NOTES

Application of isotopic exchange in gaschromatographic columns for labelling of organic compounds

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The schematic drawing of the assembly used in the experiments is shown in Figure 1. The packing of the gaschromatograph is introduced into a 2 m long, 20 mm diameter U-shaped glass tube. As stationary phase 25 % diglycerol or 35 % polyethylene glycol with 10 % KOH catalyst is used on solid support (e.g. Sterchamol). The compounds are injected into the column by syringe through the silicon rubber plugs (1, 2) at each end of the column. The appearance of the individual fractions is observed by conductivity detector (3). Dry nitrogen is employed as carrier gas at flow rates from 100 to 300 ml/min. The direction of gas flow on the column can be varied by the two-way

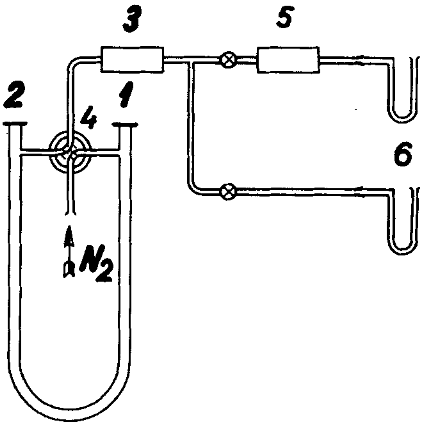


FIG. 1. Experimental apparatus.

1.2 — silicon rubber plugs.
3 — conductivity detector.
4 — two-way tap.
5 — ignition tube.
6 — freezing trap.

tap ⁽⁴⁾. The deuterium content of the products is evaluated from the measured refraction index of the water obtained on their ignition ⁽⁵⁾. The deuterized compounds are freezed out with a cooling mixture in trap ⁽⁶⁾.

On the injection of heavy water in successive fractions into the column, the hydrogens of the hydroxil groups in the packing exchange with deuterium. Passing subsequently the compound one wants to deuterize through the column its exchangeable hydrogen atoms are replaced in turn by deuterium.

The isotopic exchange was investigated on a model column packed with diglycerol (May and Baker L. T. D. product, average molar weight 166 ± 10) passing through it either water or methanol. The deuterium exchange coefficients were evaluated in both cases from measurements at the temperature of 20° C. The measurements show the enrichment in deuterium to take place always in diglycerol, while the difference between the isotopic ratios is higher for water than for methanol, since we have

$$(D/H)_{\text{water}} / (D/H)_{\text{digl.}} = 0.856$$

$$(D/H)_{\text{methanol}} / (D/H)_{\text{digl.}} = 0.927$$

The whole exchange cycle on the gas chromatograph column was studied following up the total deuterization of the diglycerol on the column during the passage of water or methanol. Water or methanol was injected in fractions, 0.5 ml each, with 0.0554 and 0.0124 gram equivalent exchangeable hydrogen content, respectively. The deuterium content of each fraction was determined after its passage through the column. The curves for deuterization and dedeuterization were the plotted from the experimental data in Figures 2 and 3. The slope of the S-shaped curve is in either case steeper for the deuterization of diglycerol as to be expected also from the parallel equilibrium measurements which showed higher D/H ratios for diglycerol in both cases. The relative value of the exchange coefficients is in agreement with the greater difference between the slopes of the curves plotted for the water — than for the methanol — diglycerol system showing the deuterium enrichment of diglycerol to be higher in the former case. The data suggest an analogy between the gas chromatographic isotope exchange and ion exchange processes in general.

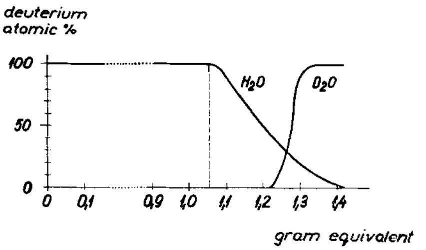


FIG. 2. Deuterization and de-deuterization of the diglycerol column with water.

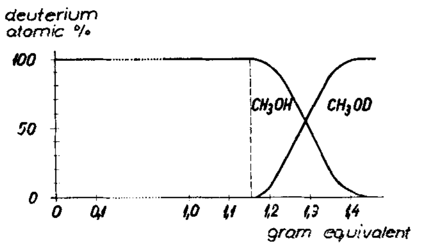
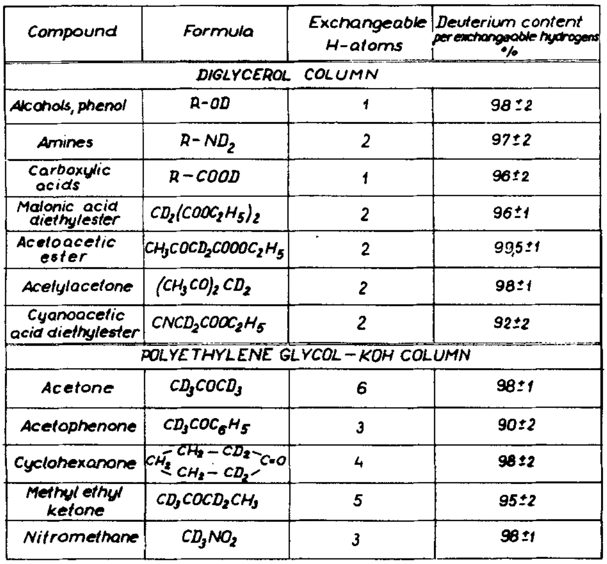


FIG. 3. Deuterization and de-deuterization of the diglycerol column with methanol.

