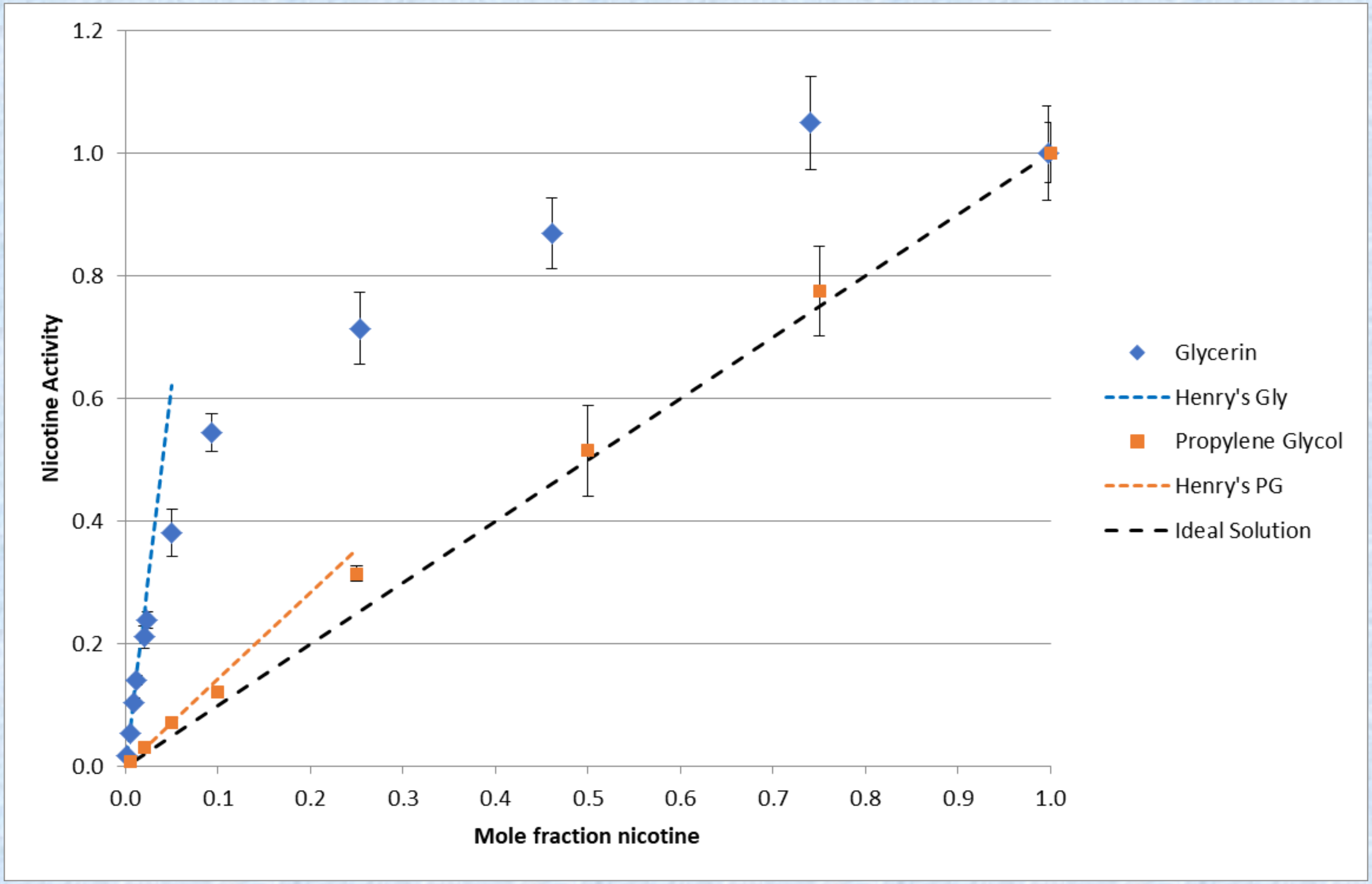
u = standard uncertainty
U = expanded uncertainty

Putting it all together

- Glycerin with hydroxyl units on all carbons exhibits much stronger bonding with other glycerin molecules than with less polar nicotine molecules
- Nicotine in Glycerin similar to Nicotine in Water
  - Activity coefficient in Glycerin ~ 11 below 0.02 mole fraction
  - Activity coefficient in Water = 13 for 0.016 mole fraction[a]
- Nicotine in PG, with 2 hydroxyl units & 1 fully protonated carbon, approaches an Ideal Solution
- Strong narcissism of glycerin evident in vapor pressure
  - Glycerin vapor pressure @ 25 ^{o}C ~ 0.022 Pa (0.13% of PG VP)
  - Vapor pressure @ 25 ^{o}C : PG ~ 17 Pa, Nicotine ~ 4 Pa

[a] Banyasz, J.L. The physical chemistry of nicotine. In Gorrod J.W.; Jacob III P., Eds. *Analytical Determination of Nicotine and Related Compounds and their Metabolites*; Elsevier, New York, 1999; pp 149-190.

Putting it all together



Conclusions

Summary

- Nicotine partial pressures in binary mixtures with glycerin and with propylene glycol were measured over a wide range of nicotine concentration
- Nicotine activity, activity coefficient and Henry's law volatility constant were calculated
- Nicotine partial pressure and activity vs mole fraction for both systems exhibited a positive deviation from an Ideal Solution
- The deviation for glycerin mixtures was much greater than that for propylene glycol mixtures

Summary

- Henry's Law vaporization constant for nicotine in glycerin was about an order of magnitude greater that that for nicotine in propylene glycol.
- Glycerin, with hydroxyl units on all carbons, exhibits much stronger bonding with other glycerin molecules than with less polar nicotine in a manner similar to nicotine in water.
- Nicotine in propylene glycol approached Ideal Solution behavior

Thanks to

- R.J. Reynolds Tobacco Company Research and Development
- You for listening

Questions ?