In the deuterization on gas chromatograph deuterium is transferred from D_2O to a given compound. An important point from the practical aspect is the efficiency of this procedure. It is determined actually by the combined efficiency of the two processes involved, namely, deuterization of the column with heavy water and its dedeuterization by the compound passed through the column. The former can be defined as the ratio of exchangeable hydrogen on the column to the deuterium (both in gram equivalents) required for its total deuterization. The efficiency of de-deuterization, on the other hand, is determined by the fraction of deuterium on the column utilizable for 100 % labelling of the compound. The efficiency in either case can be evaluated from the process curves. It is apparent from the results in Figure 4 that a higher gradient of the slope means better efficiency. The economics of isotope utilization can be improved by interrupting the deuterization of the column before the breakthrough and passing the compound for deuterization in the reverse sense, that is to employ in general the technique of feeding the column at one end always with heavy water, at the other with the compound to be deuterized. An additional advantage of this reverse current technique is that the column need not be fully deuterized before use, since it is sufficient if it contains as much deuterium as one wants to introduce for labelling.

Reaction	Efficiency
$CH_3OH \rightarrow CH_3OD$	0.89
$CH_3OD \rightarrow CH_3OH$	0.91
$H_2O \rightarrow D_2O$	0.84
$D_2O \rightarrow H_2O$	0.94

FIG. 4. Efficiency of the gas chromatographic deuterium labelling.



Compound	Formula	Exchangeable H-atoms	Deuterium content per exchangeable hydrogens %
DIGLYCEROL COLUMN			
Alcohols, phenol	$R-OD$	1	98±2
Amines	$R-ND_2$	2	97±2
Carboxylic acids	$R-COOD$	1	96±2
Malonic acid diethylester	$CD_2(COOC_2H_5)_2$	2	96±1
Acetoacetic ester	$CH_3COCD_2COOOC_2H_5$	2	99,5±1
Acetylacetone	$(CH_3CO)_2CD_2$	2	98±1
Cyanoacetic acid diethylester	$CNCD_2COOC_2H_5$	2	92±2
POLYETHYLENE GLYCOL – KOH COLUMN			
Acetone	CD_3COCD_3	6	98±1
Acetophenone	$CD_3COC_6H_5$	3	90±2
Cyclohexanone	$CH_2\begin{matrix}CH_2-CD_2\\CH_2-CD_2\end{matrix}C{=}O$	4	98±2
Methyl ethyl ketone	$CD_3COCD_2CH_3$	5	95±2
Nitromethane	CD_3NO_2	3	98±1

FIG. 5. Compounds deuterized on gas chromatograph.

Gas chromatographic labelling is practicable only for systems with enough exchangeable atoms capable to take part in the isotopic exchange, that is, if they are in sufficiently loose bonds. Such is the case of hydrogens bonded to highly electronegative atoms with free electron pair (oxygen, sulphur, nitrogen) or even hydrogens bonded to carbon exhibiting under some structural conditions acidic behaviour. The products obtained on columns with diglycerol are shown in Figure 5. Compounds of the type acetyl acetone, aceto-acetic ester etc. with keto-enol tautomerism containing hydrogens loosened on both sides are deuterized on this column while the hydrogens of mono-oxo systems like acetone, methylethylketone etc. cannot be exchanged.

If one adds 10 % KOH as catalyst to a column with polyethylene glycol also the mono-oxo systems will deuterize. The hydrogens of nitromethane which can be only partly exchanged without catalyst deuterize to almost 100 % in the presence of the latter (Fig. 5).

The activation energy of H-D isotopic exchange can be evaluated from the gas chromatograph temperature dependence of the deuterium concentration in the deuterized product. In the case of e.g. cyclo-hexanone it is 8 kcal/mol.

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Some possibilities in hot synthesis of radio-halogen labelled organic compounds

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The stabilization processes of the energetic ^{38}Cl were studied in binary mixtures of carbontetrachloride with aliphatic alcohols and aromatic compounds as well in both liquid and solid states over a wide range of relative concentrations.

The irradiations were performed in the 2.5 MW VVR-S type reactor using a pneumatic tube for short time irradiations. Mixtures in solid state were irradiated at liquid nitrogen temperature.

The organic radiolabelled products were separated and identified by gaschromatographic technique. The inorganic activity was adsorbed on potassium ferrocyanide. Tricresyl phosphate was used as stationary phase. The assembly comprised two detectors. A Catharometer was used for measuring the chlorinated hydrocarbon retention time. The activities of the labelled compounds were measured by Geiger counter method and automatic recorder.

In CCl_4-ROH system, in addition to the formation of labelled CCl_4 in macroconcentration, that of a substantial amount of labelled alkylchloride ($R^{38}Cl$) with the same alkyl radical as that of the starting alcohol can be obser